



COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

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The old and the new

Lee S. Schwartzberg, MD, FACP, Editor-in-Chief

I recently attended the 14th World Conference on Lung Cancer (WCLC), a biennial multidisciplinary meeting for medical oncologists, surgeons, pulmonologists, radiation oncologists, and pathologists. The medical oncology portion of this conference was abuzz with excitement about the prospects of molecularly targeted therapies. Five years ago, few would have predicted that lung cancer would be the disease leading the way into the personalized medicine era in oncology. The recent discovery of a small number of critical genes that act as driving mutations for non-small cell lung cancer (NSCLC) has set the stage for the development of targeted agents against these mutations.



Gene mutations and molecular targeting

The Lung Cancer Mutation Consortium, comprised of 14 US-based cancer centers and sponsored by the National Cancer Institute, reported at the conference that mutations could be identified in 54% of adenocarcinomas, including genes such as *KRAS*, *EGFR*, *BRAF*, *HER2*, *PI3KCA*, *ALK*, *MET*, and others. Each of these genes has drugs either in clinical development or already marketed for other diseases with the same genetic alterations. Of note is that 97% of these mutations were mutually exclusive, suggesting that only one drug will be necessary to treat each of the subgroups. Proof of this concept is the development of crizotinib, a small molecule that inhibits the EML4-ALK fusion gene/protein with remarkable activity—over 80% of patients respond to this drug. Its approval is eagerly awaited.

Another exciting report presented at the WCLC investigated genetic abnormalities in the second most common subtype of NSCLC—squamous cell. Investigators used a combination of methods to identify genetic mutations, amplifications, or deletions in almost two-thirds of patients with this disease, setting the stage for molecularly

targeted treatment in this group as well.

We already have adopted pathway inhibition as a standard in lung cancer patients who harbor an epidermal growth factor receptor (EGFR) mutation, with increasing evidence suggesting that tyrosine kinase inhibitors such as erlotinib (Tarceva) are superior for first-line treatment of EGFR-mutated adenocarcinoma. Molecular diagnostics to guide treatment in the community setting is now firmly established in the most common diseases we see—breast, colon, and lung cancers.

And yet amid all of this excitement regarding novel pathways, validated targets, next-generation massively parallel sequencing, and so on, we must not forget that the majority of cancers are treated in both the adjuvant and metastatic setting with tried-and-true chemotherapeutic or endocrine agents. I even make a point of telling the fellows training with me that I am fairly confident that they will be giving chemotherapy throughout their careers, although it will certainly not dominate as it does today.

Revisiting mechanisms of action

All oncologists need to refamiliarize themselves with the mechanisms of action for the drugs that we use daily. In truth, each of the traditional chemotherapy agents are in fact targeting a cellular molecular pathway. It's just that we previously lacked the technology and knowledge to identify the specific target. For that reason, I am excited about two comprehensive reviews in this issue of COMMUNITY ONCOLOGY.

The first is a discussion of the estrogen receptor signaling pathway by Adam Brufsky (page 343). Much exciting knowledge has been gained over the past decade in understanding mechanisms of resistance to this oldest of validated targets. Now, trying to block alternative pathways of estrogen receptor activation in conjunction with aromatase inhibitors or other endocrine agents is the focus of much active research.

Also in this issue is a comprehensive review by Michael Trigg and Anne Flanagan-Minick of the mechanisms of action of commonly used anticancer agents (page 357). This is essential reading, as it discusses both classic cytotoxic agents and newer signal transduction modifiers. But perhaps most importantly, this review emphasizes the current thinking that most advanced epithelial tumors will not be brought under control with a single therapeutic agent, a lesson we learned in the era of cytotoxic drugs only. In fact, it is likely that the landscape will be dramatically more complex as agents from different classes are necessarily combined to achieve maximum effect.

More and more it appears that integrating personalized medicine into a system of practice-based

guidelines will be a formidable challenge. Still, there is a great opportunity for community oncologists to prove value to their third-party payers and directly to patients for the high-level decision making required to provide optimal care. Such decision making must be part of the value equation as reimbursement moves away from margins on drug acquisition and to oncologists providing the best care based on their knowledge and informatics resources.

A handwritten signature in black ink, reading "Lee Schwartzberg". The signature is written in a cursive style with a large, stylized "L" and "S".

Lee S. Schwartzberg, MD, FACP

Understanding the estrogen receptor signaling pathway: focus on current endocrine agents for breast cancer in postmenopausal women

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Estrogen receptor (ER) signaling plays a critical role in many breast cancers. As a result, endocrine therapy is a mainstay in the treatment plan for patients with hormone receptor-positive breast cancer. Although patients with metastatic breast cancer (MBC) are often given several lines of endocrine therapy throughout the course of their disease, the optimal sequence of and exact mechanisms of resistance to endocrine therapy remain unclear. Endocrine therapies include aromatase inhibitors, selective ER modulators, and selective ER downregulators. These agents interfere with ER signaling and inhibit breast cancer growth, but their mechanisms of action (MOAs) are distinct and potential mechanisms of resistance vary. Patient-specific factors (eg, tumor characteristics, burden of disease, patient preferences, and treatment history) and the MOAs of the available agents are important considerations. This review discusses the latest understanding of ER biology, the mechanistic differences between endocrine therapies, and future directions in endocrine therapy for MBC.

It is well established that estrogen acting via the estrogen receptor (ER) plays a role in the growth and development of hormone receptor-positive (HR+) breast cancer. As a result, over the past few decades, several endocrine therapies that limit the actions of estrogen have been developed. These endocrine therapies have played a substantial part in the treatment of breast cancer and have significantly improved the outcomes of postmenopausal women with all stages of the disease.

Although many different agents have been used in the clinic to treat these patients, aromatase inhibitors (AIs) and antiestrogens form the two major categories of endocrine therapy in current use. These two types of agents have distinct mechanisms of action (MOAs).¹ AIs reduce circulating estrogen levels by preventing the conversion of androstenedione into estrogen in peripheral tissues.¹ Antiestrogens, also referred to as ER antagonists, can be further classified into two subgroups based on their MOA: the selective ER modulators (SERMs), typified by tamoxifen, and the selective ER downregulators (SERDs), exemplified by fulvestrant (Faslodex).¹

A number of randomized clinical studies have demonstrated the efficacy of tamoxifen and the AIs (anastrozole, letrozole, and exemestane) in the

adjuvant²⁻⁵ and metastatic⁶⁻⁸ settings. Fulvestrant has demonstrated effectiveness in the metastatic setting.⁹⁻¹³

Mechanistic overview of endocrine therapies

Estrogen signaling in postmenopausal women

To understand the MOAs of available endocrine therapies, it is first essential to discuss how estrogen production and ER signaling work in postmenopausal women. Prior to menopause, the ovaries produce the majority of circulating estrogen. Following menopause, estrogen production by the ovaries ceases, and the overall concentration of circulating estrogen is decreased. However, smaller amounts of estrogen are produced by various sources outside the ovaries. This residual estrogen production can play a central role in breast cancer growth in postmenopausal women. Estrogen precursors are predominantly synthesized by the adrenal glands. Circulating estrogens (estrone and estradiol) are

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then produced by the aromatization of these estrogen precursors or androgens (androstenedione and testosterone) in a number of tissue types, including the skin and subcutaneous adipose tissue.¹⁴ For example, androgens can be converted to estrogen in the adipose fibroblasts associated with breast tumors, stimulating malignant proliferation.^{15–17}

ERs are localized in the nucleus and in the cytoplasm near the cell membrane in the presence or absence of estrogen.¹⁸ ERs shuttle back and forth between these locations to transmit signals that stimulate transcription of estrogen-responsive genes. Estrogen exerts its effects through the ER to stimulate cell growth in two major ways: ligand-dependent receptor activation (the classic pathway) and nongenomic (or non-nuclear) actions.^{19,20} The proliferative activity mediated by the ER is attributed to two structural domains—an activating function 1 (AF-1) domain and a ligand-inducible activating function 2 (AF-2) domain—which, as discussed below, have independent and synergistic effects, depending on circumstances such as the presence of ligand or various coactivator proteins.²¹ In the classic pathway of ER activation, binding of estrogen to the ER causes the receptor to dissociate from an inhibitory complex with chaperone proteins, exposing the AF-2 domain on the ER.²² This action allows formation of ER homodimers and increased nuclear localization, where these homodimers bind to sequences of DNA known as estrogen response elements (EREs) and promote transcription of key genes. This process is driven by various coactivator proteins recruited by the AF-1 and AF-2 domains. The activation of both AF domains is required for estrogen to exert its full agonist effects.²² Notably, the AF-1 domain is exposed prior to as well as after estrogen binding. Therefore, the activity of the AF-1 domain is hormone independent and is thought to

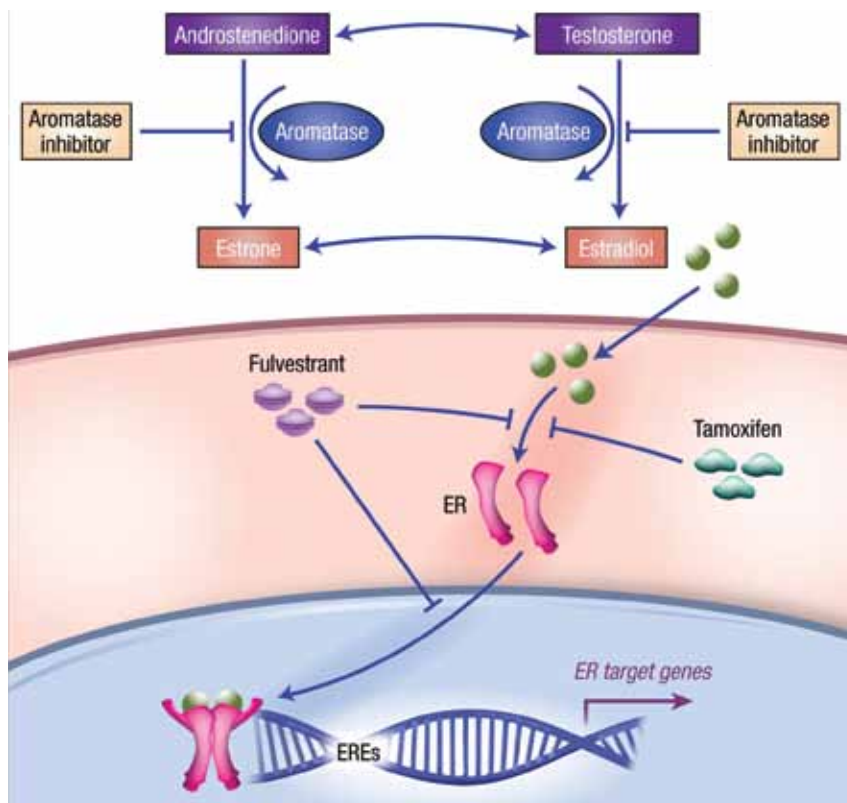


FIGURE 1 The basis for endocrine therapy in breast cancer. ER = estrogen receptor; EREs = estrogen response elements. Reprinted by permission from Macmillan Publishers Ltd: Johnston SR, Dowsett M. Aromatase inhibitors for breast cancer: lessons from the laboratory. *Nat Rev Cancer* 2003;3:821–831, Copyright 2003.

be regulated by crosstalk with other signaling pathways during ligand-independent activation of ERs.²³

In nongenomic activation, estrogen binds ERs in the cytoplasm. The activated ERs crosstalk with and activate various intracellular signal transduction pathways, such as those mediated by mitogen-activated protein kinases (MAPKs), AKT, and phosphatidylinositol 3-kinase (PI3K) to initiate gene transcription.^{19,24}

MOAs of AIs

Starting with the first-generation AI, aminoglutethimide, several AIs have been developed over the past few decades.²⁵ Fine-tuning the selectivity for aromatase has improved the safety and efficacy of these agents. The third-generation AIs (including the reversible nonsteroidal agents [ie, anastrozole and letrozole]) and the ir-

reversible steroidal agent (ie, exemestane) are currently used in clinical practice.^{25,26} Despite their structural differences, the steroidal and nonsteroidal AIs have nearly identical MOAs, except that steroidal AIs bind irreversibly, whereas nonsteroidal AIs bind reversibly. AIs inhibit the conversion of androgens into estrogens by binding to and inhibiting the enzyme aromatase (Figure 1).¹⁴ As a result, despite the subtle differences between agents, more than 95% of aromatase is suppressed and estrogen levels are reduced by about 90%.^{25,27–29}

AIs do not inhibit the production of estrogen by the ovaries and thus are not approved to treat breast cancer in premenopausal women. However, there is evidence to suggest potential for combination therapy with the AI anastrozole plus goserelin (Zoladex) in premenopausal women with advanced

breast cancer (ABC). For example, as first-line therapy, the anastrozole-goserelin combination resulted in a 98% reduction (pretreatment to 6 months) in median estradiol levels and produced a sustained clinical benefit.³⁰ Previous work by the same group has shown similar activity of this combination as second-line therapy.³¹

MOAs of antiestrogens

Antiestrogens, including SERMs and SERDs, work similarly in that they block estrogen from binding to ERs. However, within this class of drugs, the exact MOA for each agent varies in the potential for agonist effects and the effects on ER expression. The differing effects of antiestrogens are described here.

Selective ER modulators. SERMs such as tamoxifen, raloxifene (Evista), and toremifene (Fareston) have unique chemical structures and exhibit a mix of agonistic and antagonistic effects in different tissues (Figure 2).^{19,22,32} For example, tamoxifen, which binds to ERs with lower affinity compared with estrogen (about 2.5% that of estrogen), acts as a competitive inhibitor to estrogen for the ER.³³ The binding of tamoxifen to the ER induces a conformational change, which causes the AF-2 domain to become hidden, inhibiting some coactivator recruitment and transcription of genes that depend on AF-2 activation (Figure 3).^{23,34} However, the AF-1 domain remains exposed. Tamoxifen binding also induces ER dimerization and DNA binding and stimulates AF-1-mediated gene transcription.^{23,34} A combination of AF-1 activation and tissue-specific expression of ER coactivator and corepressor molecules is responsible for the partial agonist properties of tamoxifen.¹⁹

Preclinical studies of tamoxifen have shown antagonist activity in mammary tissue but partial agonist activity in the uterus as well as agonist activity in bone and cholesterol

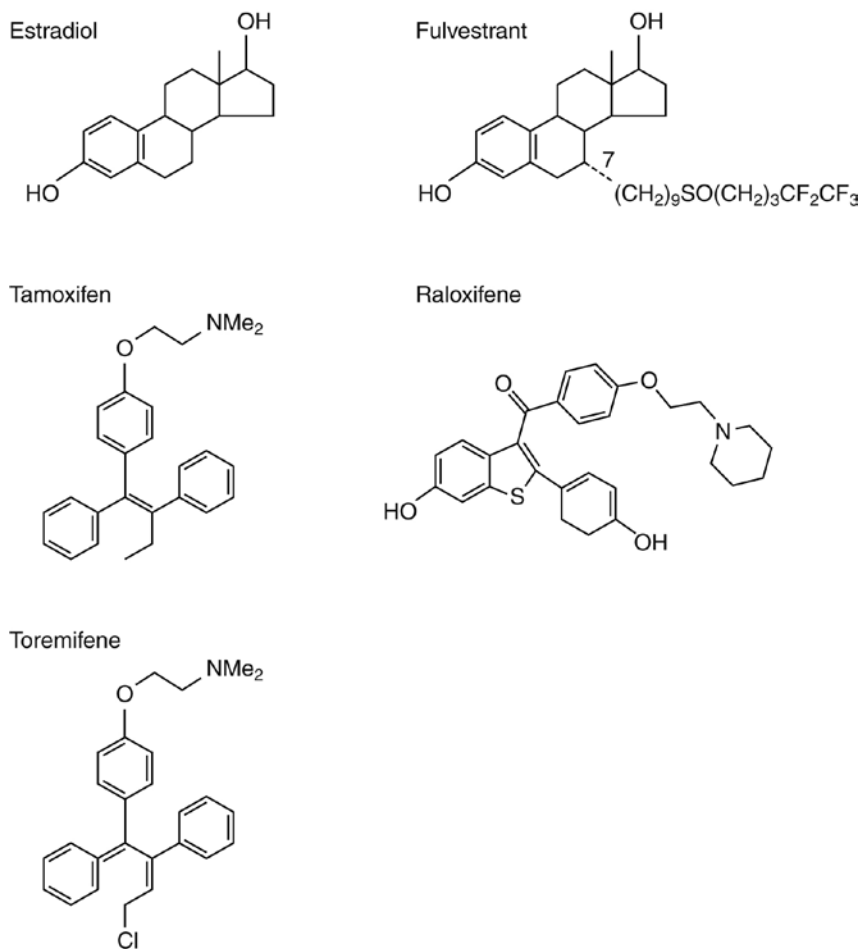


FIGURE 2 Structures of estrogen (estradiol) compared with estrogen receptor antagonists. Source: Howell²² and Buzdar and Hortobagyi.³²

ol metabolism.³⁵ Partial agonist effects of tamoxifen on the uterus were demonstrated in a preclinical study in rats.³⁶ This study showed that tamoxifen stimulated uterine proliferation (as measured by uterine weight) in a dose-dependent manner; however, the increase in uterine proliferation was less than the proliferation induced by estradiol treatment. The partial agonist activity of tamoxifen is thought to impact its clinical side-effect profile and protective effects on bone.

In contrast, raloxifene acts as an antagonist in both mammary tissue and the uterus as well as an agonist in bone and cholesterol metabolism.^{1,37} Although the exact reasons for these differences have not been fully elucidated, it is likely that structural differ-

ences among the SERMs contribute to their variable effects.

