



COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

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Pictured above: breast cancer cells

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Scientific journals are not the only medium carrying reports that could make a difference in how your practice and your patients fare. Now there are countless podcasts, videos, and real-time Web-based broadcasts of oncology conferences, panel discussions, and lectures. Here, we explore the educational offerings of some of the more popular Web sites for oncologists.

Washington Update

48 Chemotherapy drug shortages present challenges for oncologists and their patients

Alicia Ault

An ongoing shortage of some crucial chemotherapy drugs is forcing oncologists to scramble for supplies or to find therapeutically equivalent alternatives, if there are any. In some cases, oncologists are creating a triage system whereby the patient who is most likely to be cured will receive the therapy that's in short supply.

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LETTER FROM THE EDITOR

9 Beltway battles aside, oncology is ready to take on the New Year

David H. Henry, MD, FACP, Editor, *Pennsylvania Hospital, Philadelphia, PA*

In this first issue of 2011, patient care, safety, and quality of life are the subtext in articles on breast cancer and non-Hodgkin's lymphoma therapies, serotonin syndrome, and elderly cancer survivors. These articles and others in this issue provide context to the daily realities of the practice-based oncologist.

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Treatment of women with refractory metastatic breast cancer has presented a particularly difficult challenge. Now, a novel nontaxane microtubule inhibitor, eribulin (Halaven), has proved that overall survival can be extended in this patient group.

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Peter P. Lee, MD, PhD, and Peter J. Rosen, MD, *Tower Cancer Research Foundation, Beverly Hills, CA, and Roy and Patricia Disney Family Cancer Center, Providence Saint Joseph Medical Center, Burbank, CA*

Radioimmunotherapy using CD20-targeted immunoconjugates remains a viable option for patients with non-Hodgkin's lymphoma (NHL). Despite their apparent utility, these drugs have been underutilized for a variety of reasons, including the somewhat complex process of drug delivery, concerns about possible late toxicities, and economic factors. In this article, the authors review the data supporting their use in B-cell NHL and discuss other potential indications.

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Joelle L. Lichtman, MA, CAPS, LEED Green Associate, and Stuart M. Lichtman, MD, FACP, *Department of Design and Environmental Analysis, College of Human Ecology, Cornell University, Ithaca, NY, and Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, and Commack, NY*

There are more than 9.5 million cancer survivors in the United States, and the majority of them are older people who will need a safe environment to live out their lives. Appropriately designed homes for older adults can greatly enhance their quality of life and allow them to "age in place." The older person's current home usually needs modifications to ensure safety and reduce barriers to performing tasks of daily living. This article explores recommended home modifications, discusses where people can obtain help in carrying out the necessary modifications, and reviews housing options for the elderly.

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REVIEW

37 Use of MammoSite balloon brachytherapy for early-stage breast cancer

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MammoSite balloon brachytherapy (MBT) is a form of accelerated partial breast irradiation used in the setting of breast-conserving treatment for early-stage breast cancer. MBT permits effective irradiation of the tumor bed with a diminished impact on normal surrounding tissue and without the protracted course of treatment required with whole breast radiation therapy (WBRT). Although MBT remains a relatively new treatment modality compared with WBRT, mounting evidence continues to support a role for MBT as a useful alternative to WBRT.

CASE REPORT

41 A probable serotonin syndrome complicating a routine screening colonoscopy procedure

Celeste N. Rudisill, PharmD, Zaina P. Qureshi, PhD, MPH, John M. Armstrong, PhD, LeAnn B. Norris, PharmD, BCPS, BCOP, and Charles L. Bennett, MD, PhD, MPP, *South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, University of South Carolina, Columbia, SC; Lead Horse Technologies, Inc., Junction City, KS; and Hollings Cancer Center, Medical University of South Carolina, Charleston, SC*

In the medical literature, serotonin syndrome is well documented as an adverse event associated with various classes of medications. The most famous case of serotonin syndrome occurred when Libby Zion died shortly after receiving meperidine in combination with phenelzine, a monoamine oxidase inhibitor. The authors report on a patient treated with duloxetine (Cymbalta), a serotonin and norepinephrine reuptake inhibitor, who developed a probable serotonin syndrome after receiving IV meperidine and midazolam as preprocedure anesthesia for a routine screening colonoscopy.

PRACTICAL BIOSTATISTICS

43 Measuring subjective phenomena

David L. Streiner, PhD, CPsych, and Geoffrey R. Norman, PhD, *Department of Psychiatry, University of Toronto, Toronto, Canada, and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

Once we get away from body counts, direct measurements, and laboratory test results and enter the realm of phenomena such as quality of life or pain, we are trying to measure subjective states. Over the years, techniques have been developed to do this in a reliable, valid way. This article introduces readers to what to look for in scales tapping these domains.

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Beltway battles aside, oncology is ready to take on the New Year

David H. Henry, MD, FACP, Editor | Pennsylvania Hospital, Philadelphia, PA

As we gear up for 2011, a new Congress has already been sworn in, and the Republican majority has stated its intention to dismantle the healthcare reform law of 2010. So, hang on: It should be quite a ride in Washington this year. Let's hope that President Obama can reenact Bill Clinton's success in working with a Republican Congress and build on last year's progress in healthcare, rather than presiding over its demise.

Since we cannot figure out Washington, let's turn to this month's issue of *Community Oncology*. On page 15, we feature a new drug for patients with refractory metastatic breast cancer. Eribulin (Halaven), a nontaxane microtubule inhibitor, was approved this past November by the US Food and Drug Administration (FDA) for patients who have failed to respond to at least two previous chemotherapy regimens and have been treated with an anthracycline and a taxane. The drug showed an improvement in overall survival in its phase III pivotal trial.

Still in the realm of breast cancer, we have a review of MammoSite balloon brachytherapy for early-stage breast cancer (page 37). The device is inserted at the time of lumpectomy, and patients complete their course of radiation therapy in as few as 5 days with twice-daily treatments. Cosmetic and therapeutic outcomes match those achieved with traditional external-beam radiation therapy to the entire breast.

Much has been written about life after cancer in the cancer survivor population, but what if the survivor is elderly? Discharging such a patient might mean he or she has to enter an assisted-living or retirement community, instead of returning to the family home and the workplace. An article on page 32 examines how appropriately designed homes for older survivors can enhance their quality of life. It also provides information on finding help in executing the modifications and offers a review of other housing options.

Radioimmunotherapy (RIT) using CD20-targeted immunoconjugates for patients with non-Hodgkin's lymphoma continues to be underused, even though those of us in active practice are aware of it. The reasons for this are often logistical because of the drug delivery, the potential toxicity of tositumomab

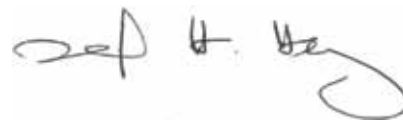
(Bexxar) and ibritumomab tiuxetan (Zevalin), and economic factors. A review of RIT for non-Hodgkin's lymphoma on page 24 reminds us of how effective these therapies can be, especially if they are cycled into the treatment regimens earlier rather than later.

Most of us in practice today are familiar with the case of Libby Zion, the young woman who died in a New York hospital from a drug-drug interaction that caused a serotonin-release syndrome. (Her untimely death led to current regulations that residents may not work more than 80 hours a week.) On page 41, we report on another probable serotonin syndrome reaction that occurred as a complication of a routine screening colonoscopy, a reminder that this syndrome can and does still occur. In the current case, the patient received preprocedure anesthesia with IV meperidine and midazolam, a short-acting benzodiazepine.

How do physicians receive their information and continue their education? The answer is online, according to our article on page 46, where sites such as OncologyTube.com and ResearchToPractice.com are examined.

This month, our biostatisticians have provided another wonderfully written and easily understandable piece on the evaluation of subjective phenomena (page 43). Washington Update (page 48) highlights a growing crisis in oncology centering on a shortage of chemotherapy drugs. The American Society of Anesthesiologists, American Society of Clinical Oncology, American Society of Health-System Pharmacists, and the Institute for Safe Medication Practices are working closely with the FDA to try to remedy this dire situation.

Oncology is truly an exciting and vibrant specialty, with courageous patients and dedicated caregivers buoyed by expanding biotechnology, which facilitates a greater understanding of how to treat cancer and what therapies are best. It's still the best specialty there is. Have a happy New Year!



David H. Henry, MD, FACP
Editor

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Eribulin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane

Novel, nontaxane microtubule dynamics inhibitor improves overall survival in patients with refractory metastatic breast cancer.

Eribulin (Halaven) is a synthetic analog of halichondrin B, a nontaxane microtubule dynamics inhibitor extracted from the marine sponge *Halichondria okadai*, with a novel mechanism of action among tubulin-targeted agents. Preclinical studies have shown that eribulin is active against cancer cell lines that are taxane resistant as a result of β -tubulin mutations.¹

A recently completed phase III trial (the EMBRACE study²) in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane showed that eribulin therapy significantly improved overall survival (OS) compared with treatment chosen by their physician. On the basis of these findings, eribulin was recently approved for the treatment of patients with metastatic breast cancer who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting and received at least two chemotherapeutic regimens for the treatment of metastatic disease.

Another ongoing phase III trial (E7389-G000-301; ClinicalTrials.gov ID No. NCT00337103) is comparing eribulin with capecitabine (Xeloda) in this treatment setting.³

Phase II trials

Two recent single-arm, open-label, phase II clinical trials have demonstrated eribulin's activity and manageable safety profile in patients with refractory metastatic breast cancer.^{4,5} In

What's new, what's important

Microtubule may not be the "sexiest" target in cancer therapy, but focusing on it is definitely helping more patients in the clinic than any other "novel targeted" therapy. Vinca alkaloids, taxanes, and epothilones are all extremely important in the treatment of breast cancer. But none of them has been shown to improve overall survival in heavily pretreated breast cancer patients. Now, to everyone's surprise, eribulin (Halaven), a novel nontaxane microtubule inhibitor, has proved that overall survival can be extended in this patient group.

It is interesting to note that in the randomized phase III study described here, the patients were treated with taxanes and anthracyclines and many received vinorelbine before being treated with eribulin. They still responded to this novel drug. It is a microtubule-stabilizing agent; unlike the taxanes and epothilones, it inhibits microtubule polymerization, which causes hyperstabilization of polymerized microtubules.

Eribulin is approved by the US Food and Drug Administration for patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for metastatic disease. The recommended dose of eribulin is 1.4 mg/m² given IV over 2–5 minutes on days 1 and 8 of a 21-day cycle. Dose modification is recommended in patients with hepatic impairment. The most common side effects of this drug are neutropenia, anemia, asthenia/fatigue, alopecia, and peripheral neuropathy.

Eribulin is a promising therapeutic option for patients with metastatic breast cancer, and future studies will define its role in the management of early-stage breast cancer.

— Jame Abraham, MD, *Section Editor*

the study reported by Vahdat et al,⁴ 103 heavily pretreated patients (median of four prior regimens) were given eribulin (1.4 mg/m²) as a 2- to 5-minute IV infusion on days 1, 8, and 15 of a 28-day cycle. Because of neutropenia at day 15, an alternative regimen of eribulin on days 1 and 8 of a 21-day cycle was administered. All of the patients had received prior treatment with an anthracycline and a taxane.

In the per-protocol cohort (n = 87), eribulin achieved an independently reviewed objective response rate (ORR) of 11.5% (all partial responses) and a clinical benefit rate (partial responses plus stable disease \geq 6 months) of 17.2%. The median duration of re-

sponse was 5.6 months; the median progression-free survival (PFS), 2.6 months; and the median OS, 9.0 months. The most common treatment-related grade 3 or 4 toxicities were neutropenia (64%), leukopenia (18%), fatigue (5%), peripheral neuropathy (5%), and febrile neutropenia (4%).

In the study reported by Cortes et al,⁵ 291 patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine were given eribulin (1.4 mg/m²) as a 2- to 5-min-

Summary by Matt Stenger, MS; reviewed by Debu Tripathy, MD, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA.

ute IV infusion on days 1 and 8 of a 21-day cycle. The ORR was 9.3% by independent review and 14.1% by investigator review (all partial responses); the stable disease rate was 46.5%; and the clinical benefit rate was 17.1%. The median duration of response was 4.1 months; the median PFS was 2.6 months; and the median OS was 10.4 months. The most common treatment-related grade 3 or 4 toxicities were neutropenia (54%), leukopenia (14%), asthenia/fatigue (10%), neuropathy (7%), and febrile neutropenia (6%).

