



COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

ORIGINAL RESEARCH

A phase II tolerability trial of neoadjuvant docetaxel with carboplatin and capecitabine in **locally advanced breast cancer**

Aruna Mani et al

REVIEW

Combining sorafenib with chemoembolization for **hepatocellular cancer**

Minsig Choi et al

COMMUNITY TRANSLATIONS

Update on romiplostim therapy for **immune thrombocytopenic purpura**

Matt Stenger

Thrombopoietin mimetics challenge the conventional wisdom about controlling ITP

Commentary by David M.J. Hoffman

Pictured above: immune thrombocytopenic purpura

CASE REPORTS

Rare case of **renal cell carcinoma** presenting as a cutaneous horn

Louise Zhou et al

Lung cancer and hypercoagulability, complicated by suspected heparin-induced thrombocytopenia

Venu Madhav Konala et al

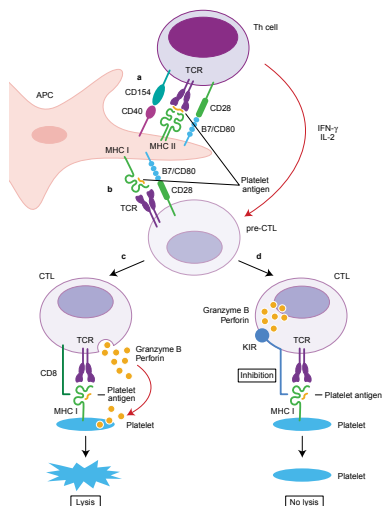
Hydroxyurea-induced palmar-plantar erythrodysesthesia in an adult with sickle cell disease

Ramandeep K. Bambrah et al

WASHINGTON UPDATE

House hears **SGR alternatives**, vows action

Francis Correa



Model of cell-mediated cytotoxicity in chronic immune thrombocytopenic purpura (ITP). A recently reported phase III trial has shown that romiplostim (Nplate) is superior to the standard of care in adults with ITP, resulting in higher platelet response rates, lower rates of treatment failure and splenectomy, fewer bleeding episodes, and fewer blood transfusions, while two earlier-stage clinical trials have demonstrated that romiplostim is well tolerated and effective in children with ITP (see page 224).

Washington Update

239 The House hears SGR alternatives, vows action

Frances Correa

A House subcommittee met with a five-person panel of experts from medical associations and health policy organizations on May 5, 2011, to consider alternatives to the current SGR formula, labeled by some participants as anything but sustainable. Rep. Michael Burgess (R-Tex) summed up the sentiment regarding Congress's protracted lack of action on the matter: "If we get to December and we're doing an extension, that's a failure on our part. We need a permanent solution that's predictable, updatable, and reasonable for this year—and nothing else will do."

LETTER FROM THE EDITOR

203 The SGR by any other name...

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

Congress might finally get serious about altering the Sustainable Growth Rate formula, if comments from a House subcommittee hearing earlier this month are anything to go by. The SGR concept worked well when times were good, but it is not geared to accommodate the complexities of today's oncology care nor weather current economic challenges. The SGR needs to be repealed, says Dr. Henry, and the fee-for-service payment system reformed so that practices that provide quality guideline-based and outcomes-driven oncology care will receive appropriate and better reimbursement.

ORIGINAL RESEARCH

209 A phase II tolerability trial of neoadjuvant docetaxel with carboplatin and capecitabine in locally advanced breast cancer

Aruna Mani, MD, Sandra X. Franco, MD, Grace Wang, MD, Neil Abramson, MD, Lee S. Schwartzberg, MD, FACP, James Jakub, MD, Elizabeth Tan-Chiu, MD, Michael A. Schwartz, MD, Cynthia Frankel, RN, OCN, Elisa A. Krill-Jackson, MD, Alisha Stein, RNC, BSN, OCN, Alejandra T. Perez, MD, and Charles L. Vogel, MD, FACP, *Memorial Cancer Institute, Pembroke Pines and Hollywood, FL; Cancer Research Network, Boca Raton, FL; Advanced Medicine Specialists, Miami, FL; Baptist Cancer Institute, University of Florida, Jacksonville, FL; The West Clinic, Memphis, TN; Mayo Clinic, Rochester, MN; Florida Cancer Care, Davie, FL; Mount Sinai Medical Center, Miami Beach, FL; and Sylvester Comprehensive Cancer Center, Deerfield Beach, FL*

In this study, investigators evaluated the tolerability and efficacy of neoadjuvant docetaxel with carboplatin and capecitabine (Xeloda) in patients with locally advanced breast cancer and found the combination had acceptable toxicity and a complete pathologic response (pCR) rate comparable with those observed in similar trials. Five of the six patients achieving a pCR had triple-negative tumors, which in the context of similar findings in other studies, suggests that further investigation is needed, specifically in *BRCA* mutation carriers and patients with triple-negative tumors to determine whether these specific patient subsets preferentially derive benefit from platinum salts in the neoadjuvant setting.

REVIEWS

216 Combining sorafenib with chemoembolization for hepatocellular cancer

Minsig Choi, MD, Jeffrey J. Critchfield, MD, and Philip A. Philip, MD, PhD, FRCP, *Department of Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, and Department of Radiology, Section of Interventional Radiology, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI*

Hepatocellular carcinoma (HCC) is considered a chemotherapy-resistant malignancy; however, combining sorafenib (Nexavar) with transcatheter arterial chemoembolization in treating patients with HCC has changed the landscape of systemic therapy for these patients and opened up new opportunities.

continued on page 202

contents 2

COMMUNITY ONCOLOGY

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REVIEWS

Community Translations

224 Update on romiplostim therapy for immune thrombocytopenic purpura

Romiplostim (Nplate) is a thrombopoietin mimetic indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura (ITP). In a recently reported phase III trial, the drug was found to be superior to the standard of care in adults with ITP. A separate study showed activity and tolerability in pediatric ITP patients.

227 Thrombopoietin mimetics challenge the conventional wisdom about controlling ITP

David M.J. Hoffman, MD, FACP, *Tower Hematology Oncology Medical Group, Beverly Hills, CA*

CASE REPORTS

230 Rare case of renal cell carcinoma presenting as a cutaneous horn

Louise Zhou, MD, Taren Ohman, MD, and Robert Zaiden, Jr., MD, *Department of Medicine, University of Florida College of Medicine, Jacksonville, FL*

Cutaneous metastases are generally a late manifestation of disseminated renal cell carcinoma (RCC), but in rare cases they can present as the first sign of active disease, as they did in this case. Because RCC may be clinically silent for most of its disease course, a high degree of suspicion is necessary.

233 A case of lung cancer and hypercoagulability, complicated by suspected heparin-induced thrombocytopenia

Venu Madhav Konala, MD, John Srandio, MD, and David H. Henry, MD, *Department of Internal Medicine, Pennsylvania Hospital, Philadelphia, and Department of Medicine, Joan Karnell Cancer Center, Philadelphia, PA*

Heparin-induced thrombocytopenia (HIT) is a life-threatening disorder that can follow exposure to unfractionated heparin or low-molecular-weight heparin (LMWH). The authors present a patient who developed thrombocytopenia after starting LMWH and who had a newly diagnosed adenocarcinoma of the lung with extensive arterial and venous thrombosis and negative serology for HIT.