Selective ER downregulators. Pure antiestrogens like fulvestrant have no known agonist effects.³⁵ Fulvestrant binds to the ER with 89% affinity compared with estradiol and prevents estrogen binding.³⁸ Fulvestrant has a structure similar to that of estrogen, except it contains a heavily fluorinated alkylamide arm at the 7 α position, which increases binding affinity for the ER relative to tamoxifen (Figure 2).^{22,38}

Fulvestrant binding induces a conformational change in the receptor, which inactivates both the AF-1 and AF-2 domains and prevents ER homodimerization (Figure 3).^{34,39-41} Because fulvestrant interferes with

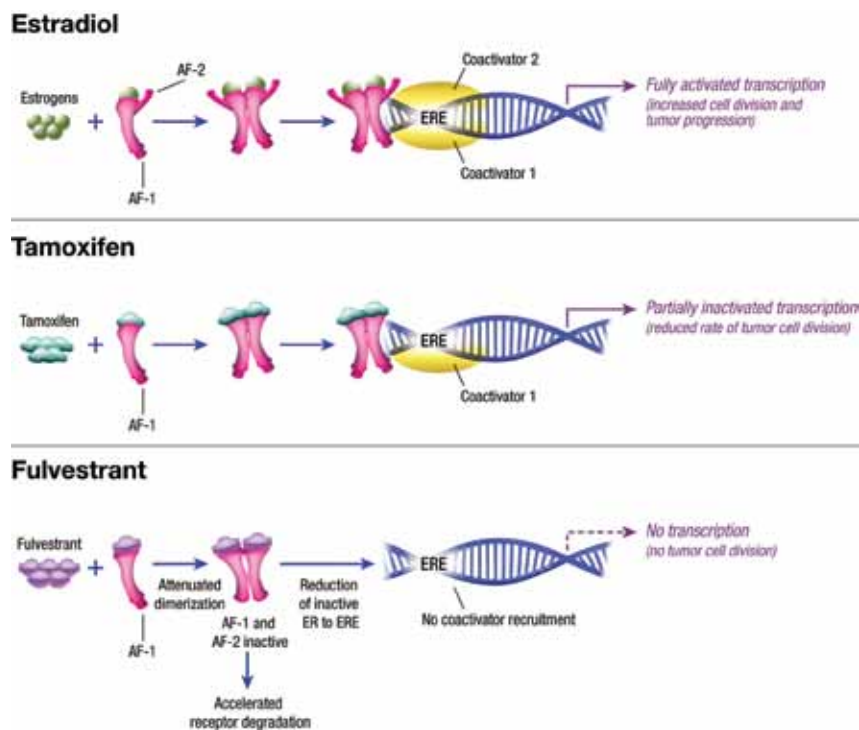


FIGURE 3 Comparison of the actions of estrogen, tamoxifen, and fulvestrant. AF-1 = activating function 1 domain; AF-2 = activating function 2 domain; ERE = estrogen response element; ER = estrogen receptor. Reprinted by permission from Wolters Kluwer Health: Howell A. Is fulvestrant ("Faslodex") just another selective estrogen receptor modulator? *Int J Gynecol Cancer* 2006;16(suppl 2):521-523, Copyright 2006.

the action of both the AF-1 and AF-2 domains, estrogen-mediated transcriptional activation is fully inhibited, resulting in no agonistic effects.^{22,42} The lack of agonist effects of fulvestrant on the uterus was demonstrated in a preclinical study in rats.³⁸ Unlike tamoxifen, fulvestrant had no effects on uterine proliferation when compared with estradiol treatment, which stimulated uterine proliferation and increased uterine weight.

Fulvestrant treatment also impairs shuttling of ER between the nucleus and the cytoplasm, essentially trapping ER in the cytoplasm.⁴³ Fulvestrant treatment results in an increased ER turnover and decreased ER half-life, which lead to a reduction in ER levels.^{40,42,44,45} Fulvestrant binding induces rapid degradation of ER via the ubiquitin-proteasome pathway.⁴⁶⁻⁴⁸

In a neoadjuvant clinical study, fulvestrant treatment significantly reduced ER and progesterone recep-

tor (PgR) levels in a dose-dependent manner, as measured in tissue samples taken before and during surgery (Figure 4).⁴⁵ Notably, tissue samples taken from patients treated with tamoxifen showed a reduction in ER levels but an increase in PgR levels. The increase in PgR levels associated with tamoxifen is likely due to its partial agonist activity, as PgR expression is controlled by ER signaling and indicates at least some ER activity.⁴⁵

The phase II NEWEST trial compared high-dose fulvestrant (500 mg/month plus 500 mg on day 14 of month 1) with low-dose fulvestrant (250 mg/month) in the neoadjuvant setting for postmenopausal women with newly diagnosed, ER-positive, local ABC. Data showed that the high-dose fulvestrant regimen resulted in greater reductions in the Ki67 labeling index and superior downregulation of both ER and PgR expression.^{49,50}

Although fulvestrant induces rap-

id ER degradation, production of new ERs is not affected. Therefore, the tumor remains ER positive, and the patient remains eligible for subsequent hormonal therapy, if appropriate. Retrospective analyses of data from phase II/III trials of fulvestrant support the fact that patients may retain sensitivity to other hormonal agents after treatment with fulvestrant.^{51,52} In one study, of the 54 patients who derived clinical benefit from fulvestrant in a second-line setting and went on to receive subsequent hormonal therapy, 25 had a clinical benefit (4, partial responses; 21, stable disease).⁵¹ In another study, of 28 patients achieving an initial clinical benefit on fulvestrant, subsequent endocrine therapy resulted in 2 partial responders, 11 patients with stable disease, and 15 patients with progressive disease at 6 months.⁵²

The MOAs of fulvestrant and tamoxifen are similar; however, a number of distinct actions of each agent support their sequential use. In addition, preclinical and clinical evidence has shown that fulvestrant prevents tumor growth and improves clinical outcomes in tamoxifen-resistant tumors, further supporting the fact that fulvestrant is not cross-resistant with tamoxifen.^{11,53}

Two relatively recent studies have also examined the optimal dosage of fulvestrant in postmenopausal patients with HR+ ABC; they have shed light on another important aspect of the use of endocrine therapy, one related to pharmacokinetics and dose-related effects.^{12,13} The FIRST trial compared anastrozole (1 mg/day) with fulvestrant (500 mg/month). Investigators demonstrated that fulvestrant was at least as effective as anastrozole in terms of clinical benefit rate and had a longer median time to disease progression.¹³

The CONFIRM trial was a large phase III study that compared 500 mg and 250 mg of fulvestrant in patients with HR+ ABC that had progressed or relapsed following previous

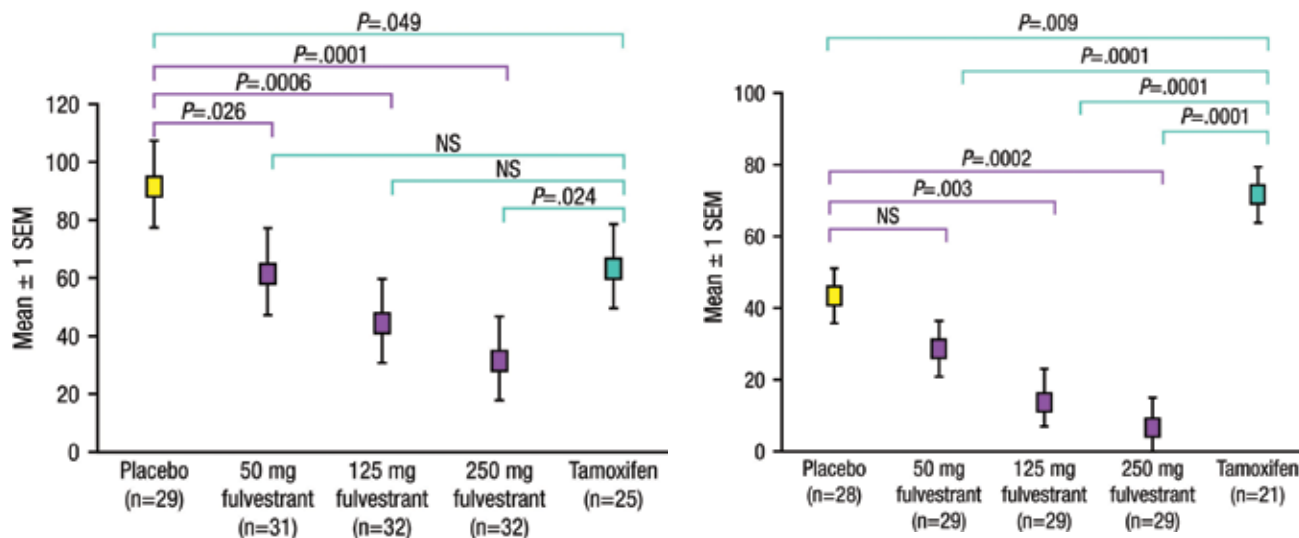


FIGURE 4 Effects of fulvestrant and tamoxifen on estrogen receptor (*left*) and progesterone receptor (*right*) expression. SEM = standard error of the mean; NS = not significant. Cancer research by Robertson JF, et al. Copyright 2001 by American Association for Cancer Research. Reproduced with permission of American Association for Cancer Research in the format Journal via Copyright Clearance Center.

hormonal therapy.¹² Compared with 250 mg, the 500-mg dose significantly improved progression-free survival (PFS; 5.5 months vs 6.5 months, respectively; hazard ratio, 0.80 [95% confidence interval: 0.68, 0.94]; $P = .006$). As a result of these studies, both the US Food and Drug Administration and the European Union have recently granted approval of fulvestrant at the 500-mg/month dose for the treatment of postmenopausal women with HR+ MBC whose disease has recurred or progressed after antiestrogen treatment.

Considerations for endocrine sequencing

Despite the success of these agents in the treatment of breast cancer, up to 40% of women with early breast cancer and most patients with MBC experience disease progression.⁵⁴ However, preclinical and clinical data suggest that after the development of resistance to one type of endocrine therapy, ER signaling still plays an important role.⁵⁵ Approximately 40%–50% of patients who initially respond to endocrine therapy are likely to respond to subsequent endocrine therapies.⁵⁶ Therefore, many of these

patients may benefit from sequential use of endocrine therapy at the time of disease progression.^{56,57}

Although a substantial amount of preclinical and clinical data support the use of sequential endocrine therapy in patients with disease progression after initial endocrine therapy, the optimal sequence is only beginning to be determined.⁵⁸ For example, the phase III EFECT study showed that exemestane and fulvestrant were similar in terms of time to disease progression, overall response rate, and clinical benefit rate in postmenopausal women with hormone-positive ABC who received prior treatment for breast cancer with a nonsteroidal AI.⁵⁹

In addition, current guidelines do not specify which MBC treatment would be optimal after resistance develops to initial endocrine therapy. The National Comprehensive Cancer Network clinical practice guidelines for invasive breast cancer recommend AIs (tamoxifen or toremifene), fulvestrant, megestrol, fluoxymesterone, and estradiol as options for second-line therapy.⁵⁷ Thus, clinicians must decide which sequence of therapies to use for individual patients based on multiple patient-specific factors, such

as tumor characteristics (eg, human epidermal growth factor receptor 2 [HER2] status), burden of disease (eg, sites of metastases, symptoms), convenience of administration, and history with prior endocrine agent(s) with respect to MOA, duration of response, and time to disease progression.⁵⁶ In addition—and apart from clinical efficacy—tolerability, safety, and quality of life are also important factors to consider when sequencing the various endocrine therapies. When selecting a second-line endocrine therapy for patients with HR+ MBC, it is important to consider both how the MOAs of available endocrine therapies differ as well as the potential mechanisms of resistance to endocrine therapy.

Acquired resistance to endocrine therapy

Although the exact mechanisms of acquired resistance to endocrine therapy are unknown, they are likely linked to the MOA of the endocrine agent. A significant amount of laboratory research has identified numerous potential molecular mechanisms of acquired resistance, which fall under several major categories: (1) estrogen hypersensitivity; (2) ER status modifications (eg, ER loss, mutation,

TABLE 1

Molecular mechanisms of resistance to endocrine therapies in breast cancer

Mechanism of resistance	Aromatase inhibitors	SERMs	SERDs
Estrogen hypersensitivity	✓	✓	
Loss of estrogen receptor α	✓	✓	✓
Mutated estrogen receptor α		✓	
Estrogen receptor β expression		✓	
Lack of progesterone receptor		✓	
Drug metabolism		✓	
Coactivator/corepressor expression		✓	
Increased growth factor signaling	✓	✓	✓
Increased estrogen receptor sensitivity	✓		

SERMs = selective estrogen receptor modulators; SERDs = selective estrogen receptor downregulators.

Source: Zilli et al¹⁹; Hurvitz and Pietras⁵⁸; Dowsett et al⁶⁹ Reprinted from Zilli M, Grassadonia A, Tinari N, et al. Molecular mechanisms of endocrine resistance and their implication in the therapy of breast cancer. *Biochim Biophys Acta* 2009;1795:62–81, Copyright 2009, with permission from Elsevier.

or change in gene expression); (3) changes in the intracellular molecular environment (eg, loss of PgR, changes in expression of cofactors); and (4) increased growth factor signaling and crosstalk between the ER and growth factor signaling pathways.¹⁹ Some of these mechanisms contribute to resistance to all endocrine agents, whereas other mechanisms are specific to a particular agent (Table 1).¹⁹

Estrogen hypersensitivity, the ability of cells to grow in the presence of low levels of estrogen, is a major mechanism by which breast cancer cells become resistant to endocrine therapy in the presence of long-term estrogen deprivation (LTED).^{19,60} In preclinical models of estrogen hypersensitivity, breast cancer cells function and retain ER signaling in the presence of estrogen concentrations up to 10,000 times lower than normal by upregulating ER expression and expression of other estradiol-stimulated genes.⁶¹ This hypersensitivity is thought to explain why some patients develop resistance to tamoxifen or AIs after long-term treatment.^{60,61} Notably, a preclinical study showed that treatment with fulvestrant, but not tamoxifen, inhibited the growth of breast cancer cells resistant to LTED.⁶²

Several studies also suggest that

low-dose estrogen (LDE) can be used to overcome estrogen resistance.^{58,63} Preclinical investigation suggests that LDE treatment may revert resistant tumors back to a sensitive state.⁵⁸ Experiments with tamoxifen-resistant breast cancer cell lines showed that treatment with LDE enabled cells to regain susceptibility to tamoxifen as well as AIs and fulvestrant.⁶³

The second mechanism of endocrine resistance is alteration in ER expression (eg, increased/decreased expression of ER α or ER β , or ER mutations).¹⁹ Abnormal DNA methylation or increased histone deacetylation has been associated with ER-negative status in breast cancer; as a result, agents that inhibit DNA methylation and histone deacetylation are being explored. Mutations in ER-producing nonfunctioning receptors have been found in patients with tamoxifen-resistant breast cancer, but they are not common.^{19,54} In contrast, loss of ER expression is a key mechanism thought to play a role in the development of acquired resistance to fulvestrant in HER2-positive tumors.¹⁹

Results from laboratory experiments and retrospective clinical studies suggest that increased growth factor signaling and modifications in the expression of coregulatory molecules

(coactivators and corepressors) may contribute to the development of resistance to endocrine therapies.^{19,54} For example, the overexpression of the coactivator amplified in breast cancer, AIB1, has been associated with a poorer prognosis in patients treated with tamoxifen for HER2-positive or HER3-positive breast cancer.^{64–66} Also, endocrine resistance has been reported in vitro when cells express low levels of ER corepressors such as the nuclear receptor corepressor 1 (NCOR1), which can bind to ERs and inhibit partial agonist activity of tamoxifen.¹⁹ As a result, low NCOR1 mRNA expression correlates with shorter relapse-free survival and may be an independent predictor of tamoxifen resistance.^{67,68}

ER signaling participates in an autocrine signaling loop with epidermal growth factor receptor (EGFR) and HER2 to regulate cellular proliferation.¹⁹ Suppression of ER by endocrine therapies increases the expression of EGFR and HER2, activating downstream MAPK/AKT signaling cascades, which result in proliferative effects that counter the antitumor effects of endocrine therapy. Thus, increased signaling by HER2-regulated pathways is an important contributor to intrinsic and acquired endocrine resistance in breast cancer.^{69,70}

Also, in the absence of estrogen, the AF-1 domain of ERs can be activated by the MAPK, PI3K, or other signaling pathways that are triggered by crosstalk with activated EGFR and insulin-like growth factor receptor 1.^{19,70} Growth factor receptor crosstalk is thought to be important in the development of resistance to tamoxifen in ER-positive tumors because this agent does not inhibit AF-1 transcriptional activation.¹⁹

Future directions

Developing endocrine-based combination therapies

The low toxicity and differing MOAs of endocrine therapies pro-

vide a rationale to develop combination endocrine therapies. However, this approach has had mixed success in both preclinical and clinical studies. In a mouse breast cancer model, the combination of letrozole with tamoxifen did not produce a better antitumor response than either agent alone.⁷¹⁻⁷³ In contrast, in the same tumor model, the combination of exemestane and tamoxifen was more effective in reducing tumor growth compared with either agent alone.⁷⁴ Although some investigators have reported an additive effect in vivo when an AI or tamoxifen was combined with fulvestrant,^{75,76} others have found that these combinations were no more effective than the AI alone.^{71,72} It should be noted that the combination arm in the phase III ATAC study was quickly discontinued because of lack of efficacy at 33 months of follow-up.⁷⁷ Thus, despite a strong rationale for using an AI in combination with tamoxifen, the data are largely conflicting and likely require further study.

Some of these endocrine combination therapies are being tested in clinical trials. The FACT phase III randomized study showed no improvement in clinical benefit with the addition of a fulvestrant loading dose (LD; administered at 500 mg on day 0, 250 mg on day 14, 250 mg on day 28, and then 250 mg monthly) to anastrozole compared with anastrozole alone at first relapse in postmenopausal women with HR+ ABC.⁷⁸ Results from two additional phase III studies are pending. The first, SWOG-S0226,⁷⁹ is comparing anastrozole with anastrozole plus a fulvestrant LD as first-line therapy in postmenopausal women with MBC, and the second, SOFEA,⁸⁰ is comparing a fulvestrant LD with or without anastrozole versus single-agent exemestane in postmenopausal women with ABC or MBC following disease progression on nonsteroidal AIs.

Preclinical studies also provide a

rationale for combining endocrine therapy with signal transduction inhibitors such as the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib (Tykerb), the anti-HER2 monoclonal antibody trastuzumab (Herceptin), the anti-vascular endothelial growth factor monoclonal antibody bevacizumab (Avastin), and the mammalian target of rapamycin inhibitor temsirolimus (Torisel).⁸¹ Certain interesting combinations are currently in phase III studies, and so far, they have shown excellent efficacy at the cost of higher toxicities. Results from the recently completed TAnDEM study showed improved PFS with anastrozole plus trastuzumab compared with anastrozole alone in postmenopausal women with HER2+ and HR+ MBC; however, the number of adverse events and serious adverse events was considerably higher in the combination arm.⁸²

In another phase III randomized study, the addition of lapatinib to letrozole significantly improved PFS and clinical benefit compared with letrozole alone as first-line therapy for women with HR+ MBC.⁸³ Grade 3 or 4 adverse events were more common in the letrozole plus lapatinib arms than in the letrozole monotherapy arm. An ongoing four-arm phase III study is comparing fulvestrant versus fulvestrant plus an AI (exemestane, anastrozole, or letrozole), versus fulvestrant plus lapatinib, versus fulvestrant plus an AI plus lapatinib in postmenopausal women with MBC after disease progression with a previous AI.⁸⁴

Identifying the molecular drivers of breast cancer

In addition to clinical investigations to improve combination therapy, preclinical research is also needed to further understand the molecular drivers of breast cancer growth and metastasis. Although progress has been made, much remains to be learned to clarify the networked re-

dundancy of resistance pathways that breast tumors enlist to counter endocrine therapies.