EMBRACE study results

In the EMBRACE study (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin; ClinicalTrials.gov ID No. NCT00388726),² 762 patients with locally recurrent or metastatic breast cancer with disease progression within 6 months of their last chemotherapy regimen were randomized 2:1 in open-label fashion to receive eribulin 1.4 mg/m² IV over 2–5 minutes on days 1 and 8 every 21 days (n = 508) or the treatment of their physician's choice (n = 254) selected prior to randomization. The physician's choice of treatment consisted of any single-agent therapy (chemotherapy, hormonal, or biologic therapy) or supportive care only. Eligible patients had to have received two to five prior chemotherapy regimens, including at least two for advanced disease and including prior anthracycline and taxane treatment in the adjuvant or metastatic setting. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and were ineligible if they had pre-existing neuropathy higher than grade 2. The primary endpoint was OS.

Patient population

The median age was 55–56 years in the two patient groups. Each group had received a median of four prior treatments with chemotherapy; 73%–74%

TABLE 1

Key efficacy outcomes in the EMBRACE study

Outcome measure	Eribulin (n = 503)	Treatment of physician's choice (n = 247)
OS at 12 months, %	53.9	43.7
Median OS, months	13.12	10.65
Hazard ratio	0.81 (P = 0.041)	

Outcome measure	Independent review (n = 508)		Investigator review (n = 254)	
	Eribulin	Treatment of physician's choice	Eribulin	Treatment of physician's choice
Median PFS, months	3.7	2.2	3.6	2.2
Hazard ratio	0.87 (P = 0.14)		0.76 (P = 0.002)	

Outcome measure	Independent review (n = 468)		Investigator review (n = 214)	
	Eribulin	Treatment of physician's choice	Eribulin	Treatment of physician's choice
ORR, %	12.2	4.7	13.2	7.5
P value	0.002		0.028	

EMBRACE = Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin; OS = overall survival; PFS = progression-free survival; ORR = overall response rate (complete responses + partial responses)
Source: Twelves et al²

TABLE 2

Percentage of patients in the EMBRACE study with grade 3 or 4 adverse events occurring with a frequency of 2% or more

Adverse event	Eribulin (n = 503)		Treatment of physician's choice (n = 247)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Neutropenia	21.1	24.1	14.2	6.9
Leukopenia	11.7	2.2	4.9	0.8
Anemia	1.8	0.2	3.2	0.4
Febrile neutropenia	3.0	1.2	0.8	0.4
Nonhematologic				
Asthenia/fatigue	8.2	0.6	10.1	0
Peripheral neuropathy	7.8	0.4	2.0	0
Nausea	1.2	0	2.4	0
Dyspnea	3.6	0	2.4	0.4
Mucosal inflammation	1.4	0	2.0	0
Hand-foot syndrome	0.4	0	3.6	0

EMBRACE = Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin
Source: Twelves et al²

had received capecitabine in the past. More than 90% of patients in each group had an ECOG performance status of 0 or 1. The treatment of physician's choice consisted of chemotherapy in 96% of patients, including (in order of frequency) vinorelbine, gem-

citabine (Gemzar), capecitabine, taxanes, and anthracyclines. A small proportion of patients received hormonal therapy; no patients received biologic therapies or best supportive care only.

Table 1 summarizes the key efficacy outcomes in this study, as reported

at the 2010 Annual Meeting of the American Society of Clinical Oncology. The data differ in small ways from the numbers reported in the official package labeling.⁶

Survival

On intent-to-treat analysis, the median OS was 13.1 months in the eribulin group versus 10.7 months in the group that received treatment of their physician's choice, yielding a significant 19% reduction in the risk of death with eribulin (hazard ratio [HR], 0.81; $P = 0.041$). OS at 1 year was 53.9% versus 43.7% for those receiving treatment chosen by their physician. In the intent-to-treat population, eribulin was associated with a nonsignificant improvement in PFS on independent review (median duration, 3.7 months vs 2.2 months; HR, 0.87; $P = 0.14$) but a statistically significant improvement on investigator review (median duration, 3.6 months vs 2.2 months; HR, 0.76; $P = 0.002$). In the per-protocol population, PFS was significant on both independent review ($P = 0.02$) and investigator review ($P < 0.001$).

Response rates

Overall response rates for eribulin and treatment of physician's choice patients were 12.2% and 4.7% (P

$= 0.002$), respectively, on independent review and 13.2% and 7.5% ($P = 0.028$), respectively, on investigator review. Clinical benefit rates (rates of complete plus partial responses and stable disease ≥ 6 months) were 22.6% versus 16.8% on independent review and 27.8% versus 20.1% on investigator review.

Safety profile

Eribulin treatment had a manageable safety profile. Overall, adverse events occurred in 99% of eribulin-treated patients and 93% of patients who received treatment of their physician's choice. Serious adverse events (grade 3 or higher) occurred in 25% and 26% of patients, respectively, and adverse events leading to discontinuation of treatment were reported in 13% and 15% of patients, respectively. Adverse events led to dose reduction in 17% and 16% of patients, respectively, and to dose delays in 35% and 32%, respectively. Fatal adverse events occurred in 4% of eribulin-treated patients and 7% of patients given treatment of their physician's choice and were considered treatment related in 1% of patients in each group.

Among hematologic adverse events, grade 3 or 4 neutropenia and leukopenia and febrile neutropenia were much

more common among patients treated with eribulin (Table 2). Among non-hematologic adverse events, grade 3 peripheral neuropathy was more common among eribulin-treated patients than among those receiving the treatment of their physician's choice.

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From the Oncologist's Perspective

Making a difference in refractory breast cancer

Debu Tripathy, MD | University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Over the years, we have adopted the dogma that we lose the ability to modify the natural history of breast cancer in later lines of therapy. In fact, the US Food and Drug Administration (FDA) has followed the

unwritten rule that a survival advantage is expected for drug approval in the first line, but beyond this, an improvement in disease-free survival alone would suffice to get the nod.

This predilection is evidenced by the approval of ixabepilone (Ix-

empra) for refractory disease in the absence of a survival advantage,^{1,2} whereas the approval of gemcitabine (Gemzar) and capecitabine (Xeloda) required trial designs that compared standard taxane therapy with and without the drug in question.^{3,4}

In fact, these trials did not allow the popular crossover-upon-disease-progression design to avoid confounding the survival endpoint.

In keeping with this paradigm, the FDA recently has begun steps to withdraw accelerated approval of bevacizumab (Avastin) in the first-line setting because of the absence of a survival benefit in breast cancer patients, despite confirmatory evidence of improved disease-free survival in multiple trials.⁵⁻⁷ The recent demonstration of a survival advantage of the microtubule inhibitor eribulin (Halaven) over standard monotherapy in patients whose disease has progressed after two or more lines of chemotherapy for advanced breast cancer has shattered the nihilistic dogma that one cannot impact survival this late in a patient's course. The early data, as well as the clinical trial design and, ultimately, the results of the pivotal eribulin trial (EMBRACE), are instructive as to how we should make decisions in later lines of therapy and may represent a paradigm for future drug development in this setting.

Finally, as with all drugs that show activity in advanced disease, there will be several potential strategies to evaluate this drug in earlier-line settings, where the impact on survival and curability would be the greatest.

Using progression-free survival as a surrogate for overall survival

The use of disease-free survival or response rate as a surrogate to overall survival continues to be controversial. Overviews of breast cancer trials have not convincingly shown this relationship, in part because most trials are not powered to detect survival differences.⁸⁻¹⁰ It has also been argued that the many therapies patients tend to receive in the refractory setting confound the ability to properly assess survival as a measure of the clinical benefit of therapies used in earlier lines.

Nevertheless, in the new world of

cost-benefit metrics, it makes sense that the new bar has moved to an improvement in either overall survival or quality of life, but not disease-free survival alone. Because median survival is lower with subsequent lines of therapy, an absolute improvement of 2-3 months would constitute a larger odds ratio for survival, and, consequently, it might be easier to demonstrate improvement in survival with active therapies, contrary to the usual thinking.¹¹ Therefore, although it may have seemed like a bold move to make survival the primary endpoint in the randomized eribulin trial, it probably was a rational decision all along. The practical design of physician's choice of treatment, as opposed to using a fixed agent in the comparator arm, was also a logical, albeit unconventional, choice for this pivotal trial, because there is no consensus on the "standard" therapy in later lines of therapy for breast cancer.

Eribulin in refractory breast cancer

The pivotal eribulin trial randomized patients with more than two prior chemotherapy regimens for advanced breast cancer, including taxane and anthracycline therapy, with about 75% of patients also having received capecitabine.¹² An improvement in median survival of 2.5 months with acceptable tolerability was the key to eribulin's approval, although this advantage was accompanied by an increase in the incidence of febrile neutropenia and neuropathy when compared with the control arm. The real-life comparator arm of chemotherapy agents commonly used in refractory disease ended up being an asset, rather than a liability, as oncologists can relate to the dilemma faced in treating these patients, with several options available but none that stands out as being particularly effective.

So far, eribulin is the only drug that has shown a survival advantage in late lines of therapy for breast can-

cer. Whether this finding is due to the lack of previous trials that have aimed for survival differences is not clear. It may also be related to the critical role of the microtubule apparatus and the fact that taxoids are highly effective drugs but are limited by mechanisms of resistance, including membrane transporters and mutations in tubulin, which do not apply to newer microtubule inhibitors such as eribulin. The fact that patients on this trial had received previous taxanes might represent the cytotoxic version of "oncogene addiction," whereby critical oncogenic drivers are postulated to be important, even after clinical resistance develops. This phenomenon has been observed with therapies that target the human epidermal growth factor receptor 2 (HER2), manifested by the effectiveness of HER2 blockade, even after disease progression occurs on trastuzumab (Herceptin).¹³⁻¹⁵ In the case of eribulin, it appears that the microtubule may be the normal cellular analogy of an oncogene—a critical cellular component that can still be targeted for clinical benefit but via a different mechanism once resistance develops to a particular class of microtubule inhibitor.

What's next for eribulin?

The benefits seen in advanced breast cancer, coupled with a reasonable side-effect profile, make eribulin a promising drug for use not only in the refractory setting but clearly as a good candidate for testing in the upfront metastatic and adjuvant settings. These trials are planned or under way. There are many questions that need to be answered. How does this drug perform in combination with alkylators and anthracyclines? Is there synergy and tolerability with trastuzumab in HER2+ disease? Can the dosing schedule be optimized, as is the case with ixabepilone and nanoparticle albumin-bound paclitaxel (Abraxane), where the FDA-approved dose might not be the most effective and

tolerable. Is there synergy, or at least impressive additivity, when eribulin is combined with HER2-targeted or antiangiogenic agents (the latter, of course, now less likely to be tested given the FDA's decision on bevacizumab)? In the adjuvant setting, eribulin could be tested as a new standard for anthracycline-free therapy. Finally, the contemporary burning question for all drugs must be explored as well—are there predictive markers or genetic signatures that predict who will derive the greatest benefit?

As the oncology community begins to use this agent more and subsequent studies further define alternative regimens and safety signals, a clearer picture will emerge on this interesting drug. The results of the next generation of studies might also demonstrate whether a survival advantage in late lines of therapy will be indicative of a much more effective drug used earlier and in the adjuvant setting.

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Radioimmunotherapy for CD20-positive B-cell non-Hodgkin's lymphoma

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Radioimmunotherapy (RIT) using CD20-targeted immunoconjugates remains a viable option for patients with non-Hodgkin's lymphoma (NHL). In addition, the use of RIT as a consolidation therapy is an appealing strategy, given the short course of well-tolerated regimens. The two available RIT agents—yttrium-90 ibritumomab and iodine-131 tositumomab—have undergone extensive trials leading to specific approvals for certain categories of indolent NHL. Despite their apparent utility, these drugs have been underutilized for a variety of reasons, including the somewhat complex process of drug delivery, concerns about possible late toxicities, and economic factors. In this article, the authors review the data supporting the label indications for use of these agents and discuss potentially interesting off-label uses of these drugs as well.