237 Hydroxyurea-induced palmar plantar erythrodysesthesia in an adult with sickle cell disease

Ramandeep K. Bambram, MD, Fauzia Rana, MD, and Dat C. Pham, MD, *Department of Medicine, University of Florida College of Medicine, Jacksonville, FL*

Palmar plantar erythrodysesthesia (hand-foot syndrome) is a known adverse reaction of certain forms of chemotherapy. In this case report, the authors describe a rare case of hand-foot syndrome in an adult with sickle cell disease who was placed on hydroxyurea without a known history of leukemia/lymphoma or exposure to other cytotoxic drugs.

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The SGR by any other name...

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

We've all heard about the Sustainable Growth Rate (SGR)—who hasn't—but what does it really mean? Congress established Medicare and Medicaid in 1965 through amendments to the Social Security Act to provide health insurance for the elderly and the poor. Initially, tax dollars were put into a fund that physicians and hospitals could access for taking care of Medicare and Medicaid recipients. All went well until health costs began spiraling upward in the 1980s and 1990s.

In 1997, the Balanced Budget Act was enacted, and the SGR was born. It was intended to tie physician reimbursement rates for Medicare Part B to the gross domestic product (GDP), so that reimbursements would increase as GDP increased. But it soon became clear that SGR was a good idea only as long as the economy was strong. By 2002, the economy began to slide, and physician costs outstripped GDP. That year, the first SGR cut was applied to physician reimbursement.

Congress consequently put the breaks on the whole system and has frozen the Medicare reimbursement rates six times in the past two years to block the cut in fees that would occur if the SGR formula were allowed to go forward. That action would translate into a cut of about 25% in reimbursement for Medicare patients in 2012 unless current reimbursement is extended—or SGR fixed—once again. Now it seems that that Congress might actually be serious about altering the SGR payment formula. On page 239, Frances Correa reports on a House subcommittee hearing earlier this month at which representatives from the medical community and health policy organizations proposed alternatives to the current SGR formula.

With hindsight, we can appreciate that the SGR can never address the complexities of today's oncology care. Clearly, the fee-for-service model is too simplistic and outdated. Fee-for-service simply says you see the patient, do something, and charge for it. But what have you done? Have you followed accepted national guidelines and addressed the patient's care in its entirety—such as chemotherapy, novel therapies, access to clinical trials, testing, symptom management, outpatient versus inpatient treatment, qual-

ity of life, and end of life? These questions suggest the need for a program that could aid and promote improved quality of cancer care, and there is one—the Quality Oncology Practice Initiative. It leads naturally into the concept of the oncology medical home, which entails the oncologist assuming total care of a patient during the patient's oncology experience.

If a new payment system is accepted, it should require that guidelines be followed, quality care delivered, and systems such as electronic health records be in place to document that quality care was delivered. Then practices that provide quality guideline-based and outcomes-driven oncology care will receive appropriate reimbursement, consistent with increasing costs of healthcare delivery.

Let's turn from running a practice to treating our patients. On page 209, Aruna Mani and her colleagues report on a trial in which they evaluated the tolerability and efficacy of neoadjuvant docetaxel with carboplatin and capecitabine (Xeloda) in patients with advanced breast cancer. They found that the combination had acceptable toxicity and a pathologic complete response rate comparable to that in similar trials.

On page 216, Minsig Choi and his colleagues review a novel concept of treating hepatocellular cancer with sorafenib (Nexavar) by adding chemoembolization via the transarterial approach or transcatheter arterial chemoembolization (TACE). Preliminary data suggest the TACE approach may be suboptimal because of angiogenic signaling that results after a TACE therapy, but the addition of a VEGF inhibitor such as sorafenib might block that action and provide better outcomes.

One of the newest treatments for immune thrombocytopenic purpura (ITP) is the thrombopoietin mimetic romiplostim (Nplate). On page 224, we review two studies, one that compared romiplostim and standard of care in adults with ITP, and another that investigated the drug's activity and tolerability in pediatric patients with ITP.

Finally, we have three interesting case reports to add to the literature: renal cell carcinoma presenting as a cutaneous lesion (p. 230); a man with lung cancer who presented with hypercoagulability and heparin-induced thrombocytopenia (p. 233); and palmar plantar erythrodysesthesia as a potential side effect of hydroxyurea (p. 237).

A phase II tolerability trial of neoadjuvant docetaxel with carboplatin and capecitabine in locally advanced breast cancer

Aruna Mani, MD,¹ Sandra X. Franco, MD,² Grace Wang, MD,³ Neil Abramson, MD,⁴ Lee S. Schwartzberg, MD, FACP,⁵ James Jakub, MD,⁶ Elizabeth Tan-Chiu, MD,^{2,7} Michael A. Schwartz, MD,⁷ Cynthia Frankel, RN, OCN,^{1,2} Elisa A. Krill-Jackson, MD,⁷ Alisha Stein, RNC, BSN, OCN,² Alejandra T. Perez, MD,^{1,2} and Charles L. Vogel, MD, FACP^{2,9}

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This multicenter phase II trial evaluated the tolerability and efficacy of neoadjuvant chemotherapy in locally advanced breast cancer with four 28-day cycles of dose-dense chemotherapy: weekly docetaxel (30 mg/m²) and carboplatin (AUC 2) on days 1, 8, and 15, plus capecitabine (625 mg/m²) twice daily on days 5–18. The primary endpoint was pathologic complete response (pCR). Among the 49 treated patients, 89% of intended chemotherapy doses (including capecitabine) were administered. In the intent-to-treat patients, grade 4 toxicities were depression (2%) and leukopenia (8%). There were no neutropenic fevers or treatment-related deaths. Of the 41 evaluable patients who received all four chemotherapy cycles, 6 (15%) achieved a pCR; all of them had negative axillary nodes. None of the patients with pCR had developed recurrent disease at a median follow-up of 48 months. We conclude that preoperative docetaxel, carboplatin, and capecitabine has an acceptable toxicity profile and a pCR rate comparable with that seen in many other phase II neoadjuvant chemotherapy trials.