In addition to the molecular complexity of endocrine intracellular signaling and crosstalk with growth factor receptor pathways, treatment of patients must contend with the influence of heterogeneity within individual tumors and among the primary tumor, locally recurrent tumors, and metastatic sites. Results from numerous studies indicate that therapeutic targets in breast cancer (ie, ER, PgR, HER2) identified in primary tumors and some metastatic sites are not necessarily homogeneously expressed.⁸⁵⁻⁸⁹ One study reported discordance rates between primary and recurrent breast cancer of 18% for ER, 40% for PgR, and 14% for HER2.⁸⁷ Another study reported discordance rates of 18% for ER, 42% for PgR, and 7% for HER2 between primary and metastatic sites and of 13% for ER, 33% for PgR, and 2% for HER2 between primary and locally recurrent lesions.⁸⁶ These data emphasize the need to evaluate ER, PgR, and HER2 status at local sites of recurrence as well as distant metastases to improve treatment planning.

To further complicate matters, with the development of microarray technology, some degree of intratumor heterogeneity in ER and PgR expression has been found in biopsy samples from breast cancer patients.^{90,91} Initial evidence suggests that this heterogeneity may have a significant impact on clinical outcomes.⁹⁰

Conclusions

Although there has been substantial success in using endocrine therapy for HR+ breast cancer over the past 2 decades, a large percentage of patients eventually develop resistance and experience disease progression. Resistance, whether intrinsic or acquired, often involves crosstalk between estrogen and growth factor receptors or is related to the effects of LTED.

These effects may ultimately lead to a hypersensitive effect of estrogen- or ligand-independent activation of estrogen signaling.

Because the mechanisms of resistance to endocrine therapy are thought to be related to the MOA of each agent, it is important to understand the distinct mechanistic properties of AIs, tamoxifen, and fulvestrant. Compared with the AIs, which inhibit the production of estrogen, tamoxifen and fulvestrant work by binding to and inhibiting ER signaling. However, despite some similarities in the MOAs of tamoxifen and fulvestrant, a number of key mechanistic differences exist between these agents with respect to effects on AF domains, ER homodimerization, ER degradation, and inhibition of nuclear translocation. The prediction and management of resistance to therapy are under investigation, and it is hoped that an enhanced understanding of the MOAs of antitumor agents, as well as the estrogen signaling process, will enable the further delay of breast cancer disease progression using the most effective sequence of endocrine therapies for each patient.

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Vandetanib in advanced hereditary medullary thyroid cancer

A novel treatment targets the activating mutations in the RET proto-oncogene responsible for this rare hereditary cancer of the thyroid.

Medullary thyroid cancer (MTC), the third most common type of thyroid cancer, presents in a sporadic form in about 75% of cases and in a hereditary form in about 25%. Ten-year survival in MTC that has been treated early is between 70% and 80% but is less than 50% in patients with distant metastatic disease. Currently, there is no effective therapy for patients with distant metastases of MTC.

Germline mutations in the *RET* proto-oncogene cause hereditary MTC, and somatic *RET* mutations are present in up to 50% of sporadic MTC cases. Thyroid tumors are vascular, and increased expression of vascular endothelial growth factor (VEGF) is associated with increased tumor growth and invasiveness.

Vandetanib (Caprelsa) is a once-daily oral agent that targets RET-dependent, VEGF receptor-dependent, and epidermal growth factor receptor-dependent signaling. In a recent open-label, single-arm, phase II study, vandetanib produced durable objective responses and disease control in patients with unresectable locally advanced or metastatic hereditary MTC.¹

Objective responses and disease control

This study consisted of 30 patients (21 women), with a median age of 49 years and a mean time since MTC diagnosis of 16 years. They received vandetanib (300 mg/day) until disease progression, unacceptable toxicity, or withdrawal of consent.

What's new, what's important

Vandetanib (Caprelsa), an oral kinase inhibitor, was approved in April 2011 by the US Food and Drug Administration for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

The recommended dose of vandetanib is 300 mg/day PO; in patients with renal impairment, it should be reduced to 200 mg/day. Treatment should be continued until disease progression or intolerable side effects occur.

Vandetanib can prolong the QT interval, and cases of torsades de pointes and sudden death were reported in clinical trials. Because of this risk, vandetanib is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

Because of the risk of QT prolongation, electrocardiograms and serum levels of potassium, calcium, magnesium, and thyroid stimulating hormone should be monitored at baseline, 2–4 weeks, and 8–12 weeks after starting treatment and every 3 months thereafter or following dose adjustments. The most common (> 20%) adverse drug reactions observed with vandetanib are diarrhea (57%), rash (53%), acne (35%), nausea (33%), hypertension (33%), headache (26%), fatigue (24%), decreased appetite (21%), and abdominal pain (21%). The most common (> 20%) laboratory abnormalities are decreases in serum calcium (57%) and glucose (24%) levels and increases in alanine aminotransferase levels (51%).

Vandetanib is a promising drug for patients with inoperable advanced or metastatic medullary thyroid cancer.

— Jame Abraham, MD, *Editor*

Twenty-nine patients had distant metastases, including metastasis to the liver (80%), lymph nodes (70%), and lungs (63%). Patients had a mean of 3.6 disease sites. All of the patients had undergone previous surgery, 37% had received radiation therapy, 20% had had chemotherapy, and 10% had received biologic therapy.

A total of 29 patients were assessable for investigator-judged response, with all 30 being included in the intent-to-treat analysis of efficacy and the safety analysis. At the time of data cutoff, after a median duration of vandetanib treatment of 18.8 months, 17 patients were still receiving vandetanib therapy, including 4 patients who had progressive disease by Response Evaluation Criteria in

Solid Tumors (RECIST) but who were judged by their physician to be receiving clinical benefit from treatment. Among the remaining patients, seven discontinued treatment because of adverse events, four discontinued treatment because of disease progression, and two withdrew consent.

On investigator assessment, a confirmed partial response (PR) was achieved in six patients (30%), with a median duration of response at data cutoff of 10.2 months (range, 1.9–16.9 months); three patients subsequently developed progressive disease, at 10.6, 27.3, and 27.9 months. Stable disease for ≥ 24 weeks was observed in 16 patients (53%), yielding a disease

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control (objective response plus stable disease) rate of 73%. Six patients had stable disease for ≥ 8 weeks but < 24 weeks, and one patient had progressive disease as best response. Overall, 25 patients (83%) had some reduction in tumor size during vandetanib treatment. In addition to the six patients with a confirmed PR, five had an unconfirmed PR; one had a single RECIST assessment indicating a PR but was found to have progressive disease at next assessment, and the PRs in the other four patients occurred at the final assessment before data cutoff. There was no apparent relationship between specific germline *RET* mutations and response to vandetanib treatment.

At the time of data cutoff, estimated median progression-free survival (PFS) was 27.9 months; 8 patients (27%) had disease progression, 20 patients (67%) had stable disease and were alive at the time of analysis, and 2 patients had died at > 3 months after the final RECIST assessment (one of cardiac failure and one of colon cancer). On independent central review, 5 patients had a confirmed PR, 22 had stable disease, 1 patient had progressive disease, and 2 patients were not evaluable; the estimated median PFS was 34.7 months.

Primarily low-grade adverse events

Toxicity of vandetanib treatment was manageable in this phase II study.

TABLE 1

Adverse events occurring in 10 or more patients, regardless of cause

Event	Total (%)	Grade 1 or 2 (%)	Grade 3 (%)
Diarrhea	70	60	10
Rash	67	63	3
Fatigue	63	57	7
Nausea	63	53	10
Headache	47	43	3
Anorexia	43	40	3
Vomiting	40	33	7
Constipation	37	33	3
Dysgeusia	33	33	na
Hypertension	33	23	10

na = Not applicable (no grade 3 dysgeusia in National Cancer Institute Common Terminology Criteria for Adverse Events, version 3)

Source: Wells et al¹

Adverse events were mostly grade 1 or 2, with the most frequent being diarrhea, rash, fatigue, and nausea (Table 1). The most common grade 3 adverse event was QTc prolongation (seven patients); next were diarrhea, nausea, and hypertension (three patients each). Two grade 4 adverse events were reported, consisting of azotemia and muscle weakness; neither one was considered to be related to vandetanib. Other notable adverse events included mild visual disturbances (grade 1) in 3 patients owing to vandetanib-related corneal changes, which were managed with a dose adjustment in vandetanib; hypophosphatemia in 3 patients (grade 2 in 2, grade 1 in 1); and increases in blood pressure > 30 mm Hg systolic in 23 patients, which did not lead to

permanent discontinuation of treatment in any of the patients.

Of the seven patients (23%) discontinuing vandetanib treatment because of adverse events, five patients had adverse events considered possibly related to vandetanib treatment, including hemorrhagic diarrhea, nausea, increased blood creatinine and blood urea nitrogen levels, acne, and asymptomatic QTc prolongation. Vandetanib dosing was reduced or interrupted in 24 patients (both in 21), with diarrhea being the most common reason (7 patients).

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Promising data, but challenges remain in selecting appropriate TKIs

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Medullary thyroid cancer (MTC) is a rare but aggressive disease. Unfortunately, there is not an effective conventional chemotherapy regimen for the disease. New strategies to treat metastatic MTC, including radioimmunotherapy and vaccine-based therapies, have been tested, with no major achievement.¹ Therefore, targeted therapy may offer a novel therapeutic approach for advanced MTC based on the role of mutations in the *RET* proto-oncogene and vascular endothelial growth factor receptor (VEGFR) activity in the pathogenesis of hereditary and sporadic MTC.² VEGFR and RET may be common targets among multitargeted tyrosine kinase inhibitors (TKIs), such as sunitinib (Sutent), sorafenib (Nexavar), cabozantinib, motesanib, and vandetanib (Caprelsa).

Early responses with multitargeted TKIs

Sunitinib targets VEGFR 1-2, platelet-derived growth factor receptor (PDGFR), c-KIT, FLT3, and RET. It was tested in 7 patients with metastatic MTC and 28 patients with radioiodine-refractory well-differentiated thyroid carcinoma in a phase II study. Of the 33 evaluable patients, 1 patient with MTC (3%) achieved a complete response, 10 patients (28%) achieved a partial response, and 16 patients (46%) had stable disease, suggesting sunitinib may have activity in MTC.³

Sunitinib was also studied in 25 patients with rapidly progressing MTC in another phase II trial. Partial response was achieved in 8 of 24 patients (33%), with a median duration of response of 37 weeks, and 54% of patients had SD, with a median duration of 32 weeks. As of May 2010, progression-free survival (PFS) was 49 weeks. Interestingly, patients with and without *RET* mutations showed a clinical benefit. Patients with the M918T *RET* mutation have a worse prognosis, and it may be associated with a durable response.⁴

Sorafenib showed clinical activity in patients with metastatic and radioiodine nonresponsive papillary thyroid carcinomas.⁵ Sorafenib inhibits the RAF, VEGFR 2-3, PDGFR β , FLT3, c-KIT, and RET kinases. It also inhibits the growth of *RET* mutation-positive and wild-type MTC in vitro and in vivo. Therefore, sorafenib was evaluated in a phase II clinical trial to investigate its activity in patients with advanced MTC. Although only one partial response was observed in patients with sporadic MTC, 50% of patients showed stable disease of ≥ 15 months, with tumor shrinkage ranging from 8%–27%. Sorafenib was reasonably well tolerated in this study. The median duration of treatment and PFS were 15 and 17.9 months, respectively. The median overall survival was not reached at the time of data analysis.⁶

Motesanib is a novel inhibitor of VEGFR 1-2-3, PDGFR, and c-KIT. It has activity in wild-type but not

mutant RET. Motesanib was studied in 91 patients with locally advanced or metastatic MTC in a phase II trial. Only two patients (2%) had an objective response, 81% of patients achieved or maintained stable disease, and 76% experienced a decrease from baseline in tumor measurement. In patients who had tumor marker analysis, 83% and 75% had a decrease in circulating concentrations of calcitonin and carcinoembryonic antigen (CEA), respectively. PFS was also 48 weeks. These data were encouraging and suggested the role of VEGF/RET-targeted therapies for MTC, as suggested in other studies.⁷

Cabozantinib (XL184) is an oral inhibitor of MET, VEGFR2, and RET. It was studied in a phase I trial in patients with different malignancies (37 had MTC). A partial response was observed in 10 patients (29%), and 25 patients (68%) had either a partial response or prolonged stable disease ≥ 6 months. Responses have been observed in patients with MTC with and without RET mutations. This study showed promising results to conduct an ongoing randomized phase III study of cabozantinib in MTC.⁸

Clinical trials of vandetanib

Wells et al presented the results of a double-blind randomized phase III trial of vandetanib in locally advanced or metastatic MTC (the ZETA trial). Vandetanib targets the RET, VEGFR, and epidermal growth factor re-

How I treat medullary thyroid cancer

Medullary thyroid carcinoma (MTC) develops from the neuroendocrine parafollicular C cells of the thyroid. These cells secrete neuroendocrine peptides, including calcitonin and carcinoembryonic antigen (CEA). The hereditary form presents as inherited tumor syndromes; they include multiple endocrine neoplasia type 2A (MEN 2A), which is the most common type; MEN 2B; and familial MTC. Typically, patients develop sporadic disease in their 50s or 60s, and those with familial forms of the disease tend to be younger.

Total thyroidectomy with or without central neck dissection is the primary treatment of locoregional disease. Ipsilateral or bilateral modified neck dissection is recommended if ipsilateral or contralateral cervical lymph nodes are clinically or radiologically evident. Adjuvant external-beam radiotherapy (EBRT) may be considered in selected cases, such as for patients with extrathyroidal disease or extensive nodal metastases.

Postoperative surveillance of patients with MTC consists of measurement of calcitonin levels, which should be checked preoperatively as a baseline as well. Following thyroidectomy, the calcitonin level reaches a new steady state in about 72 hours. In patients with undetectable calcitonin levels and a normalized CEA level, annual measurement of both markers should still be checked and annual cervical ultrasonography should be considered.

MTC most commonly metastasizes to the liver, bones, and lungs. Palliative resection, EBRT, radiofrequency ablation, or chemoembolization should be considered for patients with locoregional symptoms and distant metastasis to maintain locoregional disease control. Radioiodine treatment and conventional cytotoxic chemotherapy, such as doxorubicin- and dacarbazine-based chemotherapies, are not effective in these patients. Clinical trial enrollment and novel small molecule tyrosine kinase inhibitors targeting the RET and vascular endothelial growth factor receptor should be considered as alternative therapies.

— Hamid Mirshahidi, MD

ceptor signaling pathways. The researchers randomized 331 patients with 90% sporadic MTC 2:1 to receive vandetanib or placebo. Patients in the placebo arm crossed over after disease progression and also received vandetanib.

Statistically significant prolongation of PFS (the primary objective) was observed for vandetanib compared with placebo (hazard ratio, 0.45; $P < 0.0001$), as well as improvement in objective response rate, disease control rate, time to worsening of pain, and biochemical response.⁹ This study was the first phase III trial that showed efficacy of a new multitargeted TKI with extension of PFS and improved quality of life in MTC. Subsequent data showed a median PFS of 16.4 months in the placebo arm and at least 22.6 months in the vandetanib arm; however, there was no significant improvement in overall survival. Based on this new information, the US Food and Drug Administration approved van-

detanib as a new treatment for MTC in April 2011.

Conclusion

These are promising data suggesting efficacy of vandetanib, motesanib, cabozantinib, sorafenib, and sunitinib in the treatment of MTC. The RET-inhibitory effect of these multitargeted agents in *RET* mutation-driven MTC and their antiangiogenic effect in wild-type *RET* cases could explain the effectiveness of these agents in these patients. A comparable low partial response rate, but a high rate of stable disease, was observed in all of these phase II studies. However, the same results may not be replicable in phase III studies, as MTC is a clinically heterogeneous disorder. Many challenges remain in selecting appropriate TKIs for MTC.

Correlative studies are required to identify *RET* genotypes and markers in MTC that could predict the patterns of response or resistance to these TKIs. It would be more challenging

to identify these markers and regulatory signaling pathways in wild-type *RET* MTC. The observation made by the authors that patients without identifiable *RET* mutations had responses raises the question of whether VEGFR2 inhibition contributes to the treatment effect. We should also be cautious about selecting targeted agents and stepping forward from a phase I study to a randomized phase III trial without having sufficient knowledge of the biology that directs the disease phenotype.

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Mechanisms of action of commonly used drugs to treat cancer

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Oncologists prescribe a variety of anticancer compounds for the treatment of many different malignancies. These compounds comprise the classic cytotoxic and cytostatic agents, as well as the newer antibodies directed at particular cellular structures or targets, the epigenetic agents, and the agents that interrupt or interfere with intracellular processes. In this article, we review the mechanisms of action of 50 commonly used anticancer compounds. Although these compounds comprise only a portion of the total number of agents that are prescribed for cancer patients, the mechanism of action of each is of interest to understand how they are used in combination.