B-cell non-Hodgkin's lymphomas (NHLs) comprise at least 85% of all NHLs seen in the United States and Western countries. Almost all of these lymphomas are characterized by the presence of the CD20 antigen on the cell surface. CD20 is a stable, nonmodulated cell surface antigen; it was the first target successfully exploited by monoclonal antibody therapy when rituximab (Rituxan) was found to be clinically active in the late 1990s.¹

Treatment with the “naked” or “cold” antibody alone resulted in an overall response rate (ORR) of nearly 50% in previously treated patients with relapsed/refractory low-grade lymphomas.² Follicular lymphoma (FL) was found to be more responsive to therapy than small lymphocytic lymphoma (SLL) or chronic lymphocytic leukemia (CLL), probably due to the higher density of surface-bound CD20 present in that category of lymphoma. Other lymphoma types, including marginal zone lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL), all have showed varying degrees of response to such therapy.³⁻⁵

Subsequently, rituximab was successfully combined with standard chemotherapy regimens. The first major advance occurred in DLBCL, where the combination of rituximab with cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) was found to be superior to standard CHOP in terms of response rate (RR), progression-free survival (PFS), and overall survival (OS).⁶

More recently, rituximab-based combinations have been shown to improve RR and PFS in studies of FL and CLL.^{7,8}

The successes seen with rituximab-based therapy of low-grade lymphomas have been further amplified by the use of various programs of maintenance rituximab therapy, which are usually given over 1–2 years. In the recently presented PRIMA trial, previously untreated patients with FL were randomized between maintenance rituximab and observation. The results showed a substantial increase in PFS at 2 years (82% vs 66%) favoring maintenance rituximab therapy.⁹

Despite the obvious efficacy of rituximab, its mechanism of action has not been totally explained. The most likely mechanisms include antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, as well as direct apoptotic effect. To further exploit the efficacy of antibody therapy, the concept of “arming” the antibody with a radionuclide, toxin, or chemotherapeutic agent was conceived. In the case of the lymphomas, radioimmunotherapy (RIT) using CD20-targeted immunoconjugates was developed.

The two available RIT agents—yttrium-90 (Y-90) ibritumomab (Zevalin) and iodine-131 (I-131)

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tositumomab (Bexxar)—have undergone extensive trials leading to specific approvals for certain categories of indolent NHL. Despite their apparent utility, these drugs have been underutilized for a variety of reasons, including the somewhat complex process of drug delivery, concerns about possible late toxicities, and economic factors.¹⁰

Characteristics of Y-90 ibritumomab and I-131 tositumomab

The major structural difference between Y-90 ibritumomab and I-131 tositumomab is the tight chelation formed by tiuxetan to Y-90 leading to a stable bond. This characteristic has made it possible to calculate the dose of Y-90 ibritumomab using platelet count and weight alone. On the other hand, in the case of I-131 tositumomab, the variable rates of dehalogenation of the I-131 make whole-body counting and formal dosimetry for each patient a necessity. In the case of Y-90 ibritumomab, the monoclonal antibody is the murine version of rituximab, whereas tositumomab is a CD20-directed antibody unrelated to rituximab that targets a different but overlapping epitope on CD20 and also has a distinct mechanism of action on B-cell lines when compared with rituximab.¹¹

Yttrium-90 is a pure beta emitter and thus can be administered easily with plastic shielding in a standard office setting.¹² On the other hand, Y-90, with its lack of gamma emission, cannot be used for scanning purposes. For this reason, indium-111 (In-111) has been substituted for Y-90 for the so-called scanning dose.

Whole-body scans are required in the case of Y-90 ibritumomab to assure adequate biodistribution in the United States. The incidence of unfavorable biodistribution is so rare that the European agencies no longer require the scanning dose. In the case of I-131 tositumomab, radioactive de-

TABLE 1

Physical characteristics of indium-111, yttrium-90, and iodine-131

Characteristic	Indium-111	Yttrium-90	Iodine-131
Decay	Electron capture	Beta emission	Beta and gamma emission
Mean energy, keV	Gamma-2: 171.3 Gamma-3: 245.4	750–935	Beta: 191.6 Gamma: 364.5
Half-life, days	2.81	2.67	8.04
Radiation exposure	8.3×10^{-4} C/kg/h	8.3×10^{-3} C/kg/h	2.2 R/mCi/h
Path length, mm	–	5	0.8

C = coulomb, R = roentgen, mCi = millicurie

Source: Zevalin [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc; 2009; Bexxar [package insert]. Seattle, WA: Corixa Corp; 2003.

cay results by both gamma and beta emission, meaning that body scans and counts can be accomplished with the same isotope. The gamma decay of I-131 tositumomab requires strict precautions, including lead shielding of the drug, increased safeguards regarding patient-family interactions, and care of body fluids. In some states, hospitalization may be required until the body counts reach a determined level. The characteristics of the three radionuclides are shown in Table 1.

Treatment regimens for I-131 tositumomab and Y-90 ibritumomab

The treatment programs for both agents are shown in Figures 1 and 2. In each case, there is a day 1 scanning/dosimetry administration of radionuclide using a tracer dose followed, approximately 1 week, later by the therapeutic dose. Both the scanning and therapeutic doses are preceded by an infusion of an anti-CD20 antibody; for Y-90 ibritumomab, it is rituximab at 250 mg/m², and for I-131 tositumomab, it is tositumomab at 450 mg. This convention is employed to deplete the normal B-cell population and to enhance biodistribution of the therapeutic dose. Scans are often performed on the third or fourth day (in the case of Y-90 ibritumomab) to assess whether there is excessive accumulation of radioactivity in a normal organ, which could result in radiation-induced in-

jury. These events have been almost nonexistent and, as mentioned, have led to the abandonment of this requirement in Europe.

In the case of I-131 tositumomab, whole-body counting is used to determine the appropriate dose required to administer 75 cGy of radiation for those with platelet counts at or above 150,000/mm³. For patients with a platelet count between 100,000/mm³ and 149,999/mm³, the goal is to administer 65 cGy. With Y-90 ibritumomab, the dose is calculated based on body weight, with 0.4 mCi/kg for patients whose platelet counts are at or above 150,000/mm³ or 0.3 mCi/kg for platelet counts between 100,000/mm³ and 149,999/mm³. The dose of Y-90 ibritumomab should not exceed 32 mCi regardless of the patient's body weight.

To qualify for treatment, a bone marrow examination must show <25% involvement of the cellular marrow by lymphoma and no evidence of impaired bone marrow reserve, so as to reduce the risk of prolonged and severe cytopenias. Although repeat dosing has been studied, it is not considered a standard therapeutic approach. Likewise, use of these agents following autologous stem cell transplantation has been limited and is not advised.¹³

Safety issues

The major expected complication associated with radionuclide therapy

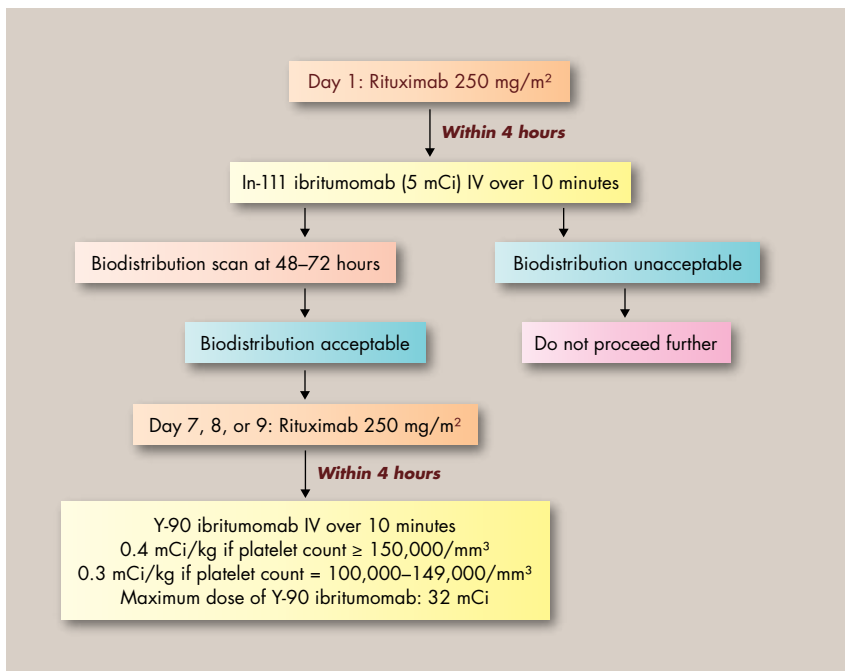


FIGURE 1 Dosing schedule for yttrium-90 (Y-90) ibritumomab. Source: Zevalin [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc; 2009.

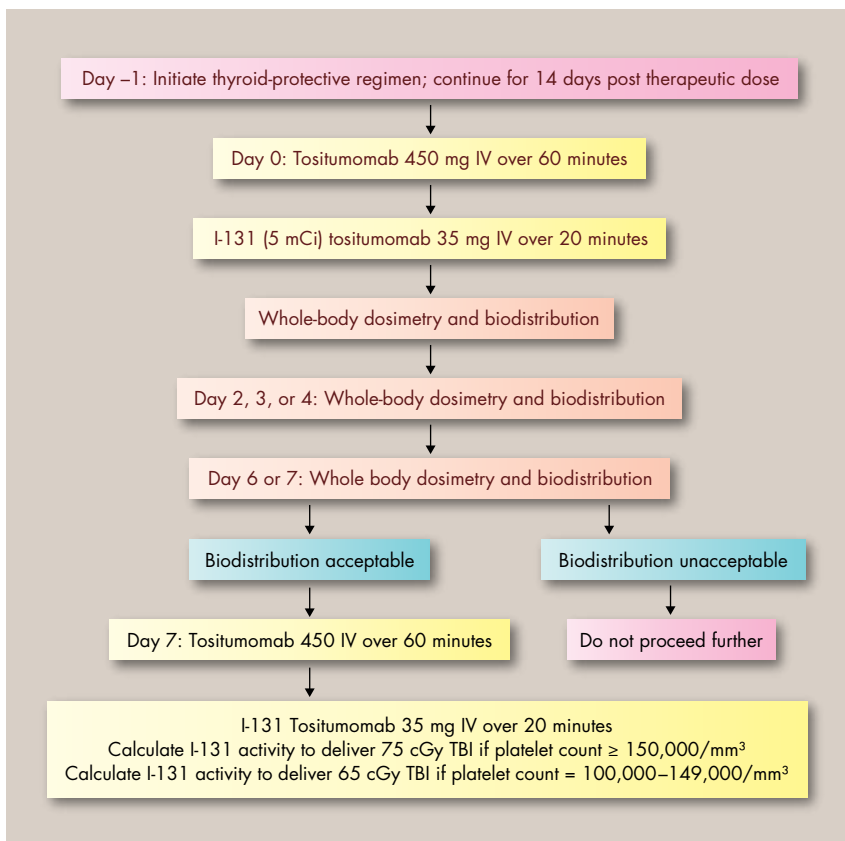


FIGURE 2 Dosing schedule for iodine-131 (I-131) tositumomab. TBI = total body irradiation. Source: Bexxar [package insert]. Seattle, WA: Corixa Corp; 2003.

is myelosuppression. This side effect differs in its timing from that seen with conventional chemotherapeutic agents, with the time of onset of neutropenia and thrombocytopenia beginning in the third to fourth week and the nadir usually occurring between weeks 5 and 7, although it may vary. Recovery is usually evident by week 12.

Typical nadir counts and times to recovery are shown in Table 2. As shown, although grades 3 and 4 events are common, the incidence of febrile neutropenia is low, probably the result of a lack of the type of mucosal injury associated with cytotoxic chemotherapy. Growth factor support is not usually required.

Other side effects of treatment include the infusion reactions associated with rituximab administration and cutaneous toxicities, which are uncommon. Reactivation of viral hepatitis B¹⁴ and development of JC virus-related progressive multifocal leukoencephalopathy¹⁵ have also been reported with rituximab. The incidence of myelodysplastic syndromes (MDS) and acute myelogenous leukemia (AML) following radionuclide therapy for NHL has been a theoretic concern, but the reported occurrences do not appear to exceed those anticipated with chemotherapeutic treatments.¹⁶

The ability to harvest stem cells and administer cytotoxic agents following RIT is a potential issue. Certainly, stem cell harvests have been successfully completed after treatment, but the number of reports is limited. Likewise, patients are generally able to receive further cytotoxic therapies after RIT, particularly if there is a significant time interval allowed for recovery, but more data are needed.^{17,18}

In the case of I-131 tositumomab, despite the prophylactic use of Lugol's solution and similar compounds, the potential of developing hypothyroidism remains.

TABLE 2

Hematologic toxicities after Y-90 ibritumomab treatment

Toxicity	Median time to nadir, days (range)	Median time to recovery, days (range)	Percentage of patients
Grade 3 neutropenia (ANC < 1,000–500/mm ³)	44.5 (14–775)	20 (4–388)	40.2
Grade 4 neutropenia (ANC < 500/mm ³)	46 (11–70)	28 (6–385)	26.5
Grade 3 thrombocytopenia (platelet count < 50,000/mm ³ to 25,000/mm ³)	35 (14–64)	20 (4–654)	58.8
Grade 4 thrombocytopenia (platelet < 25,000/mm ³)	39.5 (36–55)	35 (24–847)	2.0

ANC = absolute neutrophil count

Source: Smith et al²⁶

Clinical studies on Y-90 ibritumomab

The current label indications for Y-90 ibritumomab are for the treatment of (1) relapsed or refractory low-grade or follicular B-cell NHL and (2) as consolidation therapy for those with FL who have achieved a partial response (PR) or a complete response (CR) to first-line chemotherapy.