The standard of care for locally advanced breast cancer (LABC) is neoadjuvant chemotherapy,¹ with LABC including clinical stages IIA, IIB, and IIIA. The goals of preoperative chemotherapy are to downstage so as to render breast conservation feasible, to eradicate disease in the axillary nodes, and to allow in vivo testing of tumor drug sensitivity, all with the ultimate aim of improving prognosis. Clinical trials have demonstrated that the pathologic in-breast response generally correlates with pathologic response in the lymph nodes. Furthermore, nodal status at the time of surgery correlates with overall survival (OS) and disease-free survival (DFS).^{2,3} A combined analysis of two large prospective neoadjuvant chemotherapy trials demonstrated significantly higher 5-year OS and DFS in patients achieving in-breast pathologic complete response (pCR), compared with those who did not (OS, 89% vs 64%; DFS, 87% vs 58%, respectively).⁴

At the start of this trial, the most effective neoad-

juvant regimen remained in question. Even now, National Comprehensive Cancer Center guidelines suggest that any recommended adjuvant regimen can be used in the neoadjuvant setting.¹ Numerous phase II and III trials have evaluated single-agent^{5–8} and combination^{9–32} chemotherapies, most of which are anthracycline-based, with pCR rates reported between 7% and 36%. In the NSABP-B27 study, patients treated preoperatively with four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of docetaxel (Taxotere) had a 26% pCR rate versus a 13% pCR rate in those receiving preoperative AC and postoperative docetaxel. Despite the doubling of pCR with neoadjuvant docetaxel, there was no difference in DFS or OS.⁹ However, as reported by Kuerer

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et al, patients achieving a pCR after completion of neoadjuvant chemotherapy appeared to have superior survival.⁴

Many previous trials (including the study reported here) did not exclude patients with human epidermal growth factor receptor 2 (HER2)-positive disease. It is now well established that such patients should be treated with neoadjuvant regimens incorporating HER2-targeted therapy. In fact, an early neoadjuvant study of paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide with or without 24 weeks of concurrent trastuzumab (Herceptin) in patients with HER2-positive tumors was closed early because patients receiving trastuzumab had a pCR rate of 65%, compared with 26% in those who did not receive it.³³ Expanded clinical trials of this approach are in progress.

The selection of capecitabine (Xeloda) and docetaxel in the present trial was based on the hypothesis that the upregulation of thymidine phosphorylase by docetaxel should increase the activity of capecitabine.³⁴⁻³⁶ Single-agent docetaxel in the neoadjuvant setting has yielded pCR rates of 7%–20%.⁶⁻⁸ Treatment with docetaxel and capecitabine together has been reported to produce pCR rates of 10%–21%.³⁷⁻³⁹ The addition of carboplatin was based on studies by Hurley et al at the University of Miami³⁹⁻⁴¹ suggesting that platinum salts appeared quite active in the neoadjuvant setting, with the combination of docetaxel and cisplatin producing a pCR rate of 20%, with no residual disease in the breast or axilla.⁴⁰ Other regimens incorporating cisplatin or carboplatin have pCR rates ranging from 16% to 24%.^{27,42-44}

Patients and methods

Study design

In this phase II multicenter study, patients were assigned to receive docetaxel (30 mg/m² IV) and carboplatin (AUC 2 IV) on days 1, 8, and 15

of each 28-day cycle plus capecitabine (625 mg/m² PO) twice daily on days 5–18. The capecitabine dose was based on observations that this dose was effective and relatively nontoxic in metastatic breast cancer (C.L. Vogel, empirical observations). Patients were to receive four cycles prior to surgical resection.

Given that this neoadjuvant regimen was under study, all of the patients were scheduled to receive a proven standard postoperative adjuvant chemotherapy regimen, starting 4–6 weeks postoperatively, with doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV) every 21 days for 4 cycles. This sequential design was prompted by studies such as the NSABP B-27 and Aberdeen trials.^{9,32}

Radiation therapy after lumpectomy or mastectomy was given according to individual institution guidelines. Patients with hormone receptor-positive tumors received appropriate antihormonal therapy. Tumor measurements were assessed at baseline and on day 1 of each cycle by physical examination with calipers. No breast or other imaging was required during the period of neoadjuvant chemotherapy or immediately preoperatively. Patients were considered evaluable if they proceeded to surgery after all intended cycles of neoadjuvant chemotherapy or if they developed disease progression during neoadjuvant therapy.

Patients

Eligible patients were men and women regardless of menopausal status \geq 18 years of age with core-needle biopsy proven locally advanced or inflammatory breast cancer. Breast cancer characteristics such as estrogen receptor (ER), progesterone receptor (PR), or HER2 status were collected but not used for inclusion/exclusion. Eligible tumors were T2 requiring mastectomy; T3N0–2; T4; and any TN2–3 that

by calipers was $>$ 2 cm or with fixed or matted axillary or imaging-detected internal mammary nodes. Patients with prior ductal carcinoma in situ (DCIS) were included, as were those with \leq T2N0M0 breast cancer $>$ 5 years prior.

Other requirements were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; life expectancy $>$ 6 months; negative metastatic workup (bone scan and CT chest/abdomen/pelvis); adequate bone marrow, liver (Table 1), and kidney function; and peripheral neuropathy \leq grade 1. All patients of child-bearing potential were required to consent to dual methods of contraception during treatment and for 3 months afterward. A negative pregnancy test was required for these women before treatment, and any suspicion of pregnancy had to be reported to the treating physician.

Study endpoints

The primary endpoint of the study was the in-breast pCR after four cycles of platinum-based neoadjuvant chemotherapy. Pathologic complete response was defined as complete disappearance of invasive and in situ disease or invasive disease alone. During the course of this trial, it became generally acceptable to include patients with only residual DCIS as equivalent to pCR.⁴⁵

The secondary endpoints were pCR in the lymph nodes; clinical response rate; tolerability; breast conservation; time to disease progression (local, regional, and distant); and OS. Also recorded was minimal residual disease (MRD), which we arbitrarily defined as \leq 1 cm invasive carcinoma at resection. The overall treatment plan included postoperative AC to provide a standard-of-care regimen to maximize curative potential.

Statistical analysis

Data were analyzed on an intent-to-treat basis. Although pCR rates

TABLE 1

Liver function: eligibility criteria

Alkaline phosphatase level	Alanine transaminase or aspartate transaminase level			
	≤ ULN	> 1 × ULN but ≤ 1.5 × ULN	> 1.5 × ULN but ≤ 5 × ULN	> 5 × ULN
≤ ULN	Eligible	Eligible	Eligible	Ineligible
> 1 × ULN but ≤ 2.5 × ULN	Eligible	Eligible	Ineligible	Ineligible
> 2.5 × ULN but ≤ 5 × ULN	Eligible	Ineligible	Ineligible	Ineligible
> 5 × ULN	Ineligible	Ineligible	Ineligible	Ineligible

ULN = upper limit of normal

with doxorubicin plus either cyclophosphamide or docetaxel have been < 15%, the studies by Smith et al²⁶ and Hurley et al³⁹ with in-breast pCR rates of at least 20% served as comparators (albeit imprecise).

Applying the min/max statistical design, the procedure tests the null hypothesis $H_0: P \leq 0.15$ against the alternative hypothesis $H_1: P \geq 0.30$. The overall level of significance and power for this design are 5% and 80%, respectively. The sample size needed for the first stage was 23 evaluable patients. If three or fewer pCR responses were observed, then the study would be terminated and the treatment regimen would not be investigated further. Otherwise, an additional 25 evaluable patients would be accrued for a total of 48 study patients. If 11 or fewer responses were observed, then the study would be terminated. Otherwise, this treatment regimen would be recommended to proceed to phase III for further investigation.