Traditionally, drug therapy for cancer was limited to cytotoxic compounds that killed a variety of cells, both benign and malignant. More recently, oncologists have witnessed the development of less toxic antitumor monoclonal antibodies and other biologic agents.¹ In addition, as researchers have identified the molecular differences and aberrancies between normal cells and cancer cells, new compounds have been identified to silence or change these intracellular processes, which may no longer function normally. Such agents are better known as “targeted therapies,” even though they may also impact similar intracellular processes in otherwise normal cells.²

The emergence of effective cancer chemotherapy, antitumor antibodies, and targeted agents represents the major advances of clinical investigation over the past 50 years.³ As a result, clinical trials have shown that most neoplasms cannot be cured with single agents and that combinations of antitumor compounds are often the best way to control an underlying malignant process or provide a cure for those with cancer. Children with leukemia and solid tumors, subgroups of patients with Hodgkin and non-Hodgkin lymphomas, women with early stages of breast cancer, and those with gestational choriocarcinoma represent a fraction of the types of malignancies that have responded to combinations of antitumor compounds, leading to either prolonged remissions or actual cures.⁴

As the clinical benefits and adverse effects of anticancer compounds were recognized, rational combinations of these drugs were designed and developed.⁵ This process continues, as newer anticancer agents are identified and tested and enter

into trials in combination with more established agents. The adverse effects of individual agents are taken into consideration as well as their mechanisms of action (MOAs). In this way, agents with a wide variety of MOAs could be combined to target malignant cells at multiple stages of development or growth/proliferation to prevent the emergence of resistant cells.

A number of anticancer compounds are currently used by oncologists. Table 1 lists 50 commonly prescribed anticancer compounds with their MOAs. In all cases, we describe the MOA of each compound as stated in its government-approved prescribing information. However, when significant additional information is available from the medical literature, it is included. In many cases, the prescribing information for a compound may list the MOA as “unknown,” when in fact considerable investigation has described the MOA, even when the prescribing information has not been updated.

Because so many compounds are used off label to treat a range of malignancies,⁶ we will not review how each compound is used, either individually or in combination with other agents. This overview is meant to be a useful resource for those interacting with patients who desire explanations and interpretations of scientific data to understand how par-

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TABLE 1

Anticancer compounds and their mechanisms of action

Type of anticancer compound	Generic name
Alkylating agents	
Nitrogen mustard derivatives	Mechlorethamine Melphalan Ifosfamide Cyclophosphamide
Nitrosoureas	Carmustine (BiCNU)
Heavy metal alkylators	Cisplatin Carboplatin Oxaliplatin
Other	Dacarbazine Temozolomide
Antimetabolites	
Pyrimidine analogs	Gemcitabine 5-Fluorouracil Cytarabine Capecitabine
Purine analogs	Mercaptopurine (6-MP)
Folic acid antagonists	Methotrexate (MTX) Pemetrexed
Mitotic/spindle inhibitors and plant alkaloids	
	Paclitaxel Docetaxel Ixabepilone Vinblastine Vincristine Vinorelbine
Topoisomerase inhibitors	
	Irinotecan (CPT-11) Topotecan Etoposide
Antitumor antibiotics	
	Mitoxantrone Dactinomycin Doxorubicin Epirubicin Bleomycin
Signal transduction inhibitors	
	Cetuximab Trastuzumab Erlotinib Bevacizumab Sorafenib Imatinib Dasatinib Temozolomide
Hormonal agents	
	Tamoxifen
Epigenetic agents	
	Vorinostat Azacitidine
Immunomodulators	
	Interferon alfa-2a and alfa-2b Rituximab
Miscellaneous agents^a	
	Lenalidomide Bexarotene Tretinoin Arsenic trioxide Asparaginase Bortezomib

^a Includes compounds with an unclear mechanism of action and those not fitting into a particular category

ticular anticancer compounds work to prevent further growth of an underlying malignancy.

Alkylating agents

Alkylating agents have been shown to work by a few different mechanisms.⁷ First, these compounds can attach alkyl groups to DNA bases. To replace the alkylated bases, this alteration results in DNA fragmentation by repair enzymes. Alkylated bases prevent DNA synthesis and RNA transcription. Second, alkylating agents can form cross-bridges, bonds between atoms in DNA. Two DNA bases are linked by an alkylating agent, which has two DNA-binding sites. Bridges can be formed within a single molecule of DNA, or a cross-bridge may connect two different DNA molecules. Subsequently, cross-linking prevents DNA from separation for synthesis or transcription. Third, alkylating agents can induce mispairing of the nucleotides leading to mutations. In a normal DNA double helix, adenine (A) bases always pair with thymine (T) bases, and guanine (G) bases always pair with cytosine (C) bases. Alkylated G bases may erroneously pair with T bases. If this altered pairing is not corrected, it may lead to a permanent mutation.

Examples of alkylating agents include nitrogen mustard derivatives, nitrosoureas, and heavy metal alkylators.

Nitrogen mustard derivatives

Mechlorethamine. Mechlorethamine is an example of a nitrogen mustard agent, which forms cyclic ammonium ions (aziridinium rings) by intramolecular displacement of the chloride by the amine nitrogen. The aziridinium group then alkylates basic centers on the DNA, thereby inducing malfunctions during replication. These alkylating agents have more than one alkylating group per molecule, meaning that they are di- or polyalkylating agents.^{8,9}

Melphalan. Otherwise known as L-phenylalanine mustard, or L-PAM, melphalan is a phenylalanine deriva-

tive of mechlorethamine. Its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N₇ position of guanine.¹⁰

Ifosfamide. Another example of a nitrogen mustard derivative is ifosfamide. As mentioned previously, nitrogen mustards cause alkylation of DNA, which causes interference with replication.¹¹

Cyclophosphamide. Cyclophosphamide is first converted by the liver into acrolein and phosphoramidate. These are the two active compounds that interfere with cell growth by interfering with the action of DNA. The phosphoramidate mustard forms both interstrand and intrastrand DNA crosslinks at guanine N₇ positions, which lead to cell death.¹²⁻¹⁴

Nitrosoureas

Carmustine (BiCNU). Carmustine is a nitrosourea, which, like most nitrosoureas, alkylates DNA and RNA, thereby interfering with synthesis of both by causing cross-linking of DNA and RNA strands. Carmustine may also inhibit several key enzymatic processes by carbamylation of amino acids in proteins, such as inhibition of DNA repair and de novo purine synthesis.¹⁵ The antineoplastic activities and toxic activities of carmustine may be due to metabolites as opposed to the parent compound. Nitrosoureas lack cross resistance with other alkylating agents.

Heavy metal alkylators

Cisplatin. The first member of a class of drugs called heavy metal alkylators is cisplatin. These platinum complexes bind to and cause cross-linking of DNA, which eventually triggers cell death.¹⁶ As discussed throughout this section, this cross-linking interferes with cell division. The damaged DNA elicits the initiation of futile cycling of DNA repair mechanisms, which, in turn, activates apoptosis.

Carboplatin. Like cisplatin, carboplatin produces predominantly inter-

strand DNA cross-links rather than DNA-protein cross-links. The effect is cell-cycle nonspecific. Although the cross-linking may occur at a slower pace than with cisplatin, the lesions and biologic effects are equivalent.¹⁷⁻¹⁹

Oxaliplatin. A third platinum-based chemotherapy agent is oxaliplatin. Like cisplatin and carboplatin, it inhibits DNA synthesis through covalent binding of DNA molecules to form intrastrand and interstrand DNA cross-links. Oxaliplatin differs molecularly from the previous two platinum compounds by its bulky DACH (diaminocyclohexane) carrier ligand, which most likely accounts for both its efficacy and lack of cross-resistance with other platinum compounds.²⁰

Other alkylating agents

Dacarbazine. Dacarbazine is an alkylating agent initially developed as an antimetabolite.^{21,22} However, its antitumor activity is not mediated via inhibition of purine biosynthesis. Dacarbazine is a prodrug; its active metabolites are methylate nucleic acids, thus inhibiting DNA, RNA, and protein synthesis. As a result, cell growth and proliferation are halted.

Temozolomide (Temodar). Sometimes referred to as TMZ, temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine. It undergoes rapid chemical conversion in the systemic circulation (at physiological pH) to the active compound, 3-methyl[triazen-1-yl]imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs primarily at the O₆ and N₇ positions of guanine, thereby interfering with DNA replication.²³ Although it accounts for only about 5% of total lesions, the most frequent cytotoxic lesion induced by temozolomide is at the O₆ position of guanine.²⁴

Antimetabolites

For DNA replication to occur, proliferating cells require a pool of nucle-

otides. Anticancer drugs developed to interfere with nucleotide metabolism are called antimetabolites. For example, to inhibit thymidine, compounds can block thymidylate synthase (TS) or dihydrofolate reductase (DHFR), two enzymes involved in the synthesis of thymidine nucleotide. Examples of drugs that inhibit these two enzymes include 5-fluorouracil (5-FU) and analogs of folic acid (methotrexate), respectively.

Pyrimidine analogs

Gemcitabine (Gemzar). Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, the diphosphate analog of gemcitabine binds to the active site of ribonucleotide reductase (RNR), which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. This binding irreversibly inactivates the enzyme. Once RNR is inhibited, the cell cannot produce the deoxyribonucleotides required for DNA replication and repair, and cell apoptosis is induced. Second, the triphosphate analog of gemcitabine replaces one of the building blocks of nucleic acids (eg, cytidine) during DNA replication. This process arrests tumor growth, as new nucleosides cannot be attached to the defective/incorrect nucleoside, resulting in apoptosis.²⁵

5-FU. Like gemcitabine, 5-FU is an antimetabolite and exerts its action when cells are in the S phase. The metabolism of 5-FU blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, resulting in a thymine deficiency; thus, the synthesis of DNA is interfered and the formation of RNA is inhibited, ultimately leading to unbalanced growth and death

of the cell. The effects of DNA and RNA deprivation are most marked on cells that grow more rapidly and take up 5-FU at a more rapid rate.²⁶

Capecitabine (Xeloda). Capecitabine is absorbed from the gastrointestinal tract and through a series of enzymatic conversions, is eventually hydrolyzed to the active drug 5-FU. Capecitabine is a prodrug of 5-FU. Many tissues express thymidine phosphorylase to achieve the final conversion to 5-FU, and some human carcinomas express this enzyme in higher concentrations than do the surrounding normal tissues. Normal cells and tumor cells metabolize 5-FU to FdUMP (fluorodeoxyuridine monophosphate) and FUTP (5-fluorouridine triphosphate), two metabolites that cause cell injury by two different mechanisms. FdUMP and a folate cofactor bind to TS and inhibit the formation of thymidylate from 2-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA. A deficiency can then inhibit cell division and thus slow the growth of tumor tissue. Nuclear transcriptional enzymes may mistakenly incorporate FUTP in place of UTP during the synthesis of RNA, and this metabolic error can interfere with RNA processing and protein synthesis.²⁷

Cytarabine (Ara-C). Cytarabine, another antimetabolite, is cytotoxic to many cell lines in vitro and primarily kills cells undergoing DNA synthesis during S phase, by blocking the progression of cells from the G₁ phase to

the S phase. The MOA is primarily due to the rapid conversion to cytosine arabinoside triphosphate. The mechanism is not completely understood but appears to act through the inhibition of DNA polymerase.^{28,29} Extensive chromosomal damage has been observed in cell cultures exposed to cytarabine.

Purine analog

Mercaptopurine (6-MP). 6-MP ribonucleotide inhibits purine nucleotide synthesis and metabolism. This process alters the synthesis and function of RNA and DNA. Mercaptopurine interferes with nucleotide interconversion and glycoprotein synthesis.³⁰

Folic acid antagonists

Folic acid (also known as vitamin B₉ or folacin) is itself not biologically active, but its biologic importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver. Vitamin B₉ (folic acid and folate inclusive) is essential to numerous bodily functions, ranging from nucleotide biosynthesis to the remethylation of homocysteine. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in biologic reactions involving folate. It is especially important during periods of rapid cell division and growth.³¹

Figure 1 illustrates how folic acid participates in both RNA and DNA synthesis.

Methotrexate (MTX). Methotrexate competitively and irreversibly inhibits DHFR, an enzyme that participates in tetrahydrofolate synthesis. The affinity of methotrexate for DHFR is about 1,000-fold that of folate for DHFR. DHFR catalyzes the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the de novo synthesis of the nucleoside thymidine, required for DNA synthesis. Also, folate is needed for purine base synthesis; thus, by blocking folate, purine synthesis will be inhibited. There-

fore, methotrexate inhibits the synthesis of DNA, RNA, thymidylates, and proteins. Methotrexate acts specifically during DNA and RNA synthesis, and thus it is cytotoxic during the S phase of the cell cycle.³²

Pemetrexed (Alimta). Chemically similar to folic acid, pemetrexed is also a folate antimetabolite. Its mode of action includes inhibiting three enzymes used in purine and pyrimidine synthesis—TS, DHFR, and glycinamide ribonucleotide formyltransferase. Like other agents in this class, pemetrexed prevents the formation of DNA and RNA by inhibiting the formation of precursor purine and pyrimidine nucleotides.³³

Mitotic/spindle inhibitors and plant alkaloids

Mitosis is the process by which a eukaryotic cell divides, thereby separating the chromosomes in its cell nucleus into two identical sets in the nuclei of the two daughter cells. It is made up of a number of phases: prophase, prometaphase, metaphase, anaphase, and telophase. Figure 2 illustrates the cell cycle, along with examples of anticancer compounds that exert their effects throughout different phases.

Paclitaxel. Paclitaxel interferes with the normal function of microtubule breakdown by hyperstabilizing the structure. This process destroys the cell's ability to use its cytoskeleton in a flexible manner. Specifically, paclitaxel binds to the β subunit of tubulin, the "building block" of microtubules, and the binding of paclitaxel locks these building blocks in place. The resulting microtubule/paclitaxel complex does not have the ability to disassemble. This limitation adversely affects cell function, as the shortening and lengthening of microtubules (termed dynamic instability) are necessary for their function as a mechanism to transport other cellular components. Further research has indicated that paclitaxel induces apoptosis in cancer

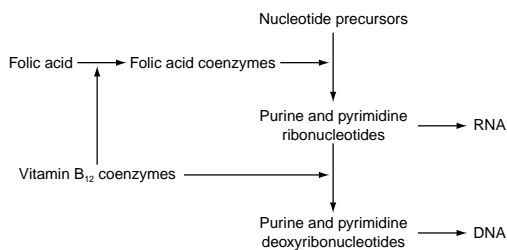


FIGURE 1 Role of folic acid in the synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).

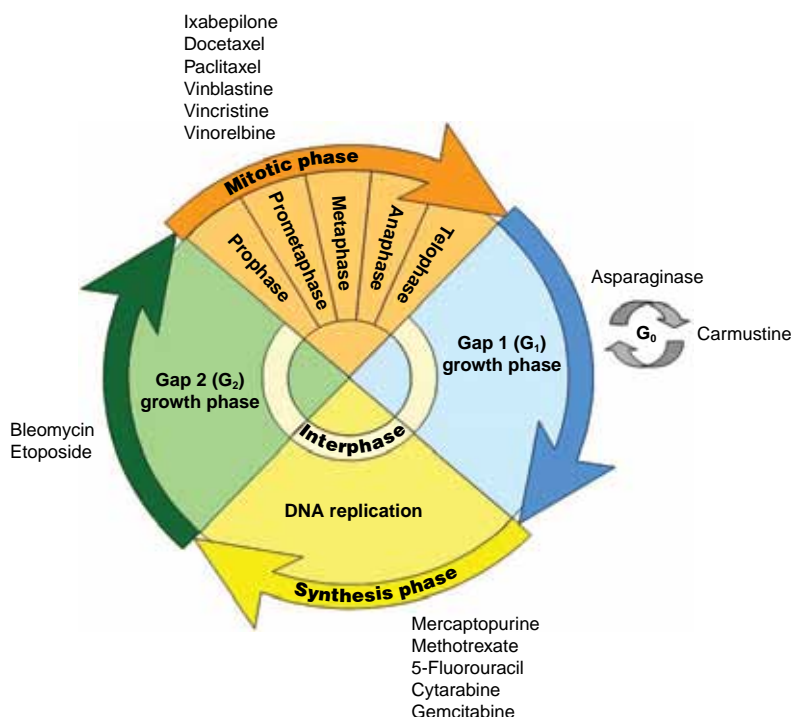


FIGURE 2 Selected anticancer drugs and their roles at different phases of the cell cycle.

cells by binding to a protein that inhibits apoptosis called Bcl-2 (B-cell leukemia 2) and arresting its function. In addition to stabilizing microtubules, paclitaxel may act as a molecular “mop” by sequestering free tubulin, effectively depleting the cells’ supply of tubulin monomers and/or dimers. This activity may trigger the aforementioned apoptosis.³⁴

Paclitaxel, nanoparticle albumin-bound (Abraxane). Protein-bound paclitaxel is an injectable formulation of paclitaxel. Its mechanism of action is attributed to its active agent, paclitaxel, as previously discussed. In this formulation, paclitaxel is bonded to albumin as a delivery vehicle. Nanoparticle albumin-bound paclitaxel has a mean particle size of approximately 130 nm. Paclitaxel exists in the particles in a noncrystalline, amorphous state.³⁵

Docetaxel (Taxotere). This antimicrotubule agent is considered to be more effective than paclitaxel. As with paclitaxel, the cytotoxic activity of docetaxel is accomplished by promot-

ing and stabilizing microtubule assembly while preventing physiologic microtubule depolymerization/dissassembly. This process leads to a decrease in free tubulin, needed for microtubule formation, resulting in inhibition of mitotic cell division between the metaphase and the anaphase. Further cell growth is then halted.³⁶

Ixabepilone (Ixempra). A semisynthetic analog of epothilone B, ixabepilone binds directly to β -tubulin subunits on microtubules, leading to suppression of microtubule dynamics. Ixabepilone suppresses the dynamic instability of $\alpha\beta$ -II and $\alpha\beta$ -III microtubules and possesses low in vitro susceptibility to multiple tumor resistance mechanisms, including efflux transporters such as MRP-1 (multi-drug resistance-associated protein 1) and P-glycoprotein (P-gp). Ixabepilone blocks cells in the mitotic phase of the cell division cycle, leading to cell death.³⁷

Vincristine. Vincristine is a member of the class of neoplastic agents called vinca alkaloids. Vinca alka-

loids are salts of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn; more properly known as *Catharanthus roseus*). Vincristine binds to tubulin dimers, inhibiting assembly of microtubule structures. Tubulin is a structural protein that polymerizes and allows assembly of microtubules.³⁸

Vinblastine. Vinblastine is a second vinca alkaloid and a chemical analog of vincristine. Like vincristine, vinblastine binds tubulin, thereby inhibiting the assembly of microtubules. The cell cytoskeleton and mitotic spindle, among other things, are made of microtubules. The disruption of microtubules arrests mitosis in the metaphase, as microtubules are a component of the mitotic spindle and the kinetochore, which are necessary for the separation of chromosomes during the anaphase of mitosis.³⁹

Vinorelbine. The first 5’NOR semisynthetic vinca alkaloid, vinorelbine is obtained by semisynthesis from alkaloids extracted from the periwinkle plant. Like the other vinca alkaloids, it binds tubulin and inhibits the assembly of microtubules. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at the metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with amino acid, cyclic AMP, and glutathione metabolism; calmodulin-dependent Ca^{++} -transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration, inducing a blockade of cells at the metaphase.⁴⁰

Topoisomerase inhibitors

Topoisomerases are enzymes that unwind the DNA double helix to

facilitate DNA replication and transcription of RNA. Although the double-stranded helix structure of DNA provides stability, the two strands of DNA are intertwined and thus need to be untwisted to access the purine and pyrimidine bases. Topoisomerases bind to either single-stranded or double-stranded DNA and cut the phosphate backbone of the DNA. This intermediate break allows the DNA to be untangled or unwound; at the end of these processes, the DNA is reconnected. Type I topoisomerases cut one strand of a DNA double helix; they can be inhibited by irinotecan (CPT-11) and topotecan (Hycamtin). Type II topoisomerases cut both strands of a DNA double helix; they can be inhibited by etoposide. Inhibition of DNA repair ultimately can lead to cell death and apoptosis.⁴¹

Irinotecan. A derivative of camptothecin, irinotecan exerts its effect by hydrolysis to an active metabolite, SN-38, which is an inhibitor of topoisomerase I. The inhibition of topoisomerase I by the active metabolite SN-38 eventually leads to inhibition of DNA replication and apoptosis.⁴²

Topotecan. Topotecan is a semisynthetic derivative of camptothecin. Like irinotecan, topotecan acts by forming a stable covalent complex with the DNA/topoisomerase I aggregate. Topotecan binds to the topoisomerase I-DNA complex and prevents relegation of single-stranded DNA breaks.⁴³

Etoposide. Commonly known as VP-16, etoposide is a semisynthetic derivative of podophyllotoxin. The exact mechanism of the antineoplastic effect of etoposide is unknown. Etoposide has been shown to be a topoisomerase II inhibitor; this appears to be the primary effect. Etoposide has been shown to cause metaphase arrest. There appears to be a dose-dependent mechanism. With high doses of etoposide, cells entering mitosis are lysed, whereas at lower concentra-

tions of etoposide, cells are inhibited from entering the prophase.^{44,45}

Antitumor antibiotics

There are a number of chemotherapy agents that are considered to be antitumor antibiotics. Generally, these agents prevent cell division via two mechanisms: binding to DNA, making it unable to separate; and inhibiting RNA, preventing enzyme/protein synthesis. However, the precise MOA of many of the antitumor antibiotics is unknown.