Results in patients with relapsed/refractory indolent lymphoma

After phase I and II studies established evidence of the efficacy and safety of Y-90 ibritumomab, several critical phase II/III trials were conducted. A phase III trial randomized patients who were rituximab-naïve to receive rituximab (375 mg/m² on days 1, 8, 15, and 22) or Y-90 ibritumomab (0.4 mCi/kg). Seventy-five percent of patients on study (n = 55) had FL; 12% had transformed lymphoma (n = 9); and the others had SLL, lymphoplasmacytic lymphoma, marginal zone lymphoma, or MALToma (mucosal-associated lymphoid tissue lymphomas; n = 9). The median number of prior regimens was two for both the rituximab and RIT arms.

The RR for the patients treated with RIT was 80%, whereas the RR for those treated with rituximab was 56%. Likewise, the CR rate favored RIT: 30% versus 16%. Despite these encouraging results, the duration of

response was insignificantly longer for RIT: 14.2 versus 12.1 months.¹⁹ These data may underestimate the efficacy of Y-90 ibritumomab in that the depth of response was greater in the case of RIT; therefore, the time to reach the baseline level of disease would have been considerably longer in the patients treated with RIT.

Results in rituximab-refractory patients

The distinct activity of RIT was shown in a small study of Y-90 ibritumomab in rituximab-refractory patients (defined as patients who either never responded to rituximab or whose duration of response was less than 6 months). The patient population on study included 95% with FL (n = 54), 4% with SLL (n = 2), and 2% with transformed lymphoma (n = 1). Of the 54 patients with FL treated, 74% achieved a response, with a CR rate of 15%. The median time to disease progression (TTP) was 6.8 months for the group and 8.7 months for responders.²⁰

Results in thrombocytopenic patients

A small phase II trial was conducted in 30 patients whose platelet counts ranged from 100,000/mm³ to 149,999/mm³. In these patients, the dose of Y-90 ibritumomab was reduced to 0.3 mCi/kg. The patient population consisted of relapsed or transformed lymphomas. FL made up 83% of the patients, whereas trans-

formed lymphoma comprised 10% of the total. The patients had received a median of two prior lines of therapy.

The ORR was 83%, with a CR rate of 37% and an unconfirmed CR rate (CRu) of 6.7%. The median TTP was 9.4 months.²¹ Grade 4 thrombocytopenia occurred in 13% of cases. Long-term remissions were seen in this study as in others, with two patients remaining in CR for 41 and 54.8 months, respectively.²²

Optimal timing

One of the major issues complicating the interpretation of the value of RIT is case selection. In many cases, RIT was administered late in the natural history of the disease, after the failure of many lines of treatment. Not surprisingly, the majority of such patients did poorly. When Emmanouilides et al examined the results of treatment for patients in first relapse as opposed to those receiving two or more lines of therapy, striking advantages to the earlier use of RIT were evident.²³ The ORR (86% vs 72%) and CR rate (CR/CRu, 49% vs 28%; *P* = 0.004) favored the earlier use of Y-90 ibritumomab. More important, the duration of CR favored RIT (22.8 months vs 14.6 months) for the group with only one prior therapy. A significant proportion of patients experienced long-lasting remissions exceeding 50 months, with some of them being resistant to rituximab. These data suggest that the optimal use of RIT would be early in the natural history of the disease.

Use as consolidation therapy

In the consolidation setting, 414 patients with stage III or IV FL who achieved a CR, CRu, or PR after various front-line therapies were randomized to receive either consolidation Y-90 ibritumomab within 3 months of induction or observation. In the observation arm, 15.6% of patients received rituximab as part of their induction regimen, compared

with 13.2% of patients in the Y-90 ibritumomab arm.

After a median observation time of 3.5 years, PFS for all Y-90 ibritumomab patients was 36.5 months, versus 13.3 months for those in the observation-only arm ($P < 0.0001$).²⁴ For the subset who achieved a CR/CRu after induction chemotherapy, PFS was 53.9 months for the Y-90 ibritumomab-treated group and 29.5 months for the observation-only group ($P = 0.0154$). The conversion rate from PR to CR/CRu after consolidation with Y-90 ibritumomab was 77%, resulting in a final CR rate of 87%.

The incidence of grade 3 or 4 neutropenia was 40.2% and 26.5%, respectively, and the incidence of grade 3 or 4 thrombocytopenia was 58.8% and 2.0%, respectively. The median days to neutrophil nadir for the Y-90 ibritumomab patients were 44.5 and 46 days for grades 3 and 4 neutropenia, respectively, and the median recovery times were 20 and 28 days, respectively. The median days to platelet nadir were 35 and 39.5 days, respectively, for grades 3 and 4 thrombocytopenia, and the median recovery times were 20 and 35 days, respectively.

Utilizing real-time quantitative polymerase chain reaction (RQ-PCR), 186 of the 414 enrolled patients were found to have a bcl-2 rearrangement and were eligible for RQ-PCR analysis. The conversion rate from bcl-2 PCR detectable to undetectable in the Y-90 ibritumomab-treated patients was 90%, compared with 36% in the observation-only group. For those who converted from PCR detectable to PCR undetectable after receiving Y-90 ibritumomab, PFS was 40.8 months, versus 24 months for those who converted from PCR detectable to undetectable in the observation-only arm ($P < 0.01$).²⁵

The major issue identified in this study is the applicability of results in the current treatment milieu. With

only 14% of patients receiving rituximab as part of the induction regimen, the results cannot be generalized to today's standard of practice, in which chemoimmunotherapy is the norm. Furthermore, in an era of increasing use of rituximab maintenance, the obvious question is whether rituximab maintenance or consolidation with RIT is the better strategy in terms of efficacy, ease of administration, and cost.

In another phase II study, consolidation Y-90 ibritumomab was administered to 56 patients with stages II-IV MCL who completed 4 cycles of R-CHOP and achieved a CR, PR, or stable disease (SD) after induction. Ninety-one percent of the patients had stage III or IV disease, 79% had more than one extranodal site involved, and 78% had marrow involvement by lymphoma. Fifty-one patients received all treatments on study, and the best response was a CR/CRu rate of 42%, with a PR rate of 32%. Improvement in response was seen in 16 patients after Y-90 ibritumomab consolidation. At a follow-up of 24.4 months, median failure-free survival was 27 months. Fifty-five percent of patients experienced grade 3 or 4 neutropenia, and 45% experienced grade 3 or 4 thrombocytopenia.²⁶

Other potential indications

Y-90 ibritumomab has been studied in a number of other circumstances. Although this article will not cover the rather extensive literature regarding its use as part of high-dose therapies requiring stem cell support, much of these data are encouraging and reviewed elsewhere. Other potential indications in which limited studies have been published include for DLBCL²⁷ and MCL.²⁸ However, more data are needed to properly assess the value of RIT for these indications. Small studies have been published in which abbreviated courses of chemotherapy have been followed by consolidation with RIT.²⁹⁻³¹ These re-

sults are encouraging but require verification in large randomized clinical trials.

Clinical studies on I-131 tositumomab

Currently, I-131 tositumomab has label indications that include treatment of FL, with and without transformation. It should be noted that there is an indication for transformed lymphoma, which is not the case for Y-90 ibritumomab, and also there is no front-line indication as yet for I-131 tositumomab.

Results in patients with rituximab-naïve relapsed or refractory NHL

Early studies with I-131 tositumomab turned to the rituximab-naïve population. One phase II trial focused on 47 rituximab-naïve patients with either low-grade (79%) or transformed (21%) NHL who did not respond or no longer responded to an anthracycline or anthracenedione regimen.³² The ORR was 57%, and the CR rate was 32%. Somewhat surprisingly, the RR for low-grade (57%) and transformed (60%) lymphomas was similar. The median duration of response was 9.9 months for all patients and 19.9 months for patients achieving a CR.

A second study also examined patients with low-grade or transformed B-cell lymphoma who had received at least two prior chemotherapy regimens and were either refractory to their last therapy or had relapsed within 6 months.³³ In that trial, the ORR was 65%, which compared favorably with the ORR of 28% experienced with their last qualifying regimen. The CR rate was 20%, with a median duration of response (DOR) of 6.5 months. The median DOR for patients achieving a CR had not been reached at 47 months, attesting to the potential durability of responses in patients who achieve a CR with RIT. In this trial, MDS was diagnosed in 4 of 60 enrolled pa-

tients at a median of 35.5 months after treatment.

Results in patients with relapsed or refractory NHL who were previously treated with rituximab

In a study of 40 patients, a heterogeneous population of patients with predominantly FL and transformed lymphoma who had progressed after rituximab, never responded to rituximab, or had responses of less than 6 months were treated.³⁴ The ORR was 65%, and the CR rate was 38%. The median PFS was 10.4 months. For those patients who attained a CR, the median PFS had not been reached at 3.3 years. Patients with FL and low-bulk disease had a PFS of 48% at 3 years, whereas patients with other types of lymphoma fared less well, with a PFS of 11%. Two of these patients developed MDS and later AML.

Use as a single agent in the front-line setting for low-grade lymphoma

Kaminski and colleagues reported on a series of patients with previously untreated mostly FL given I-131 tositumomab as their first regimen. A total of 76 patients with stage III or IV, grade 1 or 2 FL (and 1 patient with MCL) were treated. Of these patients, tumor bulk ≥ 5 cm was noted in 43%, whereas 64% had bone marrow involvement by lymphoma of 1%–25%. The ORR was 95%, and the CR rate was 75%.³⁵ Eighty percent of patients whose PCR for bcl-2 gene rearrangement was positive became negative. Bone marrow involvement by lymphoma at baseline was associated with a decreased CR rate, compared with those without bone marrow involvement. For those who achieved a CR, neither the bulk of disease ($P = 0.39$) nor the involvement of bone marrow by lymphoma ($P = 0.09$) had a significant impact on PFS. Clinical and/or chemical hypothyroidism occurred in 13% of patients at 5 years. With a median follow-up of 7.93 years, the OS rate was

86%, and the PFS rate was 50%; for those who achieved a CR, the 8-year PFS rate was 64%. No cases of MDS or AML were observed.³⁶

These findings are most provocative, showing long-term results equivalent to those reported for chemoimmunotherapy, including maintenance therapy. However, enthusiasm is tempered by the fact that the results have come from a single institution and have not been repeated. Furthermore, these patients, as a group, may have had a somewhat favorable prognosis, with more than 50% of them having a lower International Prognostic Index (IPI) score and a nonbulky tumor measuring < 5 cm.

Use as consolidation therapy

The Southwest Oncology Group (SWOG) has conducted a phase II trial of 90 patients with FL (bulky stage II, III, or IV) treated with CHOP followed by consolidation with I-131 tositumomab. Eighty-three evaluable patients received 6 cycles of CHOP. If they achieved at least a PR, they went on to receive a single course of RIT 4–8 weeks after concluding chemotherapy. Following CHOP alone, 27% of patients achieved a CR and 12%, a CRu. Forty-nine percent of patients obtained a PR, whereas 2% had SD. After I-131 tositumomab consolidation, 23 patients converted their responses from PR to CR/CRu, and 4 patients improved their responses from CRu to CR.³⁷

Thirty-eight patients were available for serial bone marrow PCR analysis of baseline positivity for (14;18) translocation, with 32 patients (84%) becoming PCR-negative after protocol therapy. Seven patients (18%) converted to PCR-negative after CHOP, and an additional 24 patients (63%) converted to PCR-negative after I-131 tositumomab. At 5 years of follow-up, the estimated OS was 87%, and the PFS was 67%.³⁸ Compared with 356 historic FL pa-

tients from two prior SWOG studies (S7426, S7713) who received CHOP alone, the 5-year OS and PFS estimates from this I-131 tositumomab consolidation study represented a 23% absolute improvement over the historic data, 67% versus 44% for PFS ($P = 0.001$) and 87% versus 64% for OS ($P = 0.0003$).

Smaller trials have also examined the potential role of I-131 tositumomab as a front-line consolidation strategy. Thirty patients with untreated FL were given 6 cycles of CVP (cyclophosphamide, vincristine, and prednisone) followed by I-131 tositumomab. Of the 30 patients, 29 had stage III or IV disease. The CR and PR rates were 53% and 47%, respectively, following CVP.³⁹ After RIT, the CR rate was 93%. Of 14 patients with a PR, 12 converted to a CR with RIT. After a median follow-up of 101 months, the 2- and 5-year PFS rates were 76% and 56%, respectively. OS rates were 96% and 83% at 2 and 5 years. One patient developed MDS 7.3 years after RIT, and another developed AML 20 months after RIT.