Tolerability assessment

At each visit, toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria, version 2.⁴⁶ Two

dose reductions were allowed for all drugs (Table 2).

Ethical considerations

The investigational nature of this study was fully disclosed to each patient. In accordance with institutional and federal guidelines, the patients were guided through and subsequently signed the informed consent approved by the appropriate site Institutional Review Board.

Literature review

The terms “neoadjuvant” and “breast” were used in a literature search on PubMed, with filters “English” and “clinical trials.” Abstracts for each of the 398 results were reviewed

We used phase II or III trials with at least 30 patients, at least four cycles of chemotherapy, and clearly defined pCR for comparison to this study.

Results

Patients

Between June 2003 and December 2006, 50 women with a median age of 49 years (range, 28–75 years) were enrolled. One patient was ineligible due to preceding lumpectomy. The 49 eligible patients were treated with ≥ 1 cycle

TABLE 2

Dose reductions

Dose level	Starting dose	First dose reduction	Second dose reduction
Docetaxel	30 mg/m ²	25 mg/m ²	20 mg/m ²
Carboplatin	AUC 2.0	AUC 2.0	AUC 1.5
Capecitabine	1,250 mg/m ²	938 mg/m ²	700 mg/m ²

AUC = area under the curve

of neoadjuvant chemotherapy between June 27, 2003, and April 12, 2007.

The baseline characteristics of the 49 eligible patients are summarized in Table 3. Thirty-one patients (63%) were premenopausal. Twenty patients (41%) were positive for either ER or PR and were negative for HER2. Eight patients (16%) had HER2-positive tumors, and 23 (46%) had triple-negative tumors. At baseline, 22 patients (45%) had clinical lymphadenopathy, and 1 patient (2%) had inflammatory breast cancer.

The 41 patients (83%) who completed all four cycles of therapy were evaluable for response; 8 (16%) were inevaluable due to noncompliance (1), grade 3 or 4 toxicity (5), or withdrawal of consent (2). The following efficacy assessments apply to the 41 evaluable patients, whereas the toxicity assessments include the 49 patients who received at least one full cycle of chemotherapy.

Clinical response

At study onset, of the 49 eligible patients, 38 (78%) had a palpable in-breast tumor (median size, 5.5 cm); 22 (45%) had enlarged nodes, and 34 (69%) had confirmed nodal involvement (by biopsy or imaging). A clinical complete response (cCR) rate in the breast was seen in 23 of 41 (56%) evaluable patients. Of 22 patients with baseline lymphadenopathy (by imaging or physical examination), 13 had axillary assessment by physical examination throughout treatment, with 12 (92%) exhibiting a cCR in the axilla.

Pathologic response

After four cycles of chemotherapy, an in-breast pCR (the primary endpoint) was demonstrated in 6 of 41 patients (15%). One of these six patients had residual DCIS and is listed separately. All of these patients had nodal pCR, whereas overall, 20 patients (49%) had negative nodes at resection.

The pathology reports of two patients were read as having invasive

TABLE 3
Baseline tumor characteristics

Characteristic ^a	Number ^b	Percent
ER+	22	45
ER-	27	55
PR+	17	35
PR-	32	65
HER2+	8	16
HER2-	41	83
Triple negative	23	47
IIb	12	24
IIIa	25	51
IIIb	3	6
IIIc	2	4
Inflammatory	1	2
T2N0	8	16
T2N1	9	18
T2N2	2	4
T2N3	1	2
T3N0	7	14
T3N1	10	20
T3N2	4	8
T4N0	1	2
T4N1	1	2
T4N2	2	4
T4N3	2	4
TON2	2	4
DCIS ^c	47	96
LCIS ^c	2	4

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ

^aMedian tumor size: 5.5 cm (range, 2–15 cm)

^bOf 49 evaluable patients

^cAssociated with the infiltrating cancer

TABLE 4
Pathologic response

Outcome	Total (n = 41)		Residual nodal disease (+ nodes)	
	Number	Percent	Number	Percent
pCR	5	12	0	0
pCR (DCIS)	1	2	0	0
MRD	14	34	8	57
T1c	9	22	5	55
T2	7	17	5	71
T3	3	7	3	100
Tx	2	5	0	0

pCR = pathologic complete response; DCIS = ductal carcinoma in situ; MRD = minimal residual disease

tumor within lymphatics and lymphovascular invasion (one each) with no measurable disease, with tumor thus sized as Tx. Neither of these patients had involved lymph nodes. Fourteen patients (34%) had MRD in the breast, and 8 of these 14 patients (57%) had residual nodal disease. Nine patients (22%) had T1c tumors (> 1–2 cm), with five of these nine patients (55%) having nodal disease. Seven patients (17%) had T2 tumors (> 2–5 cm) tumors, with five of these seven patients (71%) having nodal disease. These findings are summarized in Table 4. The correlation between in-breast cCR and pCR was 26%.

Biologic features of responders

Of interest, five of the six patients with a pCR had triple-negative tumors. This translates to a 22% pCR rate (5 of 23) in the triple-negative subset, and a pCR rate of 6% (1 of 18) in patients with ER-positive and/or PR-positive tumors. The remaining patient with a pCR had ER-, PR-, and HER2-positive disease.

One patient had inflammatory breast cancer at diagnosis, and another developed this during the course of chemotherapy; the latter patient was removed from the study for progressive disease. Interestingly, the patient who presented with inflammatory breast cancer was one of the six patients with a pCR. Both of these inflammatory disease patients had triple-negative tumors.

Conversion to breast conservation

Breast conservation was offered to patients if it was deemed appropriate by the treating surgeon. Preoperative imaging was not mandated and thus was not routinely performed. Mastectomy was ultimately performed in 4 of the 6 patients (67%) with pCR and in 22 of the 35 patients (63%) with less than a pCR. Thus, the choice for breast conservation did not correlate well with response to chemotherapy.

Time to disease progression

At a median follow-up of 48 months (range, 7–63), 36 of 41 patients (88%) remained free of disease (range, 19–63 months). Two patients had progressive disease while they were on study treatment and had T3 tumors on resection. Another three patients were found to have progressive disease at 10, 41, and 50 months from study day 1.

Of the nine patients with T1c disease, only one patient (who had positive nodes at resection) had a recurrence (at 41 months). Overall, the patients who had a recurrence had MRD (one patient), T1c (one patient), T2 (one patient), and T3 (the same two patients whose disease progressed while they were on treatment and continued to progress after surgery).

Disease-free and overall survival

Three patients were lost to follow-up, with point of last contact at 19, 34, and 59 months. Of the 41 evaluable patients, 5 patients developed progressive disease, with 2 of these patients progressing during the study treatment. Disease-free survival at 12, 24, and 36 months was 89%, 89%, and 78%, respectively. Overall survival at these same time points was 95%, 90%, and 76%. None of the patients with a pCR is known to have recurrent disease. Of the six patients achieving pCR, two were lost to follow-up after 34 and 59 months, and four continued disease-free at 38, 39, 55, and 62 months.