Mitoxantrone. Although the exact MOA is unknown, mitoxantrone appears to be most active in the late S phase of cell division. Evidence seems to indicate two effects—binding to DNA by intercalation between base pairs and a nonintercalative electrostatic interaction, resulting in inhibition of DNA and RNA synthesis.⁴⁶

Dactinomycin (Cosmegen). Dactinomycin is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Because the actinomycins are cytotoxic, they have an antineoplastic effect. Like the other antibiotics in this class, dactinomycin is believed to produce its cytotoxic effects by binding DNA and inhibiting RNA synthesis. As a result of impaired mRNA production, protein synthesis also declines after dactinomycin therapy.⁴⁷

Doxorubicin. An anthracycline antibiotic, doxorubicin is closely related to the natural product daunomycin; like all anthracyclines, doxorubicin intercalates between the strands of DNA. This intercalation inhibits the progression of the enzyme topoisomerase II, which unwinds DNA for transcription. By stabilizing the topoisomerase II complex after it has broken the DNA chain for replication, doxorubicin then prevents the DNA double helix from resealing, thereby stopping the process of replication.⁴⁸ The alternate forms of doxorubicin—pegylated liposomal doxorubicin (Doxil) and nonpegylat-

ed liposomal doxorubicin (Myocet)—have a longer half-life and also are less often deposited in cardiac muscle, thereby reducing some of the cumulative long-term cardiac toxicity.

Epirubicin. Another anthracycline antibiotic, epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Epirubicin inhibits separation of double-stranded DNA (via inhibition of the helicase enzyme) and interferes with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. Epirubicin hydrochloride is the 4-epimer of doxorubicin and is a semisynthetic derivative of daunorubicin.⁴⁹ The antiproliferative properties of epirubicin have not been completely elucidated.

Bleomycin. Bleomycin is a mixture of cytotoxic glycopeptide antibiotics isolated from bacteria. Although its exact MOA is unknown, evidence suggests that the main mode of action is the inhibition of DNA synthesis, with some inhibition of RNA and protein synthesis. Bleomycin is known to cause single-stranded, and to a lesser extent double-stranded, breaks in DNA. This DNA and RNA inhibition may occur by inhibiting incorporation of thymidine into DNA strands. It is also believed that bleomycin chelates metal ions such as iron, producing a pseudoenzyme that reacts with oxygen to produce superoxide and hydroxyl free radicals that cleave DNA. In vitro, bleomycin causes cell-cycle arrest in G₂ and in mitosis.⁵⁰

Signal transduction inhibitors

Signal transduction is defined as biochemical communication from one part of the cell to another. It is crucial for normal functioning of the cell and is highly regulated. The process begins with a receptor protein, which is bound in the cell-surface membrane.

The binding of a signaling molecule (eg, growth factor) results in the activation of the receptor. Receptors for most growth factors are enzymes called tyrosine kinases.

Signal transduction can be further described as a cascade of reactions, in which a chemical change in one molecule or protein leads to a change in another molecule or protein. The signaling process involves the transfer of a phosphate group (from ATP) to a series of protein kinases. The signal transduction process continues until an activated molecule or protein enters the nucleus, where it affects genes responsible for functioning of the cell cycle and cell division. The cancer state is typically characterized by a signaling process that is unregulated and in a continuous state of activation. Signal transduction inhibitors block signals passed from one molecule to another inside a cell, thereby inhibiting this continuous state of activation.⁵¹

Growth factors are important for regulating a variety of cellular processes and are capable of stimulating cellular growth, proliferation, and differentiation. They typically induce signaling between cells, which often promotes cell differentiation and maturation. Overexpression of various growth factors and growth factor receptors has been observed in many types of cancer.

Cetuximab (Erbiximab). A recombinant, human/mouse chimeric monoclonal antibody, cetuximab binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). This binding occurs on normal and tumor cells and competitively inhibits the binding of EGF and other ligands. The binding to the receptor blocks phosphorylation and activation of receptor-associated kinases, which results in inhibition of cell growth, induction of apoptosis, and a decrease in vascular endothelial growth factor (VEGF) production. The major effect is on tumor cells that overexpress EGFR.^{52,53}

Trastuzumab (Herceptin). A humanized monoclonal antibody, trastuzumab binds to domain IV of the extracellular segment of the HER2 (human epidermal growth factor receptor 2)/*neu* oncogenic receptor. Cells treated with trastuzumab undergo arrest during the G₁ phase of the cell cycle, resulting in reduced proliferation. It has been suggested that trastuzumab induces some of its effect by downregulation of HER2/*neu*, leading to disruption of receptor dimerization and signaling through the downstream PI3K cascade. The p27Kip1 protein is not phosphorylated and is then able to enter the nucleus and inhibit cyclin-dependent kinase 2 (CDK2) activity, causing cell-cycle arrest. Trastuzumab also suppresses angiogenesis by both induction of antiangiogenic factors and repression of proangiogenic factors.

It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of HER2/*neu*, which results in the release of the extracellular domain. Trastuzumab has been shown to inhibit HER2/*neu* ectodomain cleavage in breast cancer cells. Experiments in laboratory animals indicate that antibodies, including trastuzumab, when bound to a cell, induce immune cells to kill that cell and that such antibody-dependent cell-mediated cytotoxicity is an important mechanism of action.⁵⁴

Erlotinib (Tarceva). Erlotinib has been shown to inhibit EGFR. Inhibition of EGFR also targets the EGFR tyrosine kinase, which is highly expressed and mutated in various forms of cancer. Erlotinib binds in a reversible manner to the ATP-binding site of the receptor. By inhibiting ATP, autophosphorylation is not possible, and the signal to grow is then stopped. As mentioned previously, the EGFR is expressed on the cell surface of normal cells and many cancer cells.⁵⁵

Bevacizumab (Avastin). Bevacizumab binds to VEGF and prevents

the interaction of the VEGF ligand to its receptors (FLT-1 and KDR) on the surfaces of endothelial cells. Normally, the interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. When given to xenotransplant models of colon cancer in athymic nude mice, bevacizumab caused a reduction in microvascular growth and inhibition of metastatic disease progression.⁵⁶⁻⁵⁸

Kinases are the enzymes that transfer phosphate groups from ATP to amino acids (eg, tyrosine) on proteins in a cell.⁵¹ Phosphorylation of proteins by kinases is an important mechanism in communicating signals within a cell (signal transduction cascades) and regulating cellular activity, such as cell division. In essence, kinases can function as the “on/off” switches of many cellular functions. Mutated protein kinases can become overactive and stuck in the “on” position, causing unregulated growth of cells.

Sorafenib (Nexavar). This small molecular inhibitor of several protein kinases targets the Raf/Mek/Erk pathway (MAP kinase pathway). Sorafenib has been shown to inhibit intracellular (CRAF, BRAF, and mutant BRAF) and cell-surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor-beta [PDGFR-β]). As expected, many of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis.⁵⁹

Imatinib (Gleevec). A two-phenylaminopyrimidine derivative tyrosine kinase inhibitor, imatinib primarily affects the tyrosine kinase domain in the *ABL* gene. It is also a potent inhibitor of c-Kit, accounting for its activity in gastrointestinal stromal tumors. In chronic myeloid leukemia (CML), imatinib inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnor-

mality. Imatinib inhibits proliferation and induces apoptosis in Bcr-Abl-positive cell lines as well as fresh leukemic cells from Philadelphia chromosome-positive CML. It occupies the tyrosine kinase active site, leading to a decrease in activity. Imatinib also inhibits the receptor tyrosine kinases for PDGF and stem cell factor, c-Kit, as well as PDGF- and SCF-mediated cellular events.⁶⁰ Figure 3 depicts the primary mechanism of action of imatinib.

Dasatinib (Sprycel). At nanomolar concentrations, dasatinib inhibits a variety of kinases: Bcr-Abl, Src family, c-Kit, EPHA2, and PDGFR- β . In vitro, dasatinib was able to overcome imatinib resistance resulting from Bcr-Abl kinase domain mutations, in CML cell lines and acute lymphoblastic leukemia (ALL) cell lines overexpressing Bcr-Abl. Preclinical data indicate that dasatinib is 325-fold more potent than imatinib against cells expressing wild-type Bcr-Abl and that dasatinib is active against 18 of 19 Bcr-Abl mutations known to cause imatinib resistance.⁶¹⁻⁶³

Temsirolimus (Torisel). An inhibitor of mTOR (mammalian target of rapamycin), temsirolimus is a kinase enzyme inside the cell that collects and interprets the numerous and varied growth and survival signals received by tumor cells. When the kinase activity of mTOR is activated, its downstream effectors—the synthesis of cell-cycle proteins such as

cyclin D and hypoxia-inducible factor 1a (HIF-1a)—are increased. HIF-1a then stimulates VEGF. mTOR is activated in tumor cells by various mechanisms, including growth factor surface receptor tyrosine kinases, oncogenes, and loss of tumor suppressor genes. These activating factors are known to be important for malignant transformation and progression.

Temsirolimus binds to an intracellular protein (FKBP12), and the protein-drug complex inhibits the activity of mTOR. Inhibition of mTOR activity resulted in G₁ growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3K/AKT pathway, was blocked.⁶⁴

Hormonal agents

Hormonal therapy usually involves the manipulation of the endocrine system through exogenous administration of specific hormones or drugs that inhibit the production or activity of such hormones. As hormones are powerful drivers of gene expression in certain cancer cells, changing the level or activity of certain hormones can cause certain cancers to cease growing, or even undergo cell death. Hormonal agents have been used for several types of cancers derived from hormonally responsive tissues, including the breasts, prostate, endometrium, and adrenal cortex.

Perhaps the most familiar example of hormonal therapy in oncology is the use of tamoxifen, a selective estrogen receptor modulator (SERM), for the treatment of breast cancer.⁶⁵

Tamoxifen (Nolvadex). Tamoxifen is a prodrug; its active metabolite competitively binds to estrogen receptors on tumors, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. It is a nonsteroidal agent with potent antiestrogenic properties, which compete with estrogen for binding sites in breast and other tissues. Tamoxifen causes cells to remain in the G₀ and G₁ phases of the cell cycle. In breast tissue, the metabolite 4-hydroxytamoxifen acts as an estrogen receptor antagonist, so that transcription of estrogen-responsive genes is inhibited. Binding to the estrogen receptor in turn interacts with DNA. The estrogen receptor/tamoxifen complex recruits other proteins (known as corepressors) to stop genes from being switched “on” by estrogen. Some of these proteins include the nuclear receptor corepressor (NCoR) and SMRT.

Tamoxifen function can be regulated by a number of different variables, including growth factors. Tamoxifen blocks growth factor proteins such as ErbB2/HER2 because high levels of ErbB2 have been shown to occur in tamoxifen-resistant cancers. Tamoxifen seems to require a protein, PAX2, for its full anticancer effect. In the presence of high PAX2 expression, the tamoxifen/estrogen receptor complex is able to suppress the expression of the pro-proliferative ErbB2 protein.⁶⁶

Epigenetic agents

Figure 4 shows various epigenetic mechanisms of disease. DNA methylation occurs when methyl groups, an epigenetic factor found in some dietary sources, can tag DNA and activate or repress genes. Histones are proteins around which DNA can wind for compaction and gene regulation.

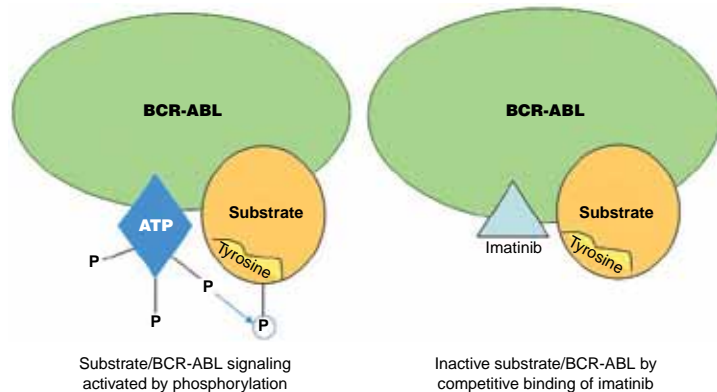


FIGURE 3 Mechanism of action of imatinib in Bcr-Abl-positive cells.

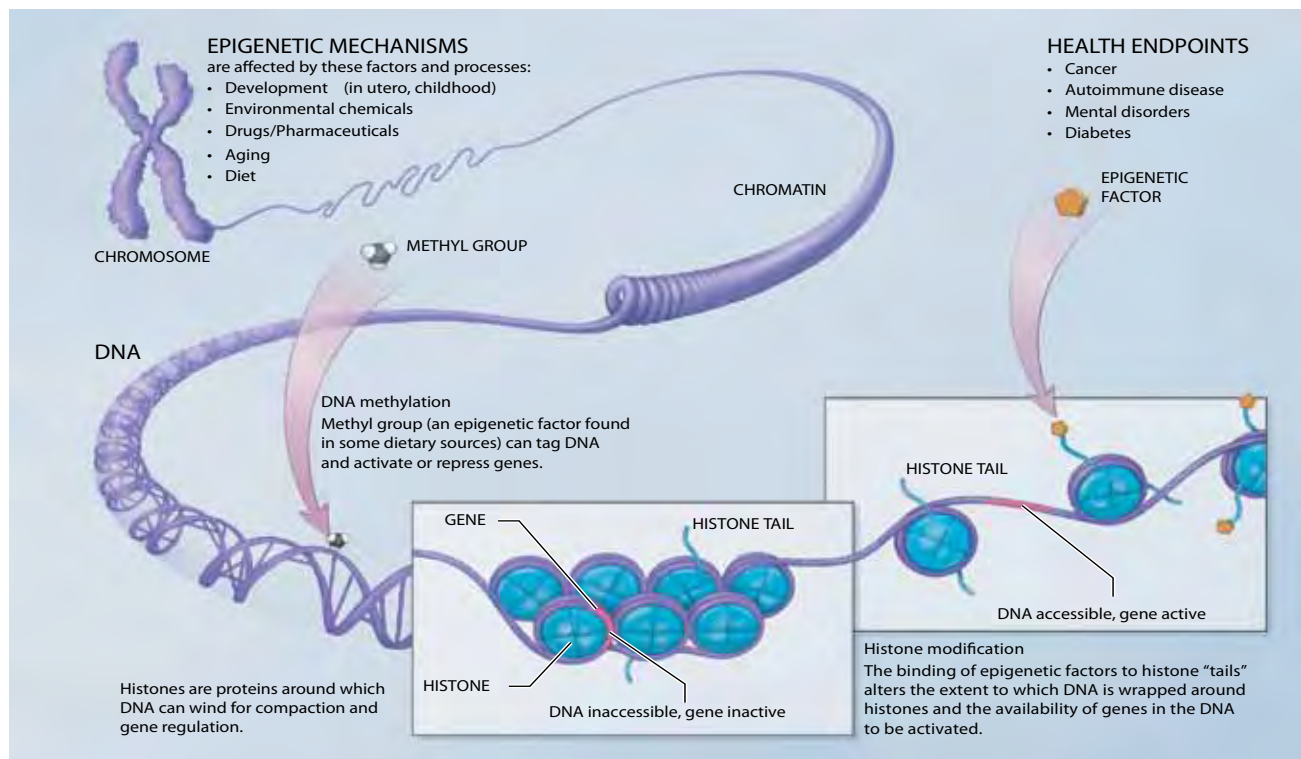


FIGURE 4 Epigenetic mechanisms of disease. These mechanisms are affected by several factors and processes, including the development in utero and in childhood, environmental chemicals, drugs and pharmaceuticals, aging, and diet. Source: The National Institutes of Health Common Fund; <http://commonfund.nih.gov/epigenomics/epigeneticmechanisms.asp>.