Conclusion

RIT for NHL remains a viable option for patients, with Y-90 ibritumomab currently approved for treatment of low-grade lymphomas including FL in the relapsed or refractory setting as well as consolidation treatment for patients with previously untreated FL who achieve a PR or CR to first-line chemotherapy. I-131 tositumomab is approved for relapsed or refractory FL, with or without transformation. The use of RIT as a consolidation therapy is an appealing strategy, given the short course of well-tolerated therapy, which must be compared with today's prevalent approach using maintenance schedules of rituximab.

The potential indications of RIT in MCL, and particularly DLBCL, await more definitive studies. Additional studies to examine the role of

Y-90 ibritumomab and I-131 tositumomab as part of conditioning regimens in stem cell transplantation are also in progress.

Advantages of RIT include the brevity of the treatment program, the reversible myelotoxicity without other common side effects, and the reduction of frequent office visits. The cost of RIT may be competitive, given the lack of rituximab maintenance costs.

At present, there has been no randomized controlled study directly comparing the efficacy and safety of Y-90 ibritumomab with those of I-131 tositumomab; hence, there is no evidence yet to allow selection of one RIT agent over another. However, in terms of ease of administration, Y-90 ibritumomab, with the requirement of platelet count and weight only for dosing, is the less complicated treatment.

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The older cancer survivor: living arrangements and social supports

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There are more than 9.5 million cancer survivors in the United States, and the majority of them are older people who will need a safe environment to live out their lives. Appropriately designed homes for older adults can greatly enhance their quality of life and allow them to “age in place.” The older person’s current home usually needs modifications to ensure safety and reduce barriers to performing tasks of daily living. This article explores recommended home modifications and discusses where people can obtain help in carrying out the necessary modifications. It also reviews housing options for the elderly, including naturally occurring retirement communities, home sharing, accessory dwelling units, congregate housing, assisted living facilities, and continuing care retirement communities.

The study of cancer and aging has emerged as a critical issue in oncologic care. Life expectancy has increased significantly over the past 100 years, and further increases are projected.

Cancer is the most common cause of death among persons younger than age 85 years, with approximately half of all cancers occurring in the population aged 65 years and older. Persons 65 years of age and older are estimated to become 20% of the US population by 2030. The over-75 age group will triple by 2030, and the group 85 years or older will double in the same period. These statistics outline an increasing older cancer population that will require oncology management and social supports specific for their needs. The place of residence of the older cancer survivors will be an important aspect of their social supports and access to healthcare.

Living alone

In 2003, 10.5 million people aged 65 or older lived alone, three-quarters of whom were women. The living arrangements of the older population reflect factors other than marital status, including health status, socioeconomic situation, and family and cultural ties.¹⁻³ Independent living arrangements—living either alone or with a spouse—are considered most desirable for older adults in the United States because they offer more autonomy. However, these living arrangements, in particular living alone, can increase social isolation and reliance upon formal social supports.¹ Older unmarried people who live alone, most of whom are widowed, are generally in better health than those who do not

live alone. At the same time, older people who live alone are more likely to reside in poverty than older people who live with their spouses. In 1910, 12% of widowed women aged 65 and older lived alone, compared with 68% in 2003.⁴ Broad social change, including mortality and fertility decline, rising incomes, and the implementation of Social Security and Medicare, has contributed to this increase.

As age increases and widowhood rates rise, the percentage of the population living alone also increases. In 2003, 29.6% of women aged 65–74 years, 47.6% aged 75–84 years, and 57% aged 85 and older lived alone; the corresponding figures for men were 15.6%, 21.2%, and 30.1%, respectively. Since 1980, both the number and share of oldest-old women (85 and older) who lived alone have increased; the number more than doubled (508,000 to 1.3 million), and the proportion increased from 45% to 57%. The most noticeable change since 1970 occurred in the share of women aged 75 and older who lived alone, which increased from 37% in 1970 to 54% in 1990 before falling to 50% in 2003.

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Housing options for senior adults

Appropriately designed homes for older adults can greatly enhance their quality of life.⁵ Those who perceive their home environment as useful and meaningful and who are independent in daily activities are in better health overall.⁶ As such, safe housing options need to be designed for the elderly, allowing them to remain independent while still receiving the care they need.

Lawton discusses the concept of environmental press in relation to an older person's competence.⁷ Environmental press is the "extent to which an environment demands a response from the person." If an environment is too demanding for an older adult's capabilities, or if it puts too few demands on him or her, there is a poor fit between the person and his or her environment.⁸ Such misfits stem from auditory, neuromotor, and musculoskeletal changes and changes to bones and muscles that occur with age. These changes can influence the ability of older adults to successfully navigate their home environment and engage in daily activities.⁹

The relationship between individual competence and environmental press is especially unstable in very old age due to the decreased ability of older adults to adapt to new environments.⁶ Environmental press can occur if residents perceive their housing hazards as uncontrollable.¹⁰ If stressful environments produce chronic stress, residents are at a greater risk of developing life-threatening conditions.¹¹ Furthermore, homes that provide an enabling environment for seniors can bring them to a higher level of functioning and can delay or prevent the need for institutionalization. High levels of environmental press are especially present in older adults living in poor housing conditions. The concept of environmental press further supports the idea that hous-

ing options for older adults need to be designed specifically for their particular needs.

Aging in place

The majority of older adults prefer to age in place, or to remain in the home they have been living in for many years. Their homes, however, may not be designed to accommodate older users. Physical barriers, such as stairs and narrow hallways, may prohibit older adults from moving easily around their homes. The Administration on Aging found that in 2007 the average home occupied by older adults was constructed in 1969, and 4.4% of these homes presented physical barriers.¹² Therefore, many of these homes do not accommodate the changing needs of older adults, since they have lived in their residences for a long time without making any substantial modifications.¹⁰ Additionally, these homes, which may be deteriorating due to their age, can have a negative effect on the physical health of the elderly residents.¹³

A properly designed home environment can ensure the health and safety of its residents. Because of natural changes that occur with age, older adults often believe that they are no longer capable of performing the daily tasks they were once able to carry out. Older adults often see themselves, rather than their environment, as the problem, attributing their loss of functional capability to their own impairments rather than to the physical barriers imposed by the environment.¹⁴ To cope with such a situation, environmental barriers must first be recognized as the source of the problem because "people may lack the knowledge or experience necessary to eliminate or modify them,"¹⁵ and many older adults are unaware of the benefits that home modifications and retrofitting can provide.¹⁰

Physical obstacles may present themselves if home modifications are not implemented, making an old-

er adult's home environment a cause for his or her deteriorating health. The most dangerous hazards for older adults in the home include falls, inadequate lighting, fire hazards, entry to the home by intruders, noise, inadequate provision of food safety, contaminated water, and hazards from excess heat and cold.¹⁰ Older adults who live in run-down buildings also tend to be physically and socially isolated because of the obstacles they confront when leaving their homes, such as steps and clutter in the hall that could pose tripping hazards.¹³

In 2007, the World Health Organization (WHO) published a preliminary overview of the LARES (Large Analysis and Review of European Housing and Health Status) survey, which sought to improve our knowledge of the impact existing housing conditions have on health, mental, and physical well-being.¹⁶ This survey was administered from 2002 to 2003 in eight European cities. Although it did not focus specifically on housing for older adults, 21% of the participants were older than age 60. In 76% of the homes analyzed in the LARES survey, there was a step at the entrance to the home, causing the residence to be inaccessible and dangerous for the elderly. The corrective measure would be to build a ramp to the front door. The survey found a number of other modifications needed in the homes of handicapped persons, including making changes to the bathroom, building an elevator, adapting staircases, extending/enlarging doors and adapting windows, installing handrails, and making changes to the kitchen.

The LARES survey concluded that "housing conditions are strongly related to the risk of accidents and injuries," including falls, burns, and cuts. In the United States, for example, unintentional falls accounted for 18,807 deaths in 2004, 80% of which were people older than age 65.¹⁷ Therefore, it is imperative for homes to be designed without potential tripping

hazards and other obstacles, such as area rugs.⁹

Home modifications help maintain the safety of the residents and allow them to live a healthy lifestyle. Those who fall and suffer moderate to severe injuries reduce their mobility and independence and increase their risk of premature death. Improving color contrast between furniture and the surrounding area and between stair treads decreases the likelihood of falls, as does installing handrails on both sides of the stairs. Grab bars in the bathroom, both in the shower and around the toilet, can ease transferring and reduce the risk of falling. Burns occurring in both the bathroom and kitchen can be reduced by installing antiscald valves on all faucets; these devices automatically reduce water flow to a trickle when it reaches 120°F. If older adults can perform tasks in the bathroom independently, their ability to maintain their autonomy and sense of self-worth will be extended.⁹ There are many other modifications that can be done to make homes safer. The AARP website and its housing publications, for example, provide checklists specifying the elements to be included in a safe and accessible home for older adults.

There are a number of initiatives in the United States to assist the aging community of all income levels in modifying their homes to make them safer environments to age in place. In 2009, the acting Surgeon General Steven K. Galson, MD, MPH, issued "The Surgeon General's Call to Action to Promote Healthy Homes."¹⁸ The document was planned to focus attention on how housing can affect health and to initiate an exchange of ideas about the importance of healthy homes among parents, homebuilders, community leaders, and policy makers. Dr. Galson stated, "We can prevent many diseases and injuries that result from health hazards in the home by following the simple steps outlined in this *Call to Action*." Some

of the simple recommendations that relate specifically to the elderly population include preventing falls by installing grab bars in showers and preparing a fire escape plan.

Rebuilding Together is a nonprofit organization that provides lower-income homeowners, including the elderly, with "free home modifications and repairs, making homes safer, more accessible, and more energy efficient."¹⁹

The National Association of Home Builders (NAHB) and AARP developed the Certified Aging-in-Place Specialist (CAPS) certification program to teach professionals (ie, remodelers, contractors, designers) "the strategies and techniques for designing and building aesthetically enriching, barrier-free living environments."²⁵ These professionals help older adults determine the home modifications they need to be able to age in place. Although these services may be expensive, CAPS specialists help consumers make informed decisions about undertaking modifications that can help them maintain their independence for a longer period.

Overall, home modifications help to improve the quality of life for older adults. Modifications make the daily routines of older adults easier to perform, ensuring they are safe in their homes and allowing them to age in place. Performing modifications promotes self-care and safe, independent living among the growing elderly population.^{13,20}

Naturally occurring retirement communities

Naturally occurring retirement communities (NORCs) emerge when an entire community of people remain in their homes for long periods or as a result of an in-migration of older adults wishing to age in a NORC.⁸ Section 422 of the 2006 Amendments to the Older Americans Act (OAA) defines a NORC as "a community with a concentrated population of older individuals, which may include a residen-

tial building, a housing complex, an area (including a rural area) of single-family residences, or a neighborhood composed of age-integrated housing," where at least 40% of the residents are older. Almost one-third of all older adults live in a NORC, and at least half of the residents are 60 years or older. NORCs are an attractive option because they provide services to the residents, including social and recreational programs, transportation, and healthcare. Living in a NORC allows residents to age in place and receive the care and assistance they may need.⁸

In the OAA reauthorization of 2006, Congress authorized the Community Innovations for Aging in Place (CIAIP) Initiative to provide grants to communities to enable older adults to age in place in their current homes and communities. For example, the New York City Department for the Aging received \$338,575 from the CIAIP Initiative to aid an existing NORC in New York City to improve the health of its residents and guide changes for aging-in-place models.