Adverse events

Five patients were removed from the study secondary to toxicities. Grade 3 and 4 toxicity events are summarized in Table 5. Grade 3 toxicities were anemia (4), diarrhea (2), epigastric pain (1), fatigue (2), hand-foot syndrome (1), infection (1), leukopenia (9), pain (5), and peripheral sensory neuropathy (1). Grade 4 toxicities were depression (1) and leukopenia (4). Toxicities (all grades) occurring in ≥ 10% of the 49 treated patients were

anemia (76%), leukopenia (70%), fatigue (67%), nausea (59%), alopecia (49%), thrombocytopenia (47%), diarrhea (47%), constipation (37%), pain (35%), vomiting (31%), epigastric pain (27%), nail changes (22%), epiphora (22%), hand-foot syndrome (20%), infection (18%), edema (16%), rash (16%), anorexia (16%), and depression (10%). In the intent-to-treat population, there were nine dose reductions among nine patients, and 19 dose delays among 15 patients.

Discussion

The combination of agents tested thus far in the neoadjuvant setting consistently produce pCR rates far less than 50% in unselected populations. This study was begun prior to the widespread use of personalized medicine. Most prior published trials had utilized anthracycline-based chemotherapy, with response rates generally ranging between 7% and 36%.^{6,9-26,28-31,41,42} The idea of thymidine phosphorylase upregulation by the combination of capecitabine and docetaxel upon which this study was largely based³⁴⁻³⁶ has since been disputed.⁴⁷ The primary endpoint of this trial of a novel platinum-based regimen was a pCR rate of 15%. It is significant that 83% of the pCRs were in triple-negative tumors. A secondary endpoint of MRD was calculated, as this was in the original design of the study, but ultimately was not relevant to the primary endpoint.

Ultimately, pCR is the more relevant point of discussion for the modern era. The 15% pCR rate seen in this phase II study was within range of those achieved in numerous other phase II/III neoadjuvant chemotherapy trials with ≥ 25 patients, ≥ 3 cycles of chemotherapy, and pCR defined as absence of carcinoma in the breast and axilla. To date, no patient in our study with a pCR has been noted to have recurrent disease. However, a recently published French study found a 22% recurrence rate at 11 years in patients with triple-negative breast cancer

TABLE 5
Grade 3 and grade 4 toxicities

Adverse event	Occurrences	Grade
Anemia	4	3
Depression	1	4
Diarrhea	2	3
Epigastric pain	1	3
Fatigue	2	3
Hand-foot syndrome	1	3
Infection	1	3
Leukopenia	9	3
Leukopenia	4	4
Pain	5	3
Peripheral sensory neuropathy	1	3

achieving pCR, highlighting the importance of longer-term follow-up.⁴⁸

The inclusion of patients with HER2-positive disease in neoadjuvant studies without HER2-targeted therapy was standard at the time that this study was conducted, but is no longer appropriate. If we were to exclude the eight HER2-positive patients from analysis, then there would be only 34 patients evaluable for response, with a pCR rate of 18%. Buzdar et al³³ demonstrated a 65% pCR rate in women with HER2-positive disease treated with neoadjuvant chemotherapy plus trastuzumab. The improvement in pCR with the addition of trastuzumab is supported by other confirmatory trials. Authors of a single-arm trial of dose-dense epirubicin and cyclophosphamide followed by dose-dense docetaxel and trastuzumab in a HER2-positive population reported a pCR rate of 57%.⁴⁹ The randomized NOAH study⁵⁰ achieved a pCR rate of 23% in 115 patients treated with trastuzumab-based chemotherapy.

It is interesting to note that five of six patients (83%) achieving a pCR in our study had triple-negative tumors. Investigators at the University of Miami presented a retrospective review of locally advanced triple-negative breast cancer treated with docetaxel and a platinum salt, with 61% of patients

also receiving AC. The authors reported a pCR rate of 34% overall and 40% for patients receiving AC.⁵¹ A pCR rate of 60% was noted in the triple-negative subset of patients in another study evaluating docetaxel, doxorubicin, and cyclophosphamide with or without vinorelbine/capecitabine (GeparTrio Study).⁵² Further, a pCR rate of 72% was achieved with single-agent cisplatin in a group of 25 women with *BRCA1* mutations, suggesting, if confirmed by others, that this largely triple-negative population may be exquisitely sensitive to platinum salts.⁴³ In contrast, in a previous study of cisplatin in *BRCA* mutation carriers, Garber et al⁴⁴ reported a pCR rate of 22%, suggesting that further trials are needed specifically in *BRCA* carriers and in triple-negative tumors to see whether these specific patient subsets preferentially derive benefit from platinum salts in the neoadjuvant setting.

The results of the current study are consistent with others indicating a low likelihood of pCR in patients with ER-positive tumors. In fact, none of our ER-positive patients had a pCR. Neoadjuvant endocrine therapy in postmenopausal women with ER- and/or PR-positive disease is a reasonable treatment option for selected patients, but endpoints other than pCR have often been used.^{53,54} It is therefore difficult to directly compare these two strategies. Currently, investigators are comparing the three aromatase inhibitors head to head in the neoadjuvant setting for postmenopausal women with hormone receptor-positive tumors.⁵⁵

The historic pCR ceiling appears to be rising, albeit slowly. Where targets such as HER2 overexpression and triple-negative biology are recognized, progress is being made. Patient eligibility criteria for neoadjuvant breast cancer studies at the time of this trial were quite broad, and it is now recognized that specific subsets of breast cancer respond differently to different classes of agents. Furthermore, our knowledge about breast cancer prog-

nostic markers continues to expand. Had this study been designed in 2011, other data points such as Ki67 would have been collected. A recently published study on neoadjuvant triple-negative breast cancer found that only patients with baseline Ki67% expression > 10% achieved pCR.⁵⁶

Given the long-term implications of not achieving pCR, optimal treatment of patients in the adjuvant setting is critical. Although neoadjuvantly treated patients with ER-positive or HER2-positive disease go on to receive adjuvant agents (antihormonal therapy for ER-positive disease and trastuzumab for HER2-positive disease), patients with triple-negative disease lack long-term therapies of proven efficacy. Perhaps, as we edge closer to defining the optimal neoadjuvant agents for each subset of patients, this will be less of a concern. Many early-phase neoadjuvant studies have been conducted, with promising reports, yet the results of larger, randomized trials continue to frustrate both investigators and clinicians. These deficits in care can only be answered by carefully planned randomized clinical trials.