Histone modification occurs when the binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated. All of these factors and processes can have an effect on health, possibly resulting in cancer.⁶⁷

Vorinostat (Zolinza). Vorinostat inhibits the enzymatic activity of histone deacetylases, HDAC1, HDAC2, and HDAC3 (class I) and HDAC6 (class II). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones. DNA is tightly coiled around histone proteins, and removal of acetyl groups from these histones has been shown to result in a condensed chromatin structure and the subsequent repression of gene transcription (tumor suppressors, for example). Thus, overexpression of HDACs associated with some cancers results in lack of tumor suppressor genetic expression, thereby

enabling cancer cells to proliferate. Inhibition of HDAC activity by vorinostat allows for the accumulation of acetyl groups on the histone lysine residues, resulting in an open chromatin structure and transcriptional activation and subsequent expression of tumor suppressor genes.⁶⁸

Azacitidine (Vidaza). Another epigenetic compound is azacitidine. Its mechanism of action is via hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Some cancer cells are associated with excessive DNA methylation, which results in a lack of cell differentiation and proliferation. Hypomethylation of DNA may restore normal function to genes that are critical for differentiation and proliferation. Nonproliferating cells are relatively insensitive to azacitidine.⁶⁹

Immunomodulators

Immunomodulating agents are often used to boost the ability of

the immune system to fight cancer. Agents used in immunotherapy include monoclonal antibodies, which have also been shown to have direct antitumor effects.⁷⁰

Interferon alfa-2a (Roferon-A) and interferon alfa-2b (Intron A). Interferons bind to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events, including the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virally infected cells.^{71,72}

Rituximab (Rituxan). Rituximab is a monoclonal antibody that binds to the cluster of differentiation 20 (CD20). CD20 is widely expressed on B cells, from early pre-B cells to later in differentiation, but it is absent on terminally differentiated plasma cells.

Although the function of CD20 is unknown, it may play a role in Ca^{2+} influx across plasma membranes, maintaining intracellular Ca^{2+} concentration and allowing activation of B cells.

The exact mode of action of rituximab is unclear, but the following effects have been found: the Fc portion of rituximab mediates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC); a general regulatory effect on the cell cycle; an increase in major histocompatibility complex class II and adhesion molecules lymphocyte function-associated antigen 1 (LFA-1) and LFA-3; shedding of CD23; and downregulation of the B-cell receptor and induction of apoptosis of CD20+ cells. The combined effect results in the elimination of B cells from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells.⁷³

Miscellaneous agents

The miscellaneous category is often used to include agents that have either multiple or unclear MOAs or compounds that do not fit into a particular category of anticancer therapy.

Lenalidomide (Revlimid). The mechanism of action of lenalidomide has yet to be fully characterized. In short, lenalidomide possesses antineoplastic, immunomodulatory, and antiangiogenic properties. The multiple proposed modes of action can be simplified by organizing them as in vitro and in vivo. In vitro, lenalidomide has exhibited three main activities: a direct antitumor effect, inhibition of the microenvironment support for tumor cells, and an immunomodulatory role. In vivo, lenalidomide has been shown to induce tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, antiangiogenic and antiosteoclastogenic effects, and immunomodulatory activity.⁷⁴

Bexarotene (Targretin). Bexarotene selectively binds and activates retinoid X receptor subtypes. Once ac-

tivated, these receptors function as transcription factors, which regulate the expression of genes that control cellular differentiation and proliferation. The exact MOA is unclear. One proposed mechanism is regulation of abnormal T-cell proliferation. Once the genes that control the growth and replication of cells are "turned on," the cells no longer grow and replicate.⁷⁵

Tretinoin (Vesanoïd). Also known as an acid form of vitamin A and all-trans retinoic acid (ATRA), tretinoin is a retinoid that induces maturation of acute promyelocytic leukemia (APL) cells in culture. Tretinoin is not a cytolytic agent; rather, it induces cytodifferentiation and decreased proliferation. The exact MOA of tretinoin remains unknown. However, APL usually involves a chromosomal translocation of chromosomes 15 and 17, resulting in fusion of the retinoic acid receptor (RAR) gene to the promyelocytic leukemia (PML) gene. This fused gene product (PML-RAR) prevents immature myeloid cells from differentiating into more mature cells. This block in differentiation is thought to cause leukemia. ATRA acts on the PML-RAR to lift this block, resulting in differentiation of the immature promyelocytes to normal mature blood cells, thus decreasing the promyelocyte population.^{76,77}

Arsenic trioxide (Trisenox). Arsenic trioxide causes morphologic changes and DNA fragmentation characteristic of apoptosis in human PML cells in vitro. Arsenic trioxide is known to cause damage or degradation of the fusion protein PML/retinoic acid receptor alpha-fusion protein. Arsenic trioxide may also affect numerous intracellular signal transduction pathways, inhibiting growth and angiogenesis and promotion of cell differentiation. The exact mechanism in vivo is not well understood.^{78,79}

Asparaginase (Elspar). An enzyme that hydrolyzes asparagine to aspartic acid, asparaginase is primarily used to treat ALL but is also used in some

mast cell tumor protocols. Unlike other chemotherapy agents, asparaginase can be administered via the intramuscular, subcutaneous, or intravenous route. Most ALL cells are unable to synthesize the nonessential amino acid asparagine, whereas normal cells are generally able to make their own asparagine. Leukemic cells then require high concentrations of asparagine for growth. Asparaginase then catalyzes the conversion of asparagine to aspartic acid and ammonia, thereby depriving the leukemia cells of circulating asparagine. This is a unique approach to therapy, based on a metabolic defect in asparagine synthesis of some malignant cells.^{80,81}

Bortezomib (Velcade): The proteasome is an enzyme complex found in most cells and plays an important role in the degradation of proteins that control the cell cycle and numerous cellular processes. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The inhibition of this proteasome results in a disruption of numerous cellular processes, including those related to the growth and survival of many cancer cells. Specifically, proteasome inhibition may prevent degradation of proapoptotic factors, permitting activation of programmed cell death in neoplastic cells, which were dependent upon suppression of proapoptotic pathways. With that suppression, neoplastic cells were permitted to grow and survive. Bortezomib is the first therapeutic proteasome inhibitor to be tested in humans.^{82,83}

Discussion

It has been estimated that physicians use some two million pieces of information to manage patients. Unfortunately, some of that information is out of date. It has become increasingly difficult to keep up with the flood of new information. In 1996, it was estimated that the doubling time of the biomedical knowledge base was

about 19 years.⁸⁴ One only has to attend a major oncology meeting and view the industry exhibits, for compounds in the market place, for compounds in development, and for new devices from infusion pumps to electronic medical record software displays, to understand how overwhelming all this information may be for the practicing oncologist and allied health care professionals. In the 1990s, surveys of physicians stated that the current volume of scientific information was unmanageable.⁸⁴

So how then do oncologists keep up with the rapidly advancing knowledge base? In particular, how do oncologists remain current about each individual oncology compound that they may prescribe each week? As we learn more about the MOA, pharmacodynamics, and pharmacokinetics of each compound, how is this information found and incorporated into practice? Is there a role for this information to address patient-related questions?

In addition to the oncology products under development and in the market place, there are a host of other non-oncology products that come into play in an oncology practice. It is common for patients to have comorbidities along with their underlying malignancy, such as type 2 diabetes, congestive heart failure, respiratory-related problems, and abnormal lipid levels, or develop cancer treatment-related adverse events or side effects. Some of these adverse events or side effects are as simple as extra electrolyte supplementation when using platinum compounds or the use of diuretics. Others are more complicated, such as infection prevention measures when neutrophil and lymphocyte counts are reduced as a direct effect on the synthetic capabilities of the bone marrow. It is estimated that utilization of oncologists' services will increase appreciably between 2005 and 2020.⁸⁵

To further quantify the magnitude of the information available to oncologists, we turned to the Clinical

Guidelines of the National Comprehensive Cancer Network (NCCN). In 2010, there were 36 NCCN Practice Guidelines for malignancies identified by site.⁸⁶ In addition, there were nine NCCN guidelines for various supportive care measures, such as antiemetics, and seven NCCN guidelines for cancer detection, prevention, and risk reduction. The number of compounds referenced in the 36 tumor site guidelines and the 9 supportive care guidelines further highlights the vast knowledge necessary in the practice of modern oncology.

What other compounds are oncology patients also taking? An informal survey (Shandhya Ramalingam, PhD, personal communication) found that 37% of oncology patients were taking vitamins; 19%, antidepressants; 19%, prophylactic antibiotics; 13%, antidiarrheals; 9%, therapeutic antibiotics; and 3%, low-molecular-weight heparin. We have no data on the actual prescriber of each of these compounds for the individual patient, but it appears likely that management of these medications may in whole or in part fall to the oncologist.

Much has been written about personalized medicine and personalized approaches to treatment of various cancers. Many of the newer agents recently approved are cytostatic and not cytotoxic and may exert more of their effects when combined with more standard chemotherapy agents. Because of the increasing newer combinations of agents that will be generated in the years ahead, we undertook this project of attempting to succinctly characterize the MOA of 50 of the more commonly utilized oncology compounds currently on the market. This list is not exhaustive, nor is it meant to be. However, it does provide a ready source of information on the more commonly used agents.

More often than not, we hear that physicians and other healthcare professionals will consult the prescribing information (PI) for a particular

compound to read about the MOA. Alternatively, they will call upon a pharmacist working with their office practice or team for this information (Mark Sorenson, University of Iowa, personal communication). Unfortunately, the information in the MOA section of a PI may be out-of-date and not as scientifically accurate as it could be, considering that the MOA may not have been as precisely known or understood at the time that approval was sought. In subsequent years, and with more research, additional information was generated on the precise MOA, but the PI was not updated. Thus, we consulted a variety of sources to provide the best understood and most precisely stated MOA for the compounds listed in this article.

The availability of an electronic medical record (EMR) often puts this information at the fingertips of physicians, yet fewer than 25% of all practices utilize the EMR for patient-related orders, according to 2006 statistics from the Centers for Disease Control and Prevention.⁸⁷ By 2007, only 2% of physicians had a fully functional EMR system, although more than half of all practicing physicians were estimated to use some basic elements of an EMR system by 2010.⁸⁸

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Multifocal bone infarctions in both knees: an unusual presentation of multiple myeloma

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Multiple myeloma (MM) is a neoplastic proliferation of monoclonal plasma cells within the bone marrow, which overproduces immunoglobulin. This disorder accounts for approximately 1% of all reported neoplasms and 12%–15% of all hematologic malignancies.¹ It is the second most common hematologic malignancy diagnosed.² The etiology is still not fully understood. MM typically affects older patients, ranging from 50–78 years (median, 61 years).³ Common clinical presentations include fatigue, anemia, renal failure, hypercalcemia, bone pain, and pathologic fractures.

Bone involvement in MM may vary at presentation. Most commonly, radiographic findings include multiple small, sharply defined, lytic, “punched-out” lesions without reactive bone formation, arising in the medullary cavity at sites of preserved hematopoiesis in adults (the axial skeleton). The pathophysiology of the bone findings is uncertain, though presumed to be resultant of either inhibition of osteoblastic activity and/or activation of osteoclastic activity. Involvement of the cortex results in endosteal scalloping, with invasion of the periosteum and occasionally extraosseous extension. Lesions are most commonly seen in the vertebrae, ribs, skull, pelvic bones, and femur, in descending order of prevalence. Distal bone involvement is less common, though cases with predominant involvement in peripheral bones have been described. Uncommon radiographic presentations include diffuse skeletal osteopenia without focal lesions or sclerotic lesions.^{4,5} To our knowledge, multiple bone infarcts

as a complication of MM have not been reported in the medical literature.

Case presentation

A 47-year-old man with no significant medical history presented after the recent onset of painless hematuria, which spontaneously resolved after 2 days. He complained of left knee pain, which he noted after doing yard work.

Routine laboratory examination showed normocytic normochromic anemia, with a hemoglobin level of 11.5 g/dL and a mildly elevated alkaline phosphatase (ALP) level at 124 units/L. An MRI of the left knee showed increased red bone marrow within the distal femur and proximal tibia/fibula, initially thought to be compatible with anemia from an unexplained inflammatory process. Further urologic and gastroenterologic workup was negative.

Several months later, our patient was noted to have progressive fatigue, with a decrease in hemoglobin level to 10.6 g/dL and a mildly elevated erythrocyte sedimentation rate. Physical examination was otherwise unremarkable. A repeat MRI of both knees showed an extensive marrow infiltrative process, with multiple presumed secondary bone infarcts in the distal femora and proximal tibias, proximal fibulae, and patellae (Figure 1). A tandem skeletal survey showed mild diffuse osteopenia and several small, rounded, lytic foci in the skull

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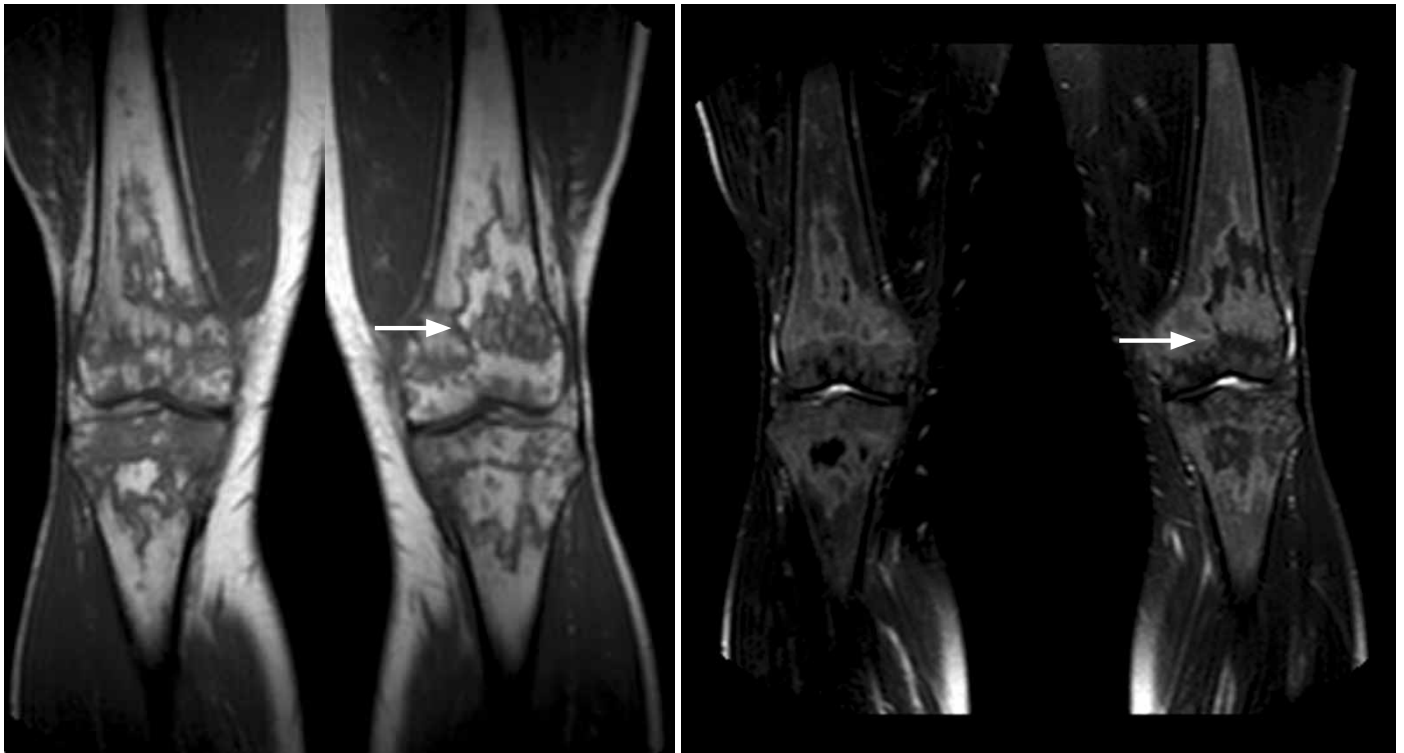


FIGURE 1 MRI examination of both knees was performed on the same day as the radiographic examination. The left images are T1 weighted, and the right images are T2 weighted with chemical fat suppression. There were extensive abnormalities in the bone marrow, with well-demarcated foci of intermediate-to-low T1 signal and high T2 signal within the fatty marrow. These geographic areas of abnormal signal are typical of bone infarctions. Multiple lesions were present, involving all bones of the knees. The arrows denotes one of these presumed bone infarctions in the left femoral metaphyseal region.



FIGURE 2 Lateral radiograph of the skull taken as part of a skeletal survey. The image was notable for multiple rounded, "punched-out," well-defined, lucent lesions of about 3–4 mm. These lesions (arrow) are typical radiographic findings of multiple myeloma. The skull was the only site of focal radiographic lesions in the skeletal survey exam.



FIGURE 3 Frontal radiographs of the right (left image) and left (right image) knee taken as part of a skeletal survey. These images revealed mild generalized osteopenia, with no focal lesions seen in either knee. These relatively unremarkable radiographs were contrasted by the strikingly abnormal MRI exam performed on the same day, seen in Figure 1.

(Figure 2), which were suspicious for MM. No focal radiographic lesions were seen (Figure 3).

Bone marrow biopsy from the left posterior iliac crest revealed hypocellular marrow (20%). An expansion of plasmacytoid cells with eccentrically placed, round nuclei, clumped chromatin, occasional nucleoli, and moderate amounts of eosinophilic cytoplasm accounted for 75% of the marrow cellularity. An aspirate smear demonstrated scattered mature plasma cells, accounting for roughly 15% of the total cellularity. Flow cytometry showed no overt evidence of

marrow involvement by a lymphocytic clone. Bone biopsy was not performed in the areas of the knees seen to be abnormal on MRI examination.

Serum protein electrophoresis (SPEP) showed a band in the beta-gamma region. Immunofixation confirmed the presence of a monoclonal paraprotein, consisting predominantly of immunoglobulin A (IgA) heavy chain and kappa light chain. A bone marrow biopsy and aspirate showed replacement of most hematopoietic elements by sheets of mature plasma cells, accounting for 75% of the total marrow cellularity (Fig-

ure 4). Confirmatory immunostains were positive for CD138, CD117, and kappa light chain (Figure 5) and negative for CD79a and lambda light chain (Figure 6). A diagnosis of MM was made based on the finding of M protein in the urine, the presence of greater than 10% clonal plasma cells in bone marrow, and related clinical symptomatology (including anemia and hypercalcemia).