Home sharing

The Administration on Aging reported that in 2008, more than half (54.6%) of noninstitutionalized people aged 65 and older lived with their spouse; however, about 30.5% of noninstitutionalized older adults were living alone.¹² Only 28.9% of women 75 years or older lived with a spouse in 2008.¹² For those who are living alone, home sharing, in which two or more unrelated individuals share a home or apartment, is an option. The tenants often pay rent, therefore providing financial assistance as well as companionship and help with household chores. In a survey, those with a yearly household income under \$50,000 found home sharing to be more appealing than those earning more than \$50,000.^{8,21}

Accessory dwelling units

Accessory dwelling units (ADUs) are an intergenerational approach

to housing older adults. An ADU is an “extra living unit on your property, complete with kitchen, bathroom and sleeping facilities.”²² One type of ADU is ECHO (elder cottage housing opportunity) housing. ECHO units, or elder cottages, can be a small modular home placed on the property of an older adult’s child or can be an extra living unit attached to the main house. These housing units allow older adults to maintain their independence by living in their own cottage while still receiving the necessary support from the host family living in the main house on the property. Although elder cottages must meet zoning regulations, most municipalities allow this type of housing if it is only temporary and is promptly removed once the resident no longer lives there.²³

Another ADU recently developed is the MEDCottage, “an alternate solution for our society that would be emotionally satisfying yet affordable... the ideal solution for families desiring to care for a family member while maintaining their current lifestyle.”²⁴ The MEDCottage is described as “a state-of-the-art high-tech temporary mobile medical home that may be placed on the caregiving family’s property...[providing] an immediate medical environment for disabled loved ones for the purpose of recovery or rehabilitation.”²⁴ These cottages provide internet cameras (web cams) and voice communications, movement locators, medicine consumption monitoring, air filtration, hazardous waste disposal, and other environmental protections. By installing a MEDCottage, some of the caregiver’s burden is relieved because of the technology built into the cottage. Caregivers do not have to keep a constant eye on their loved one because they know the monitoring systems will alert them to potential dangers. This is an innovative approach to caregiving, allowing a loved one to remain close to family during the end

of life while still receiving medical assistance.

Congregate housing

Congregate housing facilities usually have private apartments for each resident and include congregated common spaces for recreation and dining. One such environment is the Green House, a concept developed by Bill Thomas. The Green House is meant to feel and look more like a home rather than an institutional setting. It is a place where seniors can live a “full and interactive life.”²⁵ Eight to ten seniors live in a Green House, each with his or her own private room and bathroom. The Green House blends in with its neighboring community and is described as warm, smart, and green: warm in the floor plan, furnishings, and people; smart in the use of “smart-technology computers, wireless pagers, electronic ceiling lifts, and adaptive devices”; green in the amount of “sunlight, plants, and access to outdoor space.”²⁶

Assisted-living facilities

Assisted-living facilities (ALFs) provide an intermediate level of care. Many older adults move to an ALF after a major life transition, such as the death of a spouse or a major health problem. There are between 30,000 and 65,000 ALFs in the United States. The majority of residents are female (74%) and white (97%). ALFs provide meals, personal care, limited medical assistance, housekeeping, utilities, social activities, transportation, and security.¹³

The effect of living in an ALF on quality of life differs for individual ALF residents. Some may sense that moving into an ALF decreases their sense of autonomy, and their new residence does not feel like home. On the other hand, some residents feel that it enhances their quality of life because they are surrounded by people and are not isolated in their homes; however, some residents may find it diffi-

cult to form new friendships. Higher resident satisfaction has been found in smaller facilities because the environments feel homier and encourage closer personal relationships among the residents and staff,¹³ similar to the idea of the Green House previously discussed.

Many older adults move to ALFs in an attempt to age in place. However, it has been found that the average stay for residents was only 30.8 months.¹³ Therefore, moving to an ALF is usually only one step along a person’s continuum of care. A better option for aging in place might be a continuing care retirement community (discussed below).

Continuing care retirement communities

Continuing care retirement communities (CCRCs) gained popularity in the 1990s. These facilities provide three levels of care on the same campus: independent living, assisted living, and skilled nursing care. This structure allows CCRC residents the ability to age in place; once residents move to a CCRC, they intend on staying there for the rest of their lives. Because of the high costs of living in a CCRC, only 4.4% of people aged 65 and older lived in such a setting in 2007. CCRCs require an upfront fee that can range from \$25,000 to \$35,000 or as high as \$500,000 and monthly fees of \$1,500–\$2,500 and \$3,500–\$5,000. Monthly fees generally cover the cost of rent, utilities, one meal a day, access to a health clinic, and transportation.¹³

Currently, some CCRCs are beginning to resemble five-star hotels and health resorts rather than senior facilities. They may provide a variety of dining options and have many amenities including spas, all of which are located on the CCRC campus so the residents can access what they need without having to go very far.²⁷ Many CCRCs have connections to local universities, allowing residents

to attend university classes, sporting events, and lectures. In return, university students have internship opportunities at the CCRC or can receive mentoring from the residents.²⁸

Elderly cancer survivors

There are more than 9.5 million cancer survivors in the United States, and their numbers are growing. The majority of them are older cancer patients who need a safe environment to live. There are many variables when determining where one should live in later life. Regardless of which environment one chooses, it is important that it is safe environment and supports the abilities of older adults. It should also take into account the person's overall health, including comorbidities and functional status. The living environment should be integrated into the overall health planning of older cancer patients and survivors.

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Use of MammoSite balloon brachytherapy for early-stage breast cancer

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MammoSite balloon brachytherapy (MBT) is a form of accelerated partial breast irradiation that is used in the setting of breast-conserving treatment for early-stage breast cancer. MBT permits effective irradiation of the tumor bed with a diminished impact on normal surrounding tissue and without the protracted course of treatment required with whole breast radiation therapy (WBRT). Although MBT remains a relatively new treatment modality compared with WBRT, mounting evidence continues to support a role for MBT as a useful alternative to WBRT.

Breast cancer continues to be the most common non-cutaneous malignancy diagnosed in women. In 2009, it was estimated that there were 193,370 new cases of invasive breast cancer in the United States.¹ With the introduction of breast cancer screening, women are being diagnosed with earlier stage disease, resulting in decreased mortality and morbidity.² Breast-conserving surgery and whole breast radiation therapy (WBRT) have been proven equivalent to mastectomy in disease-free and overall survival^{3,4} and are now a standard option for early-stage breast cancer.

Following breast-conserving surgery, the most widely used radiation technique is WBRT. This treatment is given daily, 5 days per week, for 5–6 weeks. The time and travel commitment can be a deterrent for some patients who would be appropriate candidates for breast conservation. This problem can lead some patients to elect mastectomy or to compromise their treatment by receiving no adjuvant radiotherapy after breast-conserving surgery. In their study of the appropriateness of breast-conserving surgery, Nattinger et al reported this figure to be as high as 25%.⁵ In rural areas, where access to radiation

therapy care is logistically challenging for patients, this issue is extremely important.

Accelerated partial breast irradiation (APBI) is a form of high-dose-rate brachytherapy used as an alternative to WBRT in appropriately selected patients.⁶ APBI is commonly used as an adjuvant treatment in the setting of breast-conserving surgery and can be delivered over 5 consecutive days, rather than 5–6 weeks as with conventional WBRT. Given that most local recurrences after breast-conserving therapy occur in the tumor bed, partial breast irradiation techniques are targeted to address this pattern of failure.⁷

Over the past decade, APBI has been intensely investigated, with recently reported clinical trials describing 5-year local recurrence rates comparable to those with lumpectomy followed by WBRT, with local tumor control rates in the ipsilateral breast of at least 95%.^{8,9} There are various types of APBI delivery systems that are currently used, each with the same basic premise of delivering high-dose, conformal, localized radiation therapy to the tumor bed. To date, there is no APBI system that has been found to be superior, and the method chosen is largely dependent on the surgeon and

the oncologist. At the Medical University of South Carolina (MUSC), MammoSite (Hologic, Inc.; Bedford, MA) balloon brachytherapy (MBT) represents the mainstay of APBI for early-stage breast cancer.

What is MBT?

MBT is a form of APBI that involves the surgical placement of a balloon catheter in the lumpectomy cavity (Figure 1), CT simulation for radiation treatment planning, and radiation treatment delivery. MBT was approved for use by the US Food and Drug Administration in May 2002, and the MUSC began its partial breast irradiation program at that time.

The MBT device can be implanted either at the time of lumpectomy (open technique) or several weeks after surgery (closed technique) and can be removed after the final fraction is given. The closed technique has the advantage of permitting time

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FIGURE 1 MammoSite balloon applicator. A double-channel balloon catheter system allows for a radioactive source to be placed inside an inflatable balloon to provide a reproducible dose distribution to the surrounding tissue. The silicone balloon is connected to a shaft approximately 15 cm long. The radioactive source is placed inside the center of the balloon via the larger central channel.

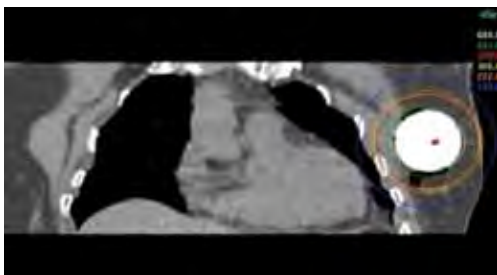


FIGURE 2 Coronal CT image of typical isodose lines achieved with the MammoSite brachytherapy device. Red line (340 cGy) represents the 100% dose line, 1 cm from the surface of the balloon.

for pathologic diagnosis, resulting in fewer incidents of catheter removal secondary to unexpected pathologic findings. Deeper placement of the catheter (> 7 mm from the skin surface), judicious use of antibiotics, and improved catheter care have all contributed to improved outcomes.¹⁰

CT planning typically occurs within 2 days of surgical placement to ensure proper placement of the device. The high-dose-rate brachytherapy involves placement of iridium-192 to a prescribed dose of 34 Gy over 10 fractions (Figure 2), administered twice daily with at least 6 hours between fractions. The dose is typically prescribed to 1 cm beyond the surface of the balloon to provide sufficient coverage of the tumor bed.

Who is eligible for MBT?

At the outset of the MUSC APBI

program, patients were deemed eligible if they had a histopathologic diagnosis of ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC), a single focus of tumor, a primary tumor of ≤ 3 cm, negative surgical margins, and \leq three positive lymph nodes. These eligibility criteria have been modified following the recent publication of guidelines for APBI in the form of a consensus statement by the American Society for Radiation Oncology, and we no longer recommend this treatment for patients with positive lymph nodes.¹¹ Eligible patients also must be able to comply with catheter care instructions (eg, by avoiding bathing and keeping the catheter dry during the course of treatment and for 24–72 hours after removal of the device).

What are the complications of MBT?

The early institution of MBT at MUSC and subsequent reporting of the acute toxicities, late toxicities, and long-term oncologic outcomes have contributed to the collective APBI experience. The earliest report described the rates of acute wound complication in the initial 37 patients treated.¹⁰ Categories used to describe the acute complications were operative wound complications, infections, skin toxicities, seromas, or catheter failures. Operative wound complications occurred in three patients (8%). Radiation Therapy Oncology Group (RTOG) grades 2 and 3 toxicities occurred in two patients (5.4%) and in one patient (2.7%), respectively. Six patients (16.2%) developed wound infections, and 12 (32.4%) developed seromas. Catheter failures occurred in two patients (5.4%) and catheter rupture, in three (8%).

Upon evaluation of these data, a number of measures were taken to reduce complications. Currently, prophylactic antibiotics are initiated on the first day of the procedure and are given throughout the course of treat-

ment. Patients are also advised not to shower to keep the site dry.

Our institutional data evaluating the incidence and prognostic factors for developing seroma after MBT have also been reported. Evaluation of 109 cases (at a median follow-up of 3 months) demonstrated development of seroma in 41% of patients. One-third of these seromas were described as clinically significant, and infection was shown to be significant in the development. The timing of catheter placement (on the day of resection vs 1 or more days after resection) was the only significant factor (59% vs 33%). Prophylactic antibiotics were shown to reduce the risk of infection from 37.5% to 6%.¹²

The effect of the dose to the chest wall has also been described. In 2005, the plans of 93 patients were reviewed. Of them, 16 patients (17%) were considered to have received a high dose to the chest wall of greater than or equal to 120% of the isodose line in contact with a rib. Two patients reported chest wall tenderness, and although neither developed acute chest wall complications, re-evaluation demonstrated the presence of rib fractures. As data continue to mature, the understanding of complications to include chest wall toxicity will continue to improve.¹³

Predictors for cosmetic outcome have also been evaluated. We reviewed 100 patients treated with MBT, and all patients had a minimum follow-up of 6 months. Of the 100 patients, 90 had adequate data and follow-up for evaluation. Cosmesis (evaluated using the Harvard Scale) was determined to be excellent in 62 patients (68.9%), good in 19 patients (21.1%), fair in 8 patients (8.9%), and poor in 1 patient (1.1%). Acute skin toxicity was also significantly increased with a balloon-to-skin distance of < 7 mm. Factors that did not predict for cosmesis were age, balloon placement technique,

balloon volume, catheter days in situ, subcutaneous toxicity, and chemotherapy or hormonal therapy.¹⁴

How effective is MBT?