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Combining sorafenib with chemoembolization for hepatocellular cancer

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The combination of the small molecule kinase inhibitor sorafenib with transarterial chemoembolization (TACE) may have the potential to improve clinical outcomes in patients with hepatocellular carcinoma (HCC) by blocking the angiogenic signaling activated by the chemoembolization. In this article, the authors offer a glimpse at some preliminary data using this treatment for advanced HCC, which is not yet recommended outside the clinical trial setting. Over the coming years, efficacy data from ongoing randomized studies will emerge, helping to optimize and perhaps extend the use of this novel treatment approach in conjunction with other locoregional therapies.

The incidence of hepatocellular carcinoma (HCC) has increased over the past decade, with an estimated 1 million new cases per year worldwide. In 2010 in the United States alone, it was expected that over 24,000 new cases would be diagnosed, with approximately 19,000 deaths.¹ The incidence of HCC in the Western world is expected to rise until 2020 because of the large population of patients infected with the hepatitis C virus.² Furthermore, epidemiologic data suggest that many patients with cryptogenic cirrhosis have non-alcoholic steatohepatitis (NASH) as the cause of their chronic liver disease.³ Due to the rise in obese patient populations, NASH could be an important risk factor for patients with cirrhosis.

Surgical resection and liver transplantation are the preferred treatments of HCC, because they both are potentially curative. Unfortunately, only 10%–15% of patients are candidates for either of these approaches.⁴ Patients with liver-limited disease who are not candidates for liver transplantation or resection may be managed by liver-directed therapies. Common treatment modalities include ablation (eg, microwave ablation, radiofrequency ablation, and cryoablation), chemoembolization, and radioembolization.

Systemic therapy for HCC

HCC is considered a chemotherapy-resistant malignancy. Systemic chemotherapy approach-

es have been ineffective in patients with HCC, with increased toxicities.⁵ However, the introduction of sorafenib (Nexavar) has changed the landscape of systemic therapy for HCC and opened up opportunities for development of new drug regimens and multidisciplinary approaches in the treatment of those patients. Sorafenib is a small-molecule kinase inhibitor that blocks multiple intracellular and cell-surface kinases (KIT, FLT3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR- β) involved in cell signaling, angiogenesis, and apoptosis.⁶

In two large international studies (SHARP and Asia-Pacific) in patients with advanced HCC, sorafenib showed improvement in time to tumor progression (TTP) as well as in overall survival compared with placebo.^{7,8} Patients in these two studies had a Child-Pugh classification of A and a favorable performance status. The hypervascularity of HCC and the predominant effect of sorafenib of vascular endothelial growth factor receptor (VEGFR)-related tyrosine kinase activity provided the proof of principle for targeting angiogenesis in this disease.

In the multicenter, phase III, double-blinded,

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placebo-controlled SHARP trial,⁷ 602 patients with advanced HCC who had not received previous systemic treatment were given either sorafenib (400 mg twice daily) or placebo. At the second planned interim analysis, 321 deaths had occurred, and the study was stopped. The median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group.⁷ In 2007, sorafenib was granted US Food and Drug Administration approval for the treatment of patients with advanced HCC.

Overview of chemoembolization

Transarterial chemoembolization (TACE) is the most widely used approach in the palliative setting and in some patients considered for liver transplantation. Embolization of the hepatic artery and its branches causes ischemic necrosis in the tumor cells that derive their blood supply predominantly from the hepatic artery. In contrast, the normal liver parenchyma is fed primarily by the portal system. The additional mechanism of action of chemoembolization is the trapping of cytotoxic agents within the embolized tissue. This process occurs because the lipiodol, which is used in most regimens, flows through the malignant tissues and parenchyma to obstruct portal vein inflow and hepatic vein wash-out, whereas particulate material employed near the end of the embolization procedure acts by entrapping the agents through blocking the hepatic arterial supply inflow.

Doxorubicin is the most commonly used cytotoxic drug in conjunction with embolization. Other agents used include mitomycin C and cisplatin. Partial responses in the range of 20%–50% have been reported in the literature.^{9,10} Two randomized trials and meta-analyses of chemoembolization in approximately 500 patients showed clinical benefit of this approach when

TABLE 1
Current clinical trials using TACE and sorafenib

Study	Number of patients	Patient characteristic	Primary endpoint
SPACE	300	Child class A	Time to tumor progression
HeiLivCa	208	Pretransplant	Time to tumor progression
ECOG 1208	400	Child class A and B7	Time to tumor progression
TACE-2	412	Child class A	Time to tumor progression and overall survival

TACE = transarterial chemoembolization

compared with conservative management in patients with HCC.^{9,10} These patients were not candidates for either resection or transplantation.

Mild systemic toxicity continues to be an advantageous part of chemoembolization. Although upward of 90% of patients experience the symptoms of postembolization syndrome, which include fever, nausea, vomiting, and abdominal pain, they are generally self-limited and confined to the immediate acute postprocedure period. More serious toxicities such as anemia, liver decompensation, and infection (including cholecystitis) are rare and mostly encountered in patients with more advanced disease.¹¹

Rationale for combining sorafenib with TACE

Treatment with TACE alone causes necrosis of tumor tissue, with transient elevations of levels of many angiogenic growth factors (such as VEGF and plasma insulin-like growth factor 2 [IGF-2]).^{12,13} High expression of stem cell likeness and tumor angiogenesis results in a poor prognosis.^{14,15} Emerging clinical data also suggest that increased VEGF levels post TACE may be associated with an increased chance of disease progression.¹⁶ These angiogenic factors may be responsible for the limited long-term benefit of TACE seen in patients with HCC. Therefore, the combination of sorafenib with TACE may have the potential to improve clinical outcomes in patients with HCC by blocking this angiogenic signaling activated by the chemoembolization.

Current status of studies combining sorafenib with TACE

Multiple clinical trials in the United States and around the world are examining this novel approach in treating patients with HCC (Table 1). Chung and colleagues presented the interim analysis of a phase II trial using the combination of sorafenib and TACE in patients with unresectable HCC at the 2010 American Society of Clinical Oncology meeting.¹⁷ Eligibility criteria included intermediate stage of HCC (BCLC stage B) and a Child-Pugh score ≤ 7 in candidates for TACE therapy. The objective of the study was to evaluate the safety and efficacy of sorafenib after TACE.

Patients were treated with sorafenib (400 mg twice daily initiated on day 4) after the first TACE treatment (day 1). Sorafenib was interrupted 4 days before TACE and 4 days after the next TACE treatment. TACE was performed using lipiodol and doxorubicin (30–60 mg), for a maximum of 6 cycles. A computed tomography (CT) scan of the abdomen and serum alpha-fetoprotein (AFP) measurements were performed 4 weeks after each TACE procedure. Patients remained on sorafenib and underwent CT and AFP analysis every 3 months.

Preliminary data suggest that this approach is feasible, with expected side effects including hand-foot syndrome, fatigue, and neutropenia. Among the 50 patients who had at least two tumor assessments and were available for efficacy analysis, 18 pa-

tients (36%) achieved a complete response (CR), 30 patients (60%) had a partial response (PR) or stable disease (SD), and 2 patients (4%) had progressive disease.¹²

Another multicenter, phase II study was conducted by Erhardt and colleagues.¹⁸ This study also investigated the combination of sorafenib and TACE for the treatment of HCC. Eligibility criteria were similar to the previous study. The primary study endpoint was TTP. Enrolled in the study were 44 patients, with a mean age of 67 years. The majority of patients had Child-Pugh A status (87%) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (79%). Disease etiology included hepatitis C (21%) and hepatitis B (23%), respectively.