The patient was started on immunomodulating therapy with lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone. Autologous stem cell transplantation

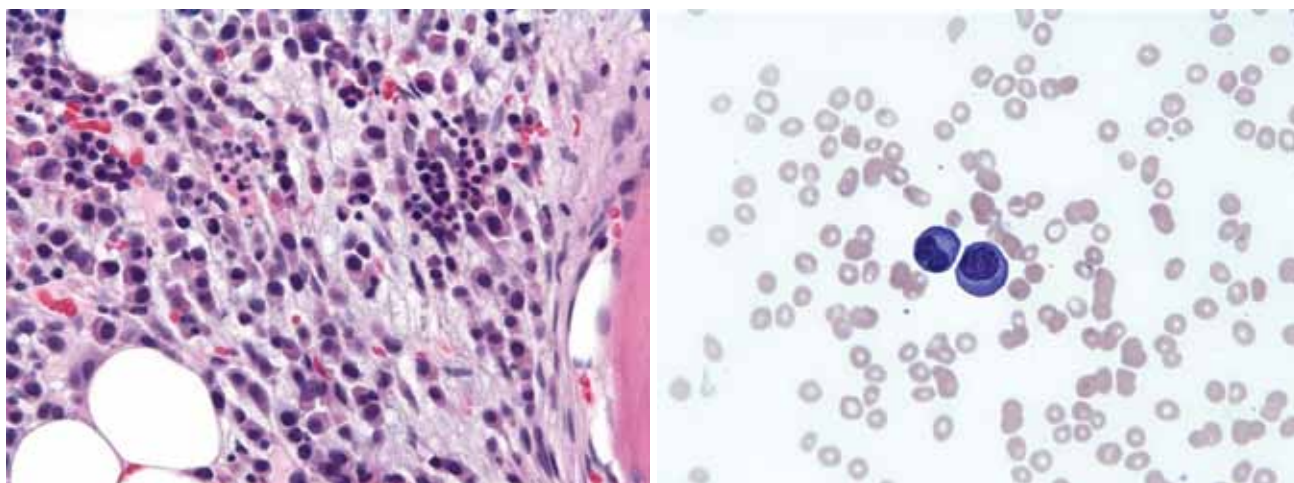


FIGURE 4 Left: The bone marrow core contains a monotonous expansion of mature plasma cells, which account for 75% of the marrow cellularity (hematoxylin and eosin stain, 40x). Right: The hemodilute aspirate shows scattered mature plasma cells, which account for 15% of the total cellularity (Wright-Giemsa stain, 50x, oil immersion).

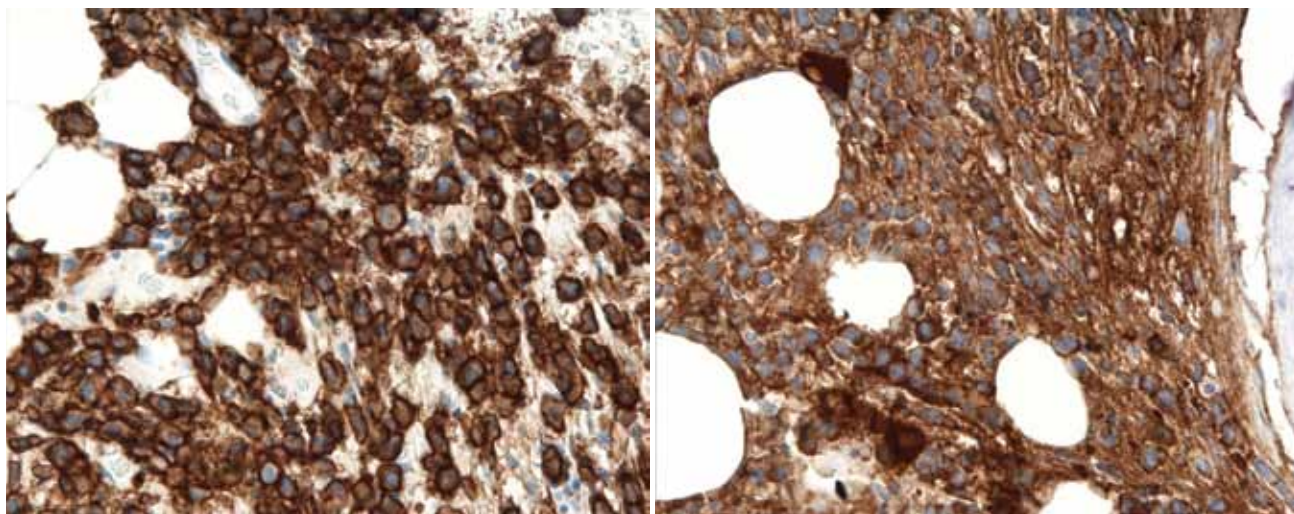


FIGURE 5 The bone marrow core shows a monotonous expansion of plasma cells, which stain for CD138 (left) and kappa light chain (right; 40x).

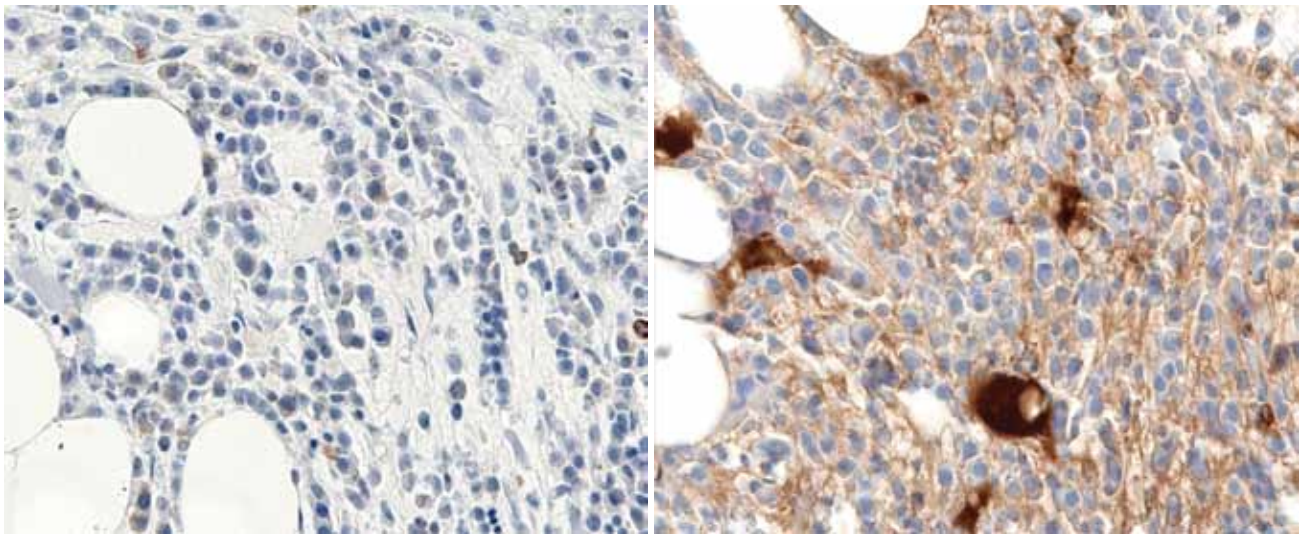


FIGURE 6 *Left:* Neoplastic plasma cells are negative for lambda light chain, which is seen only in rare benign background plasma cells. *Right:* Plasma cells demonstrate aberrant loss of pan B antigen CD79a (40 \times).

may be considered after appropriate treatment.

Discussion

We offer the case of a patient with MM who presented with bilateral knee infarcts. Synonyms of bone infarct include osteonecrosis, bone necrosis, avascular necrosis, aseptic necrosis, ischemic bone necrosis, and bone death.⁶ MRI is the most sensitive imaging modality for evaluation of the bone marrow. It can detect early osteonecrotic changes in bones well before they are visible on radiography⁷; this fact was exemplified in our case, in which the patient had only mild osteopenia on knee radiographs but extensive osteonecrotic changes on MRI examination.

Bone infarct more commonly involves the hips than the knees.⁷ Knee involvement can be differentiated into two main categories: primary and secondary. Primary, spontaneous, or idiopathic involvement tends to be unilateral and usually is seen in the elderly, although the recent literature suggests that many of these so-called spontaneous cases are actually secondary to subcortical microfractures, which are then complicated by osteonecrosis.⁵ Secondary causes tend

to present at a younger age, with bilateral and multifocal involvement.

Examples of secondary causes include steroid therapy, alcoholism, decompression syndrome, hemoglobinopathies (sickle cell disease), autoimmune disease (lupus and antiphospholipid disease), infections (human immunodeficiency virus), radiation, and trauma.^{8–15} Other causes, such as chemotherapy toxicity in pediatric leukemia¹⁶ and Gaucher disease, have been reported.⁷ Osteonecrosis of the jaw is a known treatment complication of bisphosphonate therapy in patients with MM¹⁷; however, there have been no previous reports describing the presentation of multifocal bone infarcts in both knees in patients with MM.

Although the pathogenesis of bone infarction is unclear, it is thought to be caused by the combined effects of systemic and local factors affecting the blood supply, vascular damage, increased intraosseous pressure, and mechanical stresses. These processes lead to compromise of the bone vasculature, resulting in the death of bone and marrow cells.⁹ In our case, MRI of both knees revealed an extensive marrow infiltrative process, which may have caused local vascu-

lature damage and diminished blood supply resulting in bone infarctions.

Conclusion

Bone infarction of any joint is not a well-established complication of MM. Physicians should be aware of this potential presentation. Although there is no cure for MM, early recognition of MM can lead to more effective treatment, thus slowing disease progression and improving overall clinical outcomes.

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First-bite syndrome: a novel complication of carotid body paraganglioma resection

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First-bite syndrome is a relatively uncommon and recently identified problem associated with surgery involving the parotid gland, neck tumors, parapharyngeal-space masses, and paragangliomas. Treatments for first-bite syndrome offer variable results, with botulinum toxin being perhaps the most promising option.

Case presentation

A 55-year-old man was referred for excision of an asymptomatic left parapharyngeal mass thought to be a carotid body paraganglioma. The patient had been treated previously with antibiotics for a possible sinus infection, without resolution. He underwent CT and angiographic embolization of the tumor prior to excision of the mass. Pretreatment imaging was consistent with a carotid body tumor. The patient was presented with treatment options, including surgical resection.

Preoperatively, the surgeon informed the patient of the potential for neurologic and cranial nerve-related complications and other perioperative risks. Surgery was performed via a transcervical incision. Through careful subadventitial dissection, the tumor was separated from the carotid artery and the carotid artery bifurcation. Excision of the tumor involved separation from and/or mobilization of the marginal mandibular branch of the facial nerve, hypoglossal nerve, spinal accessory nerve, glossopharyngeal nerve, and vagus nerve but was free of the sympathetic trunk and ganglion. However, the tumor was attached to and required ligation of the external carotid artery.

A few days after surgery, the patient experienced pain in his left jaw and ear immediately upon in-

gesting the first bite of solid food. The sensation was described as a “strong electrical jolt” with severe cramping, which was initially painful but then slowly dissipated after 5–15 minutes. In addition, the patient reported that the pain returned a few minutes after eating and persisted for up to 15 minutes.

About 2 weeks after surgery, the postprandial pain began to diminish in intensity, with complete resolution about 3 weeks thereafter. The first-bite syndrome pain, however, continued with similar intensity and duration 3.5 months post surgery. Self-treatment with acetaminophen and ibuprofen did not eliminate the pain.

Background discussion

First-bite syndrome is a relatively uncommon and recently identified problem associated with surgeries involving the parotid gland and/or the parapharyngeal space.¹ The current description of the syndrome was initially reported in 1998 by Netterville,² and the term “first-bite” syndrome was thought to be an appropriate name for the findings. In 1986, a gastrointestinal surgeon, Haubrich, had associated “first-bite syndrome” with a different clinical syndrome: esophageal dysfunction in patients who complained of an inability to swallow the first few bites of a meal ac-

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TABLE 1

Characteristics of patients with first-bite syndrome

Reference	Age, yr	Gender	Site of origin	Histology	Surgical approach	Horner's syndrome	Sympathetic chain sacrifice	External carotid artery ligation	Deep lobe of parotid gland resection
Kawashima et al ⁴	32	F	Sympathetic chain	Schwannoma	Transcervical	Yes	Yes	No	No
Kawashima et al ⁴	34	M	Sympathetic chain	Schwannoma	Transcervical	Yes	Yes	No	No
Kawashima et al ⁴	52	M	Sympathetic chain	Schwannoma	Transcervical-transparotid	Yes	Yes	No	No
Casserly et al ¹	45	F	Sympathetic chain	Schwannoma	NR	Yes	Yes	No	No
Kawashima et al ⁴	51	M	NR	Pleomorphic adenoma	Transcervical-transparotid	No	No	Yes	Yes
Kawashima et al ⁴	66	M	NR	Pleomorphic adenoma	Transcervical-transparotid	No	No	Yes	Yes
Kawashima et al ⁴	57	F	Deep lobe of parotid gland	Pleomorphic adenoma	Transcervical-transparotid	No	No	Yes	Yes
Kawashima et al ⁴	37	F	Unknown	Pleomorphic adenoma	Transcervical	No	No	Yes	Yes
Kawashima et al ⁴	27	F	Deep lobe of parotid gland	Pleomorphic adenoma	Transcervical-transparotid	No	No	Yes	Yes
Kawashima et al ⁴	45	F	Deep lobe of parotid gland	Pleomorphic adenoma	Transcervical-transparotid	No	No	No	Yes
This case	55	M	Carotid artery bifurcation	Carotid body tumor	Subadventitial dissection	No	No	Yes	No
Ali et al ⁵	53	F	Lymphangioma	NR	Mandibular osteotomies and parapharyngeal-space dissection	Yes	NR	NR	NR
Albasri et al ⁷	71	M	Carotid artery	NR	Carotid endarterectomy	No	NR	NR	NR
Albasri et al ⁷	24	M	Unknown	Cervical paraganglioma	NR	No	NR	NR	NR
Mandel et al ⁶	48	F	Sympathetic chain	Schwannoma	NR	Yes	NR	NR	NR

NR = not reported

accompanied by retrosternal pain. These individuals' symptoms were relieved by regurgitation.³

The true incidence of "first-bite syndrome" as characterized by Netterville is unknown, but cases have been reported after surgery of the parotid gland, neck tumors, parapharyngeal-space masses, and paragangliomas (Table 1).⁴⁻⁷ Those with the syndrome typically develop an intense, sharp, and sometimes cramping pain in the ipsilateral parotid region after the first bite of each meal.³ The severe pain lessens with each subsequent bite of the meal only to return at the first bite of the next meal.²

Netterville et al² proposed that first-bite syndrome is due to the loss of sympathetic innervation to the parotid gland, resulting in the denervation and supersensitivity of the sympathetic receptors that control the myoepithelial cells. The pain comes from a supramaximal response of the myoepithelial cells stimulated by parasympathetic neurotransmitters, causing a spasm with the initial intake of food after a period of salivary rest (Figure 1). This etiology holds true in the majority of cases, although not all. A common feature for those afflicted with first-bite syndrome is residual parotid gland tissue. In some

cases, even the thought of eating may cause a reaction by the salivary glands.

Tumors of the parapharyngeal space are rare; they typically evade diagnosis until found incidentally on imaging for another reason or grow to a size that becomes symptomatic or deforming. Imaging should be performed to evaluate the extent of the mass in the parapharyngeal area and the surrounding vascular structures preoperatively and to assure appropriate surgical planning and patient advisement.¹ Biopsy is not recommended for carotid body tumors due to the risk of vascular injury, bleeding, and more severe complications.

Common surgical procedures that can result in first-bite syndrome include parotidectomy, neck dissection, transcervical excision of a sympathetic chain schwannoma, paraganglioma excision, and excision of a deep lobe parotid pleomorphic adenoma.⁸ In a retrospective study by Kawashima et al,⁴ 9 of 22 patients who underwent surgery to remove a tumor in the parapharyngeal space postoperatively developed first-bite syndrome. All five patients who had external carotid artery ligation and resection of the deep lobe in the parotid gland during surgery developed first-bite syndrome. One patient underwent ligation of the external carotid artery from the sympathetic pathway and ligation of the auriculotemporal nerve from the parasympathetic pathway (Figure 1) and did not develop first-bite syndrome.

Therapy options

Treatments for first-bite syndrome offer variable results. Treatment outcomes experienced by patients in the various studies focusing on first-bite and Horner’s syndromes are summarized in Table 2, with only a few therapies having reported positive effects. Concomitant amitriptyline (25 mg at bedtime) reduced the intensity as well as the duration of pain, as reported by Phillips and Farquhar-Smith.⁹ In the cases from Chiu et al,⁸ two of three patients with first-bite syndrome found slight pain relief following tympanic neurectomy. Another patient found that amitriptyline and carbamazepine reduced the pain to only the first few bites.⁹ Casserly et al¹ reported on a patient with Horner’s syndrome and first-bite syndrome whose pain improved with pregabalin (Lyrica).

Perhaps the most promising treatment is botulinum toxin. In a study by Ali et al,⁵ a woman who received no benefit from multiple narcotics and surgeries received an injection of botulinum toxin into the side of the parotid gland, where the pain was most intense. Four months after un-

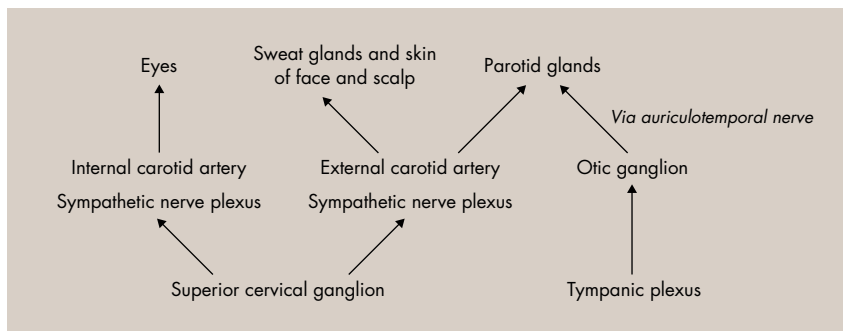


FIGURE 1 Pathways of sympathetic and parasympathetic nerve supply to the head. Adapted from Chiu et al.⁸

TABLE 2

Treatment outcomes of patients with first-bite syndrome, in order of treatment effectiveness

Treatment	Outcome
Botulinum toxin ⁵	Pain alleviated
Pregabalin ¹	Pain improved
Concomitant amitriptyline ⁹	Reduced duration of pain and intensity
Anti-inflammatory medication ¹ Carbamazepine ^{1,7,9} Analgesics ⁶ Amitriptyline ⁷ Gabapentin ⁷	Limited pain reduction
Tympanic neurectomy ⁸	Slight initial pain improvement, only to return to baseline symptoms
Local anesthetic blocks with bupivacaine ⁷	Transient pain relief; additional sensory disturbances
Gabapentin ⁹	Limited pain reduction; increased drowsiness
Oxycodone ⁹ Methadone ⁹	Ineffective and caused drowsiness
Carbamazepine ⁸ Nonsteroidal anti-inflammatory medications ⁸ Hyoscine ⁹ Acupuncture ⁹ Co-codamol and immediate-release morphine ⁹ Acetaminophen (this case) Ibuprofen (this case)	No benefit/no effect/ineffective
Local anesthetic benzocaine lozenges ⁹ Polysaccharide mucilage solution ⁹	Precipitated pain

dergoing tympanic neurectomy (to relieve the symptoms of four surgical resections including mandibular osteotomies and parapharyngeal-space dissection), the patient received an injection of 75 units of botulinum toxin diluted in 2 mL of saline solution into the right parotid gland. Less than 48 hours later, the patient reported that the pain was markedly improved.⁵ If untreated, the pain associated with

first-bite syndrome goes; it has been reported to resolve gradually, up to 21 months following its original onset.