Since its approval in 2002, evidence for the use of MBT as an alternative to WBRT has continued to mount. To date, the largest reported study, the MammoSite Breast Brachytherapy Registry Trial, reported a 2-year local recurrence rate of 1.04%.¹⁵ A series published from the William Beaumont Hospital reviewed its 5-year experience with 43 patients.⁸ From this group, 36 patients had 5.5-year data, with no recurrences noted. The outcomes for 111 women treated with MBT over a 6-year period at MUSC were recently published and demonstrated similar success.⁹ With a median follow-up of 46 months, the estimated 4-year outcomes for the entire cohort were tumor bed control of 99%, ipsilateral breast control of 95%, event-free survival of 88%, disease-free survival of 97%, and overall survival of 92%.

Although the effectiveness of MBT is believed to be comparable to that of WBRT, data are only now

accumulating to support this notion. Recently, it was shown that MBT was comparable to WBRT (median follow-up of 45 months) in women stratified into risk groups based on consensus guidelines.¹⁶ Although outcomes were similar between the two groups, future studies with longer follow-up will be required to provide definitive evidence. For example, an ongoing phase III cooperative group trial (NSABP B-39/RTOG 0413) is presently focusing on the efficacy of MBT relative to other forms of APBI and will determine the relative effectiveness of MBT, interstitial brachytherapy, and 3D-conformal external-beam radiotherapy in early-stage breast cancer.

Conclusion

Accessible at many radiation oncology facilities throughout the United States, MBT and other forms of APBI represent a proven alternative to WBRT in the treatment of early-stage breast cancer. The patient described in the case study demonstrates an excellent outcome with MBT following lumpectomy. The

device was removed without incident, and no evidence of cellulitis, seroma, or hematoma was evident afterward or on follow-up. The patient was pleased with the cosmetic outcome and continues to do well 2 years out from treatment. This case demonstrates the natural history of a patient with early-stage breast cancer who underwent successful MBT therapy following lumpectomy, highlighting the multidisciplinary nature of effective MBT therapy.

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Case study

CASE DESCRIPTION

LS is a 55-year-old postmenopausal woman whose abnormal mammogram showed suspicious masses in the upper outer quadrant of the left breast. Real-time sonographic imaging of the left breast revealed three hypoechoic lesions, measuring between 3 and 8 mm, and at least one demonstrated shadowing. She underwent stereotactic biopsy of these lesions, which revealed grade 3 (poorly differentiated), estrogen receptor-positive, progesterone receptor-negative, and HER2/*neu* (human epidermal growth factor receptor 2)-negative invasive ductal carcinoma in all three specimens.

STAGING AND TREATMENT

Eventually, she underwent lumpectomy with sentinel lymph node biopsy. The greatest linear extent of the tumor measured 0.75 cm, and her sentinel node was negative; therefore, her cancer was staged as pT1bpN0pMx. The patient elected to undergo MBT, and the catheter was placed at the time of lumpectomy; MammoSite high-dose-rate brachytherapy was initiated 9 days later. The patient received 34 Gy over 10 fractions, given twice a day over 5 days. Daily CT simulations were performed to ensure the integrity of the balloon. The balloon was deflated and the catheter removed following the administration of the final fraction, with no complications. She was evaluated by a medical oncologist, and adjuvant anastrozole was recommended.

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A probable serotonin syndrome complicating a routine screening colonoscopy procedure

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In the medical literature, serotonin syndrome is well documented as an adverse event associated with various classes of medications. The most famous case of serotonin syndrome occurred when Libby Zion died shortly after receiving meperidine in combination with phenelzine, a monoamine oxidase inhibitor. We report on a patient receiving duloxetine, a serotonin and norepinephrine reuptake inhibitor, who developed a probable serotonin syndrome following a routine colonoscopy screening procedure. For preprocedure anesthesia, the patient received IV meperidine and midazolam.

Administration of meperidine with the monoamine oxidase inhibitor (MAOI) phenelzine resulted in perhaps the most famous case of serotonin syndrome, when Libby Zion died shortly after receiving these two agents in 1984.¹ Meperidine, a short-acting opioid analgesic, and midazolam, a short-acting benzodiazepine, are widely used for procedural sedation during a colonoscopy. Although each of these drugs is associated with well-known toxicities, including central nervous system (CNS) depression, toxicity from the drug-drug interaction associated with these two agents given concomitantly has received little attention.

A potentially life-threatening adverse drug reaction from such an interaction is serotonin syndrome, which is a state of excess CNS serotonin activity. It is associated with drugs that affect serotonin neurotransmission. Increased production, enhanced serotonin release, blockade of metabolism, inhibition of reuptake from the synaptic cleft, or direct receptor agonism can be the underlying cause.² Milder

cases may occur after overdose of a single medication, but severe toxicity is almost always associated with drug combinations.²

To our knowledge, serotonin syndrome following a colonoscopy procedure has not been previously reported. We describe a patient receiving the serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine (Cymbalta). After receiving IV meperidine and midazolam as preprocedure anesthesia for a routine screening colonoscopy, this patient developed a probable severe serotonin syndrome.

Case report

A 52-year-old Caucasian woman underwent a routine colonoscopy screening at an outpatient procedure center. Her medical history was significant for mild depression that was well controlled with the SNRI duloxetine, 60 mg/d (which was discontinued 2 days prior to the procedure). She also was taking ibandronate (Boniva), 150 mg every month, for osteoporosis prevention.

At the beginning of the procedure,

the patient was medicated with IV midazolam (1 mg), meperidine (80 mg), and hyoscyamine sulfate (0.5 mg), but she was not intubated. The colonoscopy was uneventful, with no polyps identified and no biopsies performed. She was brought to the facility's postanesthesia care unit immediately after the colonoscopy. The patient reported experiencing mental confusion in the recovery setting and had difficulty changing her clothes. After leaving the changing area, the patient was assisted by her husband to the car and traveled home.

The patient did not recall the car ride home and slept much of the afternoon following the procedure. She woke that evening and reported a severe headache, which improved with ibuprofen, 400 mg. Over the course of the next 5 days, the patient was pri-

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marily bed-bound and experienced an array of symptoms, including mental confusion, nausea, severe headaches, dizziness, agitation, shivering, diaphoresis, amnesia, and myoclonus. Two days after the colonoscopy, her physician prescribed promethazine, 25 mg rectally, to treat the nausea. Although the nausea resolved, the other symptoms persisted. Six days after the colonoscopy, the abnormal clinical findings resolved spontaneously, and the patient resumed taking duloxetine. She did not experience a recurrence of her symptoms.

Discussion

The most likely diagnosis for these findings is serotonin syndrome. This diagnosis is clinical and based upon signs, symptoms, and medication history. In 1991, Sternbach published criteria for serotonin syndrome based upon a review of 38 cases, including the recent addition or increase in dose of a serotonergic drug, but excluding alternative diagnoses, and three or more of the following features: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.³ This patient had received an SNRI and exhibited myoclonus, mental status changes, agitation, shivering, and fevers during the days following the colonoscopy procedure. Concomitant use of agents with serotonergic activity, such as selective serotonin reuptake inhibitors or SNRIs, MAO-Is, tricyclic antidepressants, 5-HT₁ (5-hydroxytryptamine 1) receptor agonists, ergot alkaloids, lithium, St.

John's wort, phenylpiperidine opioids (meperidine, in this case), dextromethorphan, and tryptophan can potentiate the risks of serotonin syndrome. The syndrome is rare but serious, potentially fatal, and thought to result from hyperstimulation of brainstem 5-HT_{1A} and 5-HT_{2A} receptors.⁴

The treating gastroenterologist and anesthesiologist may have been unaware of the potential for serotonin syndrome developing in this patient, who had discontinued taking her SNRI 2 days prior to the procedure. Similarly, most clinicians are unaware of the details of serotonin syndrome.⁵ Ontology-based, search term expansion technology-driven data mining of the US Food and Drug Administration's Adverse Event Reporting System (AERS) MedWatch database identified reports of serotonin syndrome associated with duloxetine (n = 234), meperidine (n = 11), and midazolam (n = 46).⁶

In the adverse events section, the package insert for duloxetine highlights rare instances of serotonin syndrome. However, the Web site www.drugs.com identifies a major drug interaction and posts a strong warning against administering meperidine and duloxetine concomitantly because of concerns over possible serotonin syndrome.⁷ As noted above, a longer washout period for duloxetine (rather than a 2-day washout period, as in this case) and increased pharmacovigilance should be considered when patients undergo routine screening colonoscopy with meperidine and midazolam.

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Measuring subjective phenomena

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Once we get away from counting bodies and using lab tests and enter the realm of phenomena such as quality of life or pain, we are trying to measure subjective states. Over the years, techniques have been developed to do this in a reliable, valid way. This article introduces readers to what to look for in scales tapping these domains.

The statistical articles in this series have discussed various ways of analyzing data. For the most part, the data have consisted of body counts, direct measurements, or laboratory test results—how many people are still alive after a certain number of years or whether one treatment shrinks tumors more than another one does. This is fine as far as it goes, but it doesn't go far enough. Some patients may opt for radiotherapy for cancer of the larynx rather than undergo a laryngectomy, for example, because they place more emphasis on quality of life (QOL) rather than quantity of life. This raises the issue of how to measure QOL or any other subjective state, such as pain or depression.

The problem is not the lack of scales to measure these states; there are dozens, if not hundreds, of them for each domain. Rather, the issue for the practicing oncologist is how to choose among them, to decide which ones are best, and to be able to say whether a particular study used an appropriate instrument. So, we are entering the world of *psychometrics*—the design and evaluation of scales to measure subjective or unobservable phenomena. Just as you had to learn a new vocabulary when you entered medicine and read the previous articles in this series, it's necessary to expand your vocabulary even more for this new area. The first two terms are *reliability* and *validity*.

Reliability

Reliability is, formally, a number between 0 and 1 that tells the extent to which a measure can discriminate among people with a lot or a little of the characteristic of interest. A reliability of 1 says that all variation in scores is due to real differences between people; a coefficient of 0 says that all variation is just measurement error. There are a number of terms that are almost synonyms of reliability—

stability, agreement, precision, and so on. Each of them captures one aspect of what the term means, although none is a perfect replacement term. If a patient fills out a QOL scale today, and if we assume that the person's status hasn't changed, then we would want a second administration of the scale given a week or two later to come up with a similar result. That is, we want the *test-retest* reliability of the scale to be high.

In some cases, rather than the patient completing a scale, a physician or a nurse completes it about a patient. This is done if the person is unable to fill it out himself or herself because of cognitive limitations, such as dementia or early childhood (a severe but, fortunately, time-limited condition). Under these circumstances, we would want the raters, operating independently, to come to similar conclusions—what we call *inter-rater* reliability.

Reliability is mentioned first among the properties of scale because everything follows from it. If the reliability is poor, you might as well stop there and throw the scale out; nothing can possibly redeem it. The reason is that if there's no consistency from one time to another, or from one rater to another, then we don't know which, if either, value is correct; it's like trying to measure something with a rubber ruler.

So, what's good and what's poor reliability? As we indicated, reliability is usually assessed with a statistic like the Pearson correlation, abbreviated as r , as we learned in a previous article,¹ and it can range between 0.00 and 1.00. (Pearson's r can actu-

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ally go from -1.00 to 1.00 , but a reliability coefficient is always positive.) If the scale is being used in research, we can live with a value of 0.70 or more, but we would really want it to be 0.80 or higher. If the scale is used clinically, though, and decisions about the patient will be based on the results of the scale, then we're looking for a minimum value of 0.90 .²

However, there's one important point to bear in mind. Reliability is not a fixed property of a scale; it depends on the scale itself, on the people being assessed, and on the circumstances. So, if an article says the scale has "good reliability," but if this estimation was based on college students filling out the scale as part of a classroom assignment, don't assume that you'd get the same results with patients in a clinic. Look for evidence of reliability with people similar to the ones you see (or who were part of a research study you're reading) and who completed the scale under similar circumstances. If this evidence isn't available, be very cautious in interpreting the results.

Validity

Just because a scale is reliable doesn't necessarily mean that the score tells us anything useful. Phrenologists were very reliable recording the bumps on people's heads, but that said nothing about personality or intelligence (except, perhaps, of the phrenologists themselves). Validity addresses the issue, "What can we correctly say about the person based on his or her score on the scale?"

Studies of reliability are fairly straightforward—have a group of people fill out the scale twice, about 2 weeks apart, or have two raters independently evaluate some people and then correlate the scores. Validity studies, though, come in a wide variety of flavors and are analyzed with a range of statistical tests. We can ask, for example, whether this QOL scale gives similar results as an older, but

much longer, scale. In that case, we'd give both scales to a bunch of people and correlate the scores.