Patients were treated with sorafenib (400 mg twice daily continuously), starting 2 weeks before the first TACE procedure. Sorafenib was stopped at least 3 days prior to TACE and could be resumed 1 day after improvement in liver function. TACE was performed using lipiodol and 50 mg of doxorubicin and was repeated at 6-week intervals if necessary. Patients received a mean of two TACE procedures (range, 1–10) and were treated for 6 cycles (range, 1–20).

TTP was estimated to be 491 days, progression-free survival was 242 days, and overall survival was estimated to be 356 days.¹⁸ Thirty-one patients received at least one TACE procedure and were evaluable for response. The disease control rate was 90% (28 of 31 patients), according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria.

A large phase III study of sorafenib in patients who had responded to prior TACE was reported by Okita et al.¹⁹ A total of 552 patients with advanced HCC received TACE and were assessed by CT scan for response. Those who responded to TACE were stratified according to the type of response (CR vs non-CR), ECOG per-

formance status (0 vs 1), and number of prior TACE procedures (1 vs 2) and randomized in a 1:1 ratio to receive either sorafenib (n = 229) or placebo (n = 229). The median time from TACE to receiving sorafenib was 9.3 weeks. The most common adverse events were hand-foot syndrome and elevated lipase levels.

In the analysis of the data, the median TTP was 5.4 months in the sorafenib group versus 3.7 months in the placebo group (hazard ratio [HR] = 0.87; *P* = 0.252). The median overall survival was 29.7 months in the sorafenib group and had not been reached (due to immaturity of the data) in the placebo group (HR = 1.06; *P* = 0.790).¹⁹ Hence, the addition of sorafenib did not significantly prolong the median TTP or overall survival in patients with HCC who had previously responded to TACE. The study was criticized on a number of accounts, including the delay in initiation of sorafenib and the relatively short duration of its use in most patients. Exploratory subgroup analysis showed that clinical benefit was noted in a younger Korean population.

More to learn from ongoing clinical trials

Currently, there are several multicenter clinical trials investigating the benefit of adding sorafenib to chemoembolization in patients with advanced HCC. SPACE is a multinational, randomized, double-blind, placebo-controlled study in patients with intermediate-stage HCC (BCLC stage B; defined as the presence of asymptomatic, unresectable, multinodular tumors without vascular invasion or extrahepatic spread). Major eligibility also includes Child-Pugh class A status without ascites. Eligible patients undergoing TACE with doxorubicin-eluting beads (loaded with 150 mg of doxorubicin) are randomized 1:1 to receive sorafenib (400 mg twice daily) or matching placebo orally on a continuous basis. Treatment cycles are repeated every 4

weeks until disease progression. TACE is performed on day 1 of cycles 1, 3, 7, and 13 and every 6 cycles thereafter. All endpoints will be assessed on an intent-to-treat analysis. The primary study endpoint is TTP. Secondary endpoints are overall survival, time to untreatable tumor progression, time to vascular invasion/extrahepatic tumor spread, and safety. Estimated overall accrual is 300 patients.

The HeiLivCa study,²⁰ ECOG 1208, and the TACE-2 study are also addressing similar questions with slightly different patient populations. For example, the open ECOG 1208 study randomizes patients to receive sorafenib or placebo in conjunction with TACE and allows the interventionist to choose one of a few different chemoembolization methods. Liver-directed therapy can take the form of conventional TACE, using the mixture of doxorubicin, mitomycin, and cisplatin described previously. However, embolization may also be completed by employing conventional Ethiodol (ethiodized oil) TACE, using only doxorubicin or doxorubicin-loaded beads. This varied approach may provide an analytic advantage, because the design better mirrors what is happening at institutions around the world.

The optimal scheduling of sorafenib in relation to TACE has yet to be determined, but with these trials, the elucidation of combination therapy will be discovered. For instance, the TACE-2 trial is not only comparing drug-eluting beads with and without sorafenib but is also additionally randomizing patients into two arms. One arm starts sorafenib or placebo at day 0, whereas the other arm begins with sorafenib or placebo at day 7 after TACE (2–5 weeks post randomization). This study will help to clarify the timing of combination therapy for HCC.

Conclusion

With increased angiogenic factors following embolization and the

emergence of specific agents to target those factors, a potential benefit of targeting angiogenesis as an adjunct to TACE may be expected. Although the rationale is sound and safety has been demonstrated in preliminary studies,^{21,22} using sorafenib in patients with HCC receiving chemoembolization is not yet recommended outside the clinical trial setting. Over the coming years, efficacy data from ongoing randomized studies will be available. It is best to support the current ongoing clinical trials so we may reach a definitive answer. With the increasing awareness among community oncologists and their participation in clinical trials, we should be able to optimize the use of sorafenib in combination with TACE and extend its use in conjunction with other locoregional therapies.

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Update on romiplostim therapy for immune thrombocytopenic purpura

Matt Stenger, MS

Thrombopoietin mimetic is superior to standard of care in adults with immune thrombocytopenic purpura (ITP) and demonstrates activity and tolerability in pediatric ITP patients

Romiplostim (Nplate) is a thrombopoietin receptor agonist that is currently indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. In a recently reported phase III trial,¹ romiplostim treatment was associated with a number of benefits compared with the standard of care in nonsplenectomized ITP patients: higher platelet response rate, lower rates of treatment failure and splenectomy, fewer bleeding events, and fewer blood transfusions.

The safety and efficacy of romiplostim in children with ITP have not yet been established. A recently reported placebo-controlled trial indicates good response and good tolerability of romiplostim in children with chronic refractory ITP.²

Romiplostim versus standard of care in adult nonsplenectomized patients

In a 52-week, multicenter, open-label trial,¹ patients with ITP who had not undergone splenectomy, had received at least one prior treatment for ITP, and had a platelet count of less than $50 \times 10^9/L$ were randomized to receive weekly SC injections of romiplostim ($n = 157$) or standard-of-care treatment ($n = 77$). Romiplostim was started at a dose of $3 \mu\text{g}/\text{kg}$, which could be increased up to a maximum of $10 \mu\text{g}/\text{kg}$ to achieve a target platelet

What's new, what's important

According to the international consensus report on the investigation and management of primary immune thrombocytopenia (ITP), the first-line treatment options for adult patients with ITP are intravenous anti-D immunoglobulin, corticosteroids, and intravenous immunoglobulin (*Provan D et al. Blood 2010;115:168–186*). Second-line agents for treating ITP in this population include immunosuppressive agents, splenectomy, rituximab (Rituxan), and thrombopoietin-receptor agonists, such as romiplostim (Nplate) and eltrombopag (Promacta).