Conclusion

The potential for first-bite syndrome should be included in the preoperative discussion for those undergoing surgery of the parotid gland, neck, and/or parapharyngeal space. Patients who undergo external carot-

id artery ligation as part of these surgeries or who develop Horner's syndrome postoperatively appear to be at highest risk for development of first-bite syndrome. Additional reports on the efficacy of botulinum toxin in alleviating the pain associated with first-bite syndrome are eagerly awaited.

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Size, follow-up, data analysis—good; post hoc analysis, interpretation—not so much

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It's easy to know whether a critique of some article or other was written by a statistician or a methodologist—it states how badly the study was done and how incompetently the data were analyzed. Indeed, it is extremely easy to criticize any study, no matter how well it was conducted, because all applied research involves compromises of one sort or another. Well, be prepared for a surprise. In this column, we will be discussing a study that we believe was carried out well and analyzed correctly. That's not to say that we agree with their conclusions (we don't), but at least the study yields data that people can argue about without dismissing the paper as a whole.

Impressive study size and follow-up

Crawford et al¹ reported on the results of a large randomized controlled trial to determine the potential benefits of screening for prostate cancer. They conclude that “Selective use of PSA [prostate-specific antigen] screening for men in good health appears to reduce the risk of PCSM [prostate cancer-specific mortality] with minimal overtreatment.” So, why do we shine our countenance upon this paper, and why do we disagree with the conclusions? Let's start off with the positives.

First, we are impressed by the study's size. Although it is not always true that bigger is better (we can indulge in all sorts of off-color jokes at this point, but we will restrain ourselves), it definitely is the case when we are studying the natural history of a disorder. This is especially true for diseases such as prostate cancer, which (thankfully) have a low prevalence. In the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,² whose data were reanalyzed in the Crawford study, the sample size was 76,693 men, of whom 60 died of prostate cancer. If the study were much smaller, it still would have come up with estimates of mortality in the screened and unscreened groups, but the confidence intervals around those estimates³ would have been much wider, meaning that we would be less sure of the numbers (after all, that's why they're called confidence intervals).

The second aspect of the study that impresses us is the follow-up rate. Research that tries to determine the natural history of a disorder has to balance two competing demands. On the one side, its duration must be long enough to allow time for the outcome to appear. The study would have been of limited usefulness if the men were followed for only 1 or 2 years, because most of the cases of cancer would have developed long after the study had ended. On the other side, the longer the study, the more difficult it is to have complete data on everyone who entered the study. People lose interest in the study and drop out, they may move or die without notifying the researchers beforehand, and so forth.

Moreover, as we've said in a previous article,⁴ people do not drop out of studies for trivial reasons. In a study of this sort, they may quit because they were assigned to one group but wanted to be in the other, could not be bothered with filling out forms, or a host of other reasons. The result would be that those who remain in the study become a biased, unrepresentative sample. In this study, though, 96% of the men were available for mortality analysis 10 years after they were enrolled. Even if the other 4% were different from the completers in some substantive way, their numbers are not large enough to seriously bias the results.

Finally, the data were competently analyzed, using “competing risks regression.” Without going into the details (and they are messy), what this means is that despite what we're told by health food and exercise experts, everyone is going to die of something; if you don't get knocked off by one thing, you'll be done in by something else. The problem (at least from the statistician's viewpoint) is that if

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a person in this study died because of an infarct, this changes his probability of dying of prostate cancer (to zero, to be precise). Any analysis of outcomes must take this into account, and this study did.

The dangers of post hoc analyses

So, with all of this going for it, why are we sitting at our desks, writing this review, rather than running out getting PSA tests and biopsies? There are a number of reasons. First, as we mentioned previously, this paper is a reanalysis of the PLCO study,² which concluded that the risk of dying of prostate cancer was equally low in both the screened and unscreened groups. In essence, it is a post hoc analysis, dividing the groups by comorbidity status and finding benefit only among men with minimal comorbidity but no difference in the group with at least one significant comorbidity.

It is a well-known dictum in statistics that any unplanned, after-the-fact analyses are *hypothesis-generating* only, and the results should not be taken as definitive. The prime example of this is the famous ISIS-2 (Second International Study of Infarct Survival).⁵ After being pressured by the journal editor to perform some post hoc analyses, the authors stipulated that they would do those suggested by the editor as long as the journal published all of the subgroup analyses. They then went to town and divided the groups according to when they were born, concluding that “subdivision of the patients in ISIS-2 with respect to their astrological birth sign appears to indicate that for persons born under Gemini or Libra, there was a slightly adverse effect of aspirin on mortality (9% increase, standard deviation [SD] 13; nonsignificant), whereas for patients born under all other astrological signs, there was a striking

beneficial effect (28% reduction, SD 5; $2p < 0.00001$).” The moral of the story? Don’t trust post hoc analyses—if you do enough of them, something is bound to show up.

The second reason we’re somewhat dubious is that our interpretation of the results is different from theirs. The authors found that to prevent one death from prostate cancer at 10 years, 723 men would have to be screened and 5 treated, and they concluded that screening was worthwhile. We look at those same numbers and draw a different conclusion. For one thing, doing 723 PSA tests to find 5 cases reflects a tremendous cost to the system, which may be better spent in other ways.

More important, though, it ignores the fact that there will be a large number of false-positive findings. Let’s take the best available version of the PSA test—the complexed PSA. According to one study,⁶ using the ideal cut-point results in a sensitivity of 0.85 (ie, 85% of cases are detected by the test) and a specificity of 0.35 (35% of those who are cancer-free are correctly identified).

One of the best estimates of the incidence of prostate cancer comes from a review, in which the figure was 61.8 per 100,000 white men.⁷ Now let’s use the lessons from previous articles^{8,9} with these data and assume we screen 100,000 men. What we find is shown in Table 1. There will be 65,013 positive test results, of which only 53 will be from men who actually have cancer—a false-positive rate of over 98%! And, the test will still miss nine men who have cancer. These findings mean that nearly 65,000 men will have unnecessary follow-up tests, probably including biopsies, with all of the associated costs, risks, and side effects. Our take on things? Thanks, but no thanks.

So, the bottom line is that the study

TABLE 1
Hypothetical results of screening for prostate cancer

Test results	Actually have prostate cancer ^a		Total
	Yes	No	
Positive	53	64,960	65,013
Negative	9	34,978	34,987
Total	62	99,938	100,000

^aBased on a reported incidence of 61.8 cases per 100,000 adult white males in the United States⁷

was well done. We have some reservations about the findings, because they were based on post hoc analyses, and we read the results in a different light than do the authors. (Then again, we don’t make our living ordering PSA tests.) However, as we said earlier, we can argue about the interpretation, but we have a solid basis for the numbers we use in our arguments.

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Apps for the iPad and other tablets

John J. Fried

Almost as soon as the iPhone—and then its imitators—colonized belts, bags, and lab coat pockets, the effort to stay abreast of the latest developments in oncology took on a new dimension. Medical book publishers, medical organizations, and journals flooded iTunes, Android Market, and other Web sites with oncology-related apps for the devices.

Thus, in the smartphone era, while standing by a patient's bedside, you could tap the eOpioid icon, stab at the screen a couple of times, and obtain the guidance you need to convert her to a different painkiller. In an examining room, you could turn to Blausen Cancer Atlas to help you explain the disease to a prostate cancer patient. Upon learning that a patient had started taking vitamins while receiving chemotherapy, you might consult Epocrates to help your patient avoid harmful interactions.

Somewhere along the line, however, it may have become apparent that there could be drawbacks to using those smartphone apps. The device's small screen forces you to resort to a lot of finger flicking to move through articles and other printed materials, and it can be difficult to discern important details in graphics. Also, if you are, ahem, of a certain age, the small font size can prove a challenge.

When the iPad—and its imitators—came along, there was reason to hope that there would also be apps designed to take advantage of the larger screens. The endless scrolling and the squinting would be things of the past. Well, in many cases, it has not worked out that way.

Some publishers have gone the

extra mile, adapting their medical apps to the much more generous screen size of tablets. Others, however, have taken the easy way out, doing no more than making their existing smartphone apps sort of compatible with tablets. Download many an app to your tablet and you'll find that the app only fills in a 4-inch area within the tablet's large screen.

Here, then, is a look at the way some important and popular apps are likely to function on your tablet. Note: All apps were reviewed on an iPad only. Some apps, as noted, are also available for some other devices.

NCCN Guidelines

WWW.NCCN.ORG/MOBILE/DEFAULT.ASP

As of July 2011, the National Comprehensive Cancer Network (NCCN) was still trying to decide whether it should develop a full-sized tablet app, according to an e-mail I received from the network's tech support. While it agonizes over that issue, you will only be able to use the smartphone version of the NCCN Guidelines app on your tablet.

Look on the bright side: If you are already familiar with the smartphone app, you are not likely to find many (if any) surprises when you load it onto your tablet. You will find any guideline of importance to you by selecting it from an alphabetical list or by entering appropriate key words in a search box. You can save the guidelines to your tablet, in case you have to consult them off line. Need help? Click the Settings icon, and then click on Help. You'll find an e-mail link to use for obtaining support.

You can use the 2× magnifier icon in the lower right-hand corner of the

tablet to fill the screen. However, you may find the resolution of the text a little fuzzy and probably not of much help. An app also is available for Android mobile devices.

Epocrates

WWW.EPOCRATES.COM/PRODUCTS

In case you have not run across Epocrates or have not paid attention to it in a while, its products include more than half a dozen digital references and medical tools. Some are free, including a guide to drugs (with a drug interaction checker) as well as an app with more than 100 CME-related activities. Others carry subscription fees. For \$99 a year, for example, you get access to Epocrates Rx Pro, which includes an infectious disease treatment guide and a guide to more than 600 herbal medicines. For \$159 a year, you get what is included in Epocrates Rx Pro plus hundreds of disease monographs, high-resolution disease images, and lots of diagnostic and laboratory tests. If you have \$199 a year to spare, you can buy Epocrates Essentials Deluxe, which also brings you ICD-9 and CPT codes in addition to the tools included in the other Epocrates works.

The bad news? The apps are smartphone size. As with the NCCN Guidelines app, you can use 2× resolution to fill the tablet screen. But look out for the fuzzy type.

The Epocrates Web site says that as of July 2011, Epocrates "supports Android tablets with OS version 2.2 only. Android tablets with OS 2.3 or higher are not yet officially supported...." That "officially" might be code for "download and see what happens." Moreover, the website adds, "although it remains possible to install

Epocrates to Android tablets with OS 2.3 or higher, the assistance that could be offered in the event of difficulties may be limited.” Support for BlackBerry, the publishers say, is still under consideration.

Medscape

WWW.MEDSCAPE.COM

Strictly speaking, Medscape is not an oncology reference work. However, with its tools for researching drugs and drug interactions; obtaining up-to-date information on 4,000 diseases; reading medical news articles; enrolling in CME courses; and viewing images, videos, and tables, it can come in handy in almost any clinical setting.

To view its 2,500-plus images, watch its 150 videos, obtain the latest medical news, or take a CME course,

you'll need to keep your tablet connected to the Internet. To save battery life, however, you can download much of Medscape's text-based information to the tablet and read it offline. And, yes, it takes full advantage of every millimeter of your tablet's screen. There is a Medscape for Android devices running OS 2.1, according to a Medscape representative.

TNM 7.0

WWW.CANCERSTAGING.ORG/STAGING

The TNM 7.0 app may be simplicity at its best. You need only tell it the size of your patient's primary tumor, whether there are cells in nearby lymph nodes, and whether there are metastases elsewhere in the body. In a split second, you have your answer. TNM 7.0, which will cost you \$14.99, is strictly small screen. How-

ever, given its uncomplicated interface, its inability to use a tablet's full real estate is not a disadvantage.

Care360

WWW.QUESTDIAGNOSTICS.COM/HCP/CONNECT/PHYSICIAN.HTML

If you want to see what a first-rate tablet app should look like and you refer your patients to Quest Diagnostics for lab work, check out Quest's Care360 app. It's full sized, colorful, well organized, and easy to navigate. Care360's main mission is to give you fast digital access to lab tests you ordered for your patients. You can use the app to order tests and then review the results. The basic Care360 is free. However, for \$23 a month per prescribing physician, your practice can also use Care360 to manage prescriptions.

Oncologists could face more Medicare cuts in debt deal

Mary Ellen Schneider

Legislation to raise the debt ceiling and cut the deficit, signed by the president August 2, leaves reductions in chemotherapy reimbursement rates on the table, and oncologists are concerned that a proposal to cut those rates could reemerge in the next round of cuts.

The biggest question is whether the 29.5% cut in Medicare physician fees, scheduled for January 1, 2012, will go into effect. This massive payment cut is called for under the Sustainable Growth Rate (SGR) formula, which is used to set Medicare payments to physicians.

Physicians' groups, led by the American Medical Association, lobbied Congress to include a permanent fix to the SGR in the deficit reduction package. They argued that while fixing the SGR carries a \$300 billion price tag, getting the job done now would save the government money down the road. Instead, lawmakers left the SGR out of the package completely.

The new law, the Budget Control Act of 2011, puts into place about \$1 trillion in spending cuts over the next decade from the discretionary side of the federal budget. Although these immediate cuts do not directly affect physicians, they do impact graduate medical education. Medical students who take out subsidized graduate student loans on or after July 1, 2012, will have to start paying the interest on those loans earlier.

The next round of budget cuts will be determined by the Joint Select Committee on Deficit Reduction, also known as the super com-

mittee. The 12-member panel is made up of legislators from both parties and both houses of Congress: Senators Max Baucus (D-MO), John Kerry (D-MA), Jon Kyl (R-AZ), Pat Toomey (R-PA), Patty Murray (D-WA), and Rob Portman (R-OH) and Representatives Xavier Becerra (D-CA), Dave Camp (R-MI), James E. Clyburn (D-SC), Jeb Hensarling (R-TX), Fred Upton (R-MI), and Chris Van Hollen (D-MD). The appointments were made by party leaders in the House and Senate.

The recommendations must be approved by a majority vote before the joint committee can forward them to the full Congress.

"There's a lot of concern that the committee will be deadlocked," said Edwin Park, vice president for health policy at the Center on Budget and Policy Priorities.

The law requires the joint committee to draft legislation cutting another \$1.2 trillion to \$1.5 trillion in federal spending over 10 years. The committee has broad authority to consider spending cuts, taxes, and other changes across both discretionary and mandatory government programs. Funding for Affordable Care Act programs is also on the table.

The joint committee must vote on recommendations by November 23, and lawmakers must vote on the joint committee's bill by December 23.

Oncologists will be watching to see whether the joint committee considers reductions in chemotherapy reimbursement rates. Early negotiations on the debt deal had included a proposal to reduce chemotherapy re-

imbursement from the average sales price (ASP) plus 6% to ASP plus 4%. The proposal did not make it into the final law but could reemerge when the joint committee begins looking for cuts this fall.

Dr. Allen S. Lichter, chief executive officer of the American Society of Clinical Oncology, said that type of cut would be a blow to oncology practices in the United States, especially community oncology practices. "To go from 6% to 4% would just push a huge number of practices off a cliff," Dr. Lichter said. "The ability to recover from that would be extremely difficult."

Moreover, a cut to the reimbursement rate for chemotherapy drugs would be short-sighted, Dr. Lichter said. The proposal would save an estimated \$3 billion over 10 years, but that amount is a "rounding error" when it comes to the deficit problem, he said, and would have a significant impact on the nation's ability to deliver cancer care.

To keep the legislation from getting bogged down in the Senate, the Budget Control Act requires that the joint committee's bill be given a fast-track, up-or-down vote requiring a simple majority to pass each chamber. Should the bill fail, or if the committee deadlocks, the Budget Control Act calls for automatic cuts across the federal government totaling \$1.2 trillion over 10 years.

Those cuts would include up to a 2% reduction in Medicare physician payments beginning in 2013. Under a worst-case scenario, physicians could face not only the 29.5% SGR cut in January, 2012, but another 2%

annual fee cut starting the following year.

Although there is bipartisan agreement in Congress about the need to permanently replace the SGR and to stop the looming 29.5% cut, it's impossible to know what will happen, Dr. Lichter said.

What is clear, he said, is that the cost of the fix is climbing. If the SGR had been replaced in 2006, the total cost would have been less than \$50 billion, Dr. Lichter said, but today the price tag is around \$300 billion and growing. "Everyday we wait, the

problem increases in magnitude."

ASCO has been urging Congress to replace the scheduled Medicare payment cuts with small, annual increases for a few years while Medicare officials test out new physician payment methods, including accountable care organizations and bundled payments. Once the results from those tests are in hand, policymakers could craft an SGR fix that incorporates successful new payment approaches, Dr. Lichter said.

Shawn Martin, director of government relations for the American

Osteopathic Association, said the joint committee's deliberations could give physicians a chance to open up a real debate over permanently fixing the SGR.

"We think it's an opportunity to have a very real and meaningful conversation regarding what the SGR baseline debt really means to the long-term stability of the program," Mr. Martin said.

There's no guarantee that the joint committee would repeal the SGR, Mr. Martin said, but it will at least get people talking about the problem.