Another possible question is whether scores on a pain scale decrease after people receive an analgesic. Now, we would give people the scale before and after treatment and look for differences with a paired t -test.³ We can get even fancier and do a randomized controlled trial,⁴ where one group gets the active drug and the other a placebo, in which case we would analyze the results with an analysis of variance.⁵

In fact, there are countless questions we can ask about how the scale performs with different groups of patients, and under different circumstances, so we can never say that a scale has been completely validated. This limitation makes it more difficult for people who want to use a scale; they must ask themselves whether the weight of available evidence is convincing enough (whatever that means). It's even more difficult for those who are reading an article that has used a scale, because there's rarely enough said about validity in the article on which to base a judgment. We have to assume that the authors went through this exercise themselves, and that's often a tenuous assumption.

The other thing to remember echoes what we said about reliability—it is not an immutable property of the scale but depends on the scale, the group, and the circumstances. Scales that are valid for outpatients, for example, may not work as well with inpatients. To be useful for you, the validation studies should have been done with patients who resemble yours.

Other considerations

If you're thinking of using a scale in your research or clinical practice, you also have to think about issues of practicality and feasibility:

■ **How long does it take a person to fill it out?** An inpatient may not object to spending an hour filling

out questionnaires; it may even break the boredom of lying in a hospital bed. Outpatients, however, may resent having to spend another hour in the clinic (with the associated outrageous parking charges) filling in little boxes.

■ **Is the person able to fill it out?**

If he has lines attached to every limb, it may be difficult for him to wield a pencil.

■ **Are the language and reading levels appropriate?**

The average high school graduate reads at a grade 6 level, so long words should be avoided. Be sure to check that medical jargon hasn't crept into the questions; to the person in the street (or hospital bed), a stool is something you sit on, not a euphemism for excrement; shock is what you get when you touch a live wire; and hypertension is part of the continuum of calm → tense → hyper-tense.

■ **How easy is it to score?**

Is it simply a matter of counting the number of boxes checked off, or must it be scored using a computer program? There are a number of other things you should look for, but brief⁶ and longer² guides exist.

Resources

There's one word we use when people ask us how to go about developing a new scale: "Don't!" To do it properly takes a minimum of a year and usually much longer. Also, there are already thousands of existing scales. If you want to find good scales, check out two books: *Measuring Health*⁷ and the two-volume set *Measures for Clinical Practice and Research*,^{8,9} which present the scales and evaluate how good they are with different groups.

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Learning online: keeping pace with the flood of oncology information

John J. Fried

In the mid-1980s, an oncologist friend of mine asked whether my 14-year-old son would consider a part-time job: going through the piles of medical journals littering his home office; finding in each one the articles my friend had dog-eared; and then clipping, stapling, and filing them in a beat-up metal cabinet pushed into a corner of the room.

Well, here we are some 25 years later, and the effort to keep up with information about the advances and challenges in oncology is still a headache, now super-sized. Scientific journals aren't the only medium carrying reports that could make a difference in how your practice and your patients fare. Now there are countless podcasts, videos, and real-time Web-based broadcasts of oncology conferences, panel discussions, and lectures.

Chances are you can't hire some kid down the block to scour the Web and do the modern-day equivalent of clipping and filing. So here is, perhaps, the next best thing: a guide to several Web sites where you may find worthwhile educational presentations.

You'll have to judge whether the updates on these sites are worth your time. But from a production point of view, the videos and podcasts—if not IMAX-like—are generally of good quality.

OncologyTube

WWW.ONCOLOGYTUBE.COM

Thanks to YouTube, we have become a nation of online video watchers, producers, and commentators. Therefore, it's hardly a surprise that YouTube has spawned imitators, including OncologyTube.

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As of December 2010, OncologyTube is still in its beta, or final testing, stage. Still, in offerings as well as performance, it seemed to be quite ready for prime time.

When you land on OncologyTube's home page, you can immediately dive into its videos: several that the producers of the site feel should get top billing at the moment, and almost two dozen that other visitors are watching at the moment. On the day I visited the site, those videos included offerings on sentinel lymph node biopsy, an explanation of better ways to compound hazardous IVs, and insight into the work of an oncology nurse navigator.

In addition, on the site's home page you can make use of 15 hyperlinks to navigate to pages that carry their own links to yet more videos about specific cancers, ranging from breast cancer to melanoma to pediatric cancer. Thumbnails, which act as links to individual videos, also tell you how long each video is, the number of people who have viewed the video, and a brief description of the source of the video, which can help you assess its potential value to you.

If you believe in serendipity, click on the site's Videos tab to go directly to a page where you can browse through links to all of the videos on OncologyTube. Or, use the Channels tab to go to a page where videos are listed according to the organization or group that created them. Believe in the wisdom of the crowd? Then, by all means, look for videos under the links leading to Most Discussed, Most Responded, Most Viewed, Top Favorites, and Top Rated.

Find an especially interesting video? You can share it by e-mailing it to a colleague. You can also bookmark videos so that you can revisit them in the future without digging around for them.

If you are registered with the site, you may upload videos yourself, giving the world your take on a cancer topic. The video cannot exceed 60 minutes or 300 megabytes. And, in the best tradition of social networks, you can even set up a "friends" page for yourself where you can store videos created or recommended by friends.

Research To Practice

WWW.RESEARCHTOPRACTICE.COM

The brainchild of Neil Love, MD, a Miami, Florida medical oncologist, Research To Practice has a wide array of oncology-related CDs, podcasts, articles, slides, and other e-learning offerings for doctors, nurses, and other healthcare specialists.

Research To Practice could serve as an example of what a considerate Web site should be: no eye-burning graphics, flashing banners, or margins crammed with small-print information. Instead, its home page gets right to the point. There are just five large windows: one for announcements, one containing an explanation of who is behind the Web site, a third dedicated to a list of upcoming events. A fourth window allows you to browse through the site's content according to tumor type, and the fifth frame offers access to a search engine that allows you to specify parameters to narrow your search efficiently by tumor type, treatment setting or stage, and other things.

By and large, those searches lead

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to extensive podcasts about the topic you have chosen. If you don't have time to listen at the moment, you can download the audio track or tracks and listen to them when you are out jogging or driving home.

Research To Practice also steps back into old world communications by mailing selected educational materials to oncologists.

The site's materials are available through iTunes. It also offers CME and CNE credit for activities on its site.

Imedex E-Learning Center

[HTTP://ELC.IMEDEX.COM/ELC/](http://ELC.IMEDEX.COM/ELC/)

Imedex, too, opens with a simple home page, divided into several frames, or windows.

One window provides a link to a featured activity. On the day I looked at the site, for example, the feature was a Webcast on optimizing bisphosphonates for patients with multiple myeloma. A second window offered links to other recent additions to the site. A third window presented links to individual pages focusing on oncology, hematology, gastroenterology, infectious disease, and dermatology.

Once you land on an inside page, you can scroll through its contents to find Webcasts of meetings or lectures, case presentations, podcasts, and monographs that include video as well as text.

If scrolling and surfing around

don't appeal to you as an efficient way to find topics of interest, you can always resort to the site's search box. On the inside pages you can make use of an index offering links to content according to specialty (dermatology, gastroenterology, etc); media type (audio, video, multimedia); or product type (monograph, podcast, etc).

Imedex materials are also offered via iTunes. The site's offerings qualify for continuing medical education credits.

Other sites to consider

If, after dipping into OncologyTube, Research To Practice, and Imedex, you are still hungry for more, take a look at:

Cleveland Clinic Center for Continuing Education

WWW.CLEVELANDCLINICMEDED.COM/ONLINE/WEBCAST

The Cleveland Clinic's Web site covers much of the medical world, but you can get to oncology-related content by clicking the Specialty link "Hematology/Oncology."

PrIME Oncology

WWW.PRIMEONCOLOGY.ORG

A well-organized site, it includes a wide range of multimedia presentations, including Webcasts, audio-casts, and downloadable slides from meetings.

The Doctor's Channel

WWW.THEDOCTORSCHANNEL.COM

The Doctor's Channel is also an all-medical-things site, including sections for hematology/oncology and oncology. Its videos are largely one- or two-minute affairs, accompanied by news articles. It seems to be a well-attended site: One video, Imiquimod for Anal Pre-Cancer, for example, had 27,463 views as of early December. Unfortunately, the site is plagued by annoying up-front ads you have to exit before you get to the content that interests you.

Cancer.Net

WWW.CANCER.NET

Cancer.Net, brought to you by the American Society of Clinical Oncology, carries a massive amount of information, though it may take some patience to get at specific contents from the site's home page: It is a nightmare of graphics, text, and thumbnail links.

OncologySTAT

WWW.ONCOLOGYSTAT.COM

We'd be remiss if we didn't mention Elsevier's own oncology-related Web site. Top features include the Editor's Choice oncology story of the week, news, articles that offer CME credits, journal scans of the top cancer-related articles, oncology-specific review articles, and editorials from key opinion leaders.

Chemotherapy drug shortages present challenges for oncologists and their patients

Alicia Ault

An ongoing shortage of some crucial chemotherapy drugs is forcing oncologists to scramble for supplies or to find therapeutically equivalent alternatives, if there are any. In some cases, oncologists are creating a triage system whereby the patient who is most likely to be cured will receive the therapy that's in short supply.

George Kovach, MD, medical director at Iowa Cancer Specialists, PC, in Davenport, said his practice has been struggling to get leucovorin. The drug has been in short supply since this past April, when the maker, Teva Pharmaceuticals, began a manufacturing hold at its Irvine, California, plant to update systems and processes.

Financially managing the shortage has also been an issue, Dr. Kovach said. The alternative, levoleucovorin (Fusilev), costs about 10 times more than does leucovorin. And Medicare reimburses only \$750 of the \$1,200 cost for levoleucovorin, he said. For many patients, the practice has been absorbing the loss. Others were sent to a hospital outpatient department for treatment, said Dr. Kovach, a member of the Association of Community Cancer Care Centers (ACCC) board of trustees.

Michael Neuss, MD, the immediate past chair of the American Society of Clinical Oncology (ASCO) clinical practice committee and a physician in private practice with Oncology Hematology Care in Cincinnati, said patients at his practice are prioritized to receive leucovorin based on whether administration would be

curative. His practice has managed to procure adequate supplies of levoleucovorin, but oncologists "really don't know" whether it is equivalent to leucovorin, he said.

In addition to the shortages of leucovorin and levoleucovorin in 50-mg, single-use vials, at press time the US Food and Drug Administration (FDA) and the American Society of Health-System Pharmacists (ASHP) were reporting shortages of other drugs, including cisplatin, doxorubicin (lyophilized powder and solution for injection), etoposide, some sizes of vincristine, and cytarabine injection (powder for reconstitution).

Capt. Valerie Jensen, associate director of the agency's Center for Drug Evaluation and Research Drug Shortage Program, said that many of these shortages involve older, sterile injectable drugs. Fewer companies are interested in making the low-profit injectables, she said in an e-mail, and some have also had issues with accessing raw materials or meeting the FDA's quality guidelines.

Oncologists' concerns about dosages, efficacy, and safety pertain to other alternatives as well. In the case of the oral alternative for IV etoposide, for example, myelosuppression can be more erratic with the oral form, according to Lawrence Einhorn, MD, past president of ASCO and a distinguished professor and Lance Armstrong Foundation Chair in Oncology at Indiana University, Indianapolis, asserted in an interview on the ASCO Web site.

Dr. Neuss said that his practice

had been doubling the dose of the oral version as a substitute, but "is that the exact conversion? I'm not sure."

Doxorubicin is another therapy that has been difficult to get. Steven L. D'Amato, RPh, a clinical pharmacy specialist at the Maine Center for Cancer Medicine in Scarborough, said the shortage has affected investigational protocols and the center's anthracycline-containing regimens.

In Dr. Neuss's practice, which has also had difficulty finding an adequate supply of doxorubicin, the drug is held back "for patients who are getting curative therapy."

Pediatric oncology has been hit particularly hard by the shortages. In an interview on ASCO's Web site, Michael Link, MD, a pediatric oncologist and ASCO president-elect, said there are few acceptable alternatives for many of the therapies used in children. "[Most] are treated on clinical trial protocols...so we have a very large evidence base for many of the common drugs but are lacking evidence for substitutions, particularly in complex multidrug regimens," Dr. Link said.

In early November, ASCO, ASHP, the American Society of Anesthesiologists, and the Institute for Safe Medication Practices convened a summit to discuss the shortages and possible solutions. The FDA and drug company representatives also attended. The ASHP said that work groups are developing action plans to execute the summit's recommendations.

Dr. Neuss, Dr. Kovach, Mr. D'Amato, and Dr. Link reported no conflicts of interest.