In this article we review the most recent data available on romiplostim, including promising findings from a placebo-controlled clinical trial of romiplostim in pediatric patients with ITP, and discuss current treatment approaches to ITP.

The initial dose of romiplostim is $1 \mu\text{g}/\text{kg}$ once weekly, given as a subcutaneous injection, followed by weekly dose increments, as needed, of $1 \mu\text{g}/\text{kg}$ to achieve a platelet count of $\geq 50 \times 10^9/L$. The maximum weekly dose of $10 \mu\text{g}/\text{kg}$ should not be exceeded. The drug is not approved for use in patients under 18 years of age.

Romiplostim is available only through a restricted distribution program called the Nplate NEXUS Program (www.nplatenexus.com). This program fulfills the risk evaluation and mitigation strategy (REMS) requirement that was instituted for romiplostim by the U.S. Food and Drug Administration in 2007.

— Jame Abraham, MD, *Editor*

count of $50\text{--}200 \times 10^9/L$. Standard-of-care treatment was selected by the treating physician based on standard institutional practices or therapeutic guidelines. Throughout the study, patients in either treatment group could receive additional therapies for ITP, including short-term rescue therapy, such as IV immune globulin (IVIG), but excluding other thrombopoietin mimetics, as deemed medically necessary by investigators.

Study population, endpoints, other treatments

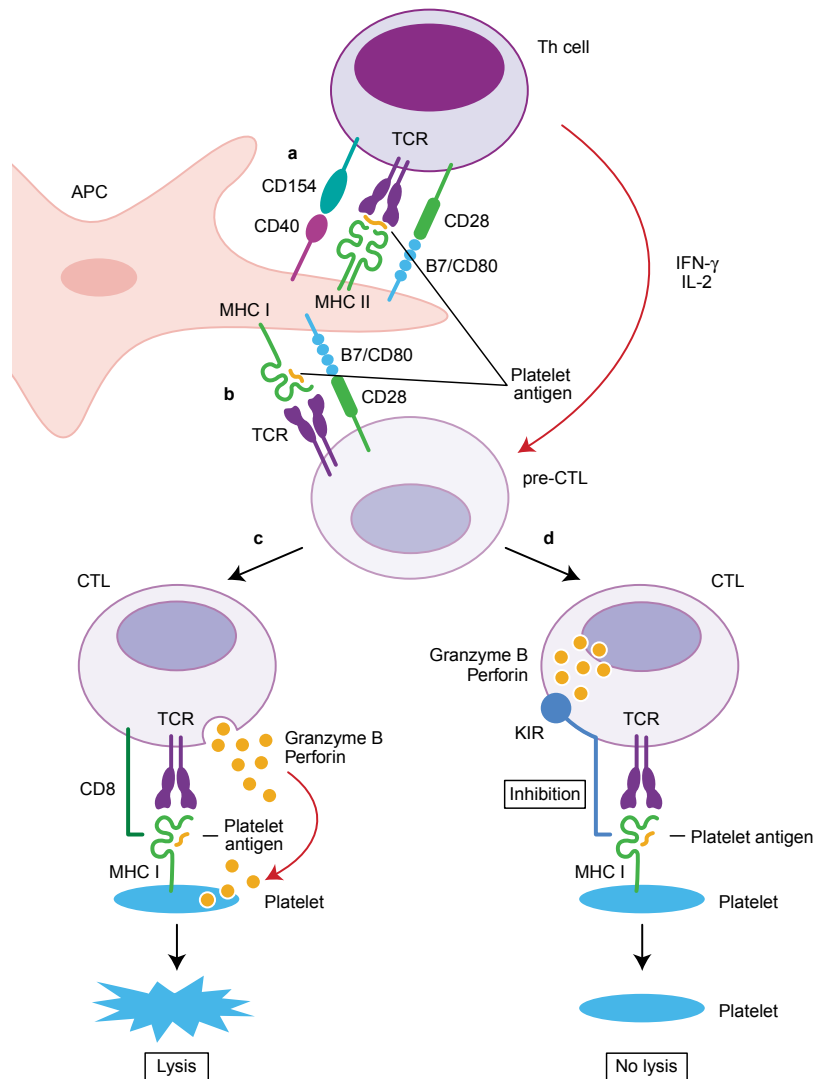
The median ages of patients in the romiplostim and standard-of-care groups were 58 and 57 years, respectively; 54% and 60% were women; the median duration since ITP diagnosis

was 2.1 and 2.3 years; baseline median platelet counts were $33 \times 10^9/L$ and $27 \times 10^9/L$; and 13% and 6% were receiving medications, primarily glucocorticoids (11% and 3%), for ITP at baseline. Splenectomy could be performed if study therapy was considered to be ineffective or was associated with severe side effects.

The primary endpoints of the trial were the incidence of splenectomy and the incidence of treatment failure, with treatment failure defined as a platelet count of $20 \times 10^9/L$ or lower for 4 consecutive weeks, a major bleeding event, or a requirement for a change in therapy (including splenectomy) due to an adverse event or bleeding. In primary endpoint analyses, patients who received any study treatment and then

Model of cell-mediated cytotoxicity in chronic immune thrombocytopenic purpura (ITP)

(a) Antigen-presenting cells (APCs) present platelet antigen in association with major histocompatibility complex (MHC) class II to T-helper (Th) cells, which become activated and secrete the Th1 cytokines interleukin (IL)-2 and interferon (IFN)- γ . **(b)** APCs also present platelet antigen associated with MHC class I to pre-cytotoxic T lymphocytes (pre-CTLs). Pre-CTLs differentiate into active CTLs. **(c)** In the case of chronic ITP in the active phase, CTLs release toxic contents, such as granzyme B and perforin, and platelet lysis occurs. **(d)** In the case of chronic ITP in remission, upregulation of killer-cell immunoglobulin-like receptors (KIRs) on the surface of CTLs could inhibit cell-mediated cytotoxicity in chronic ITP. KIRs recognize MHC class I molecules, hinder presentation of antigen to CTLs, and thereby promote termination of cytolytic activity by CTLs. This might explain the absence of platelet lysis in ITP patients in remission.



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discontinued study participation were counted as having both treatment failure and splenectomy.

During the study, ITP treatments other than romiplostim were received by 44% of patients in the romiplostim group and 79% of patients in the standard-of-care group, including glucocorticoids in 37% versus 63%, IVIG in

7% versus 33%, rituximab (Rituxan) in 1% versus 20%, azathioprine in 1% versus 9%, danazol in 2% versus 7%, other medications in 6% versus 19%, and platelet transfusions in 6% versus 16%.

Efficacy

The incidence of treatment failure was 11% in the romiplostim group

versus 30% in the standard-of-care group ($P < 0.001$). Time to treatment failure was significantly prolonged in the romiplostim group (Figure 1a). The incidence of splenectomy was 9% in the romiplostim group versus 36% in the standard-of-care group ($P < 0.001$), and time to splenectomy was significantly prolonged in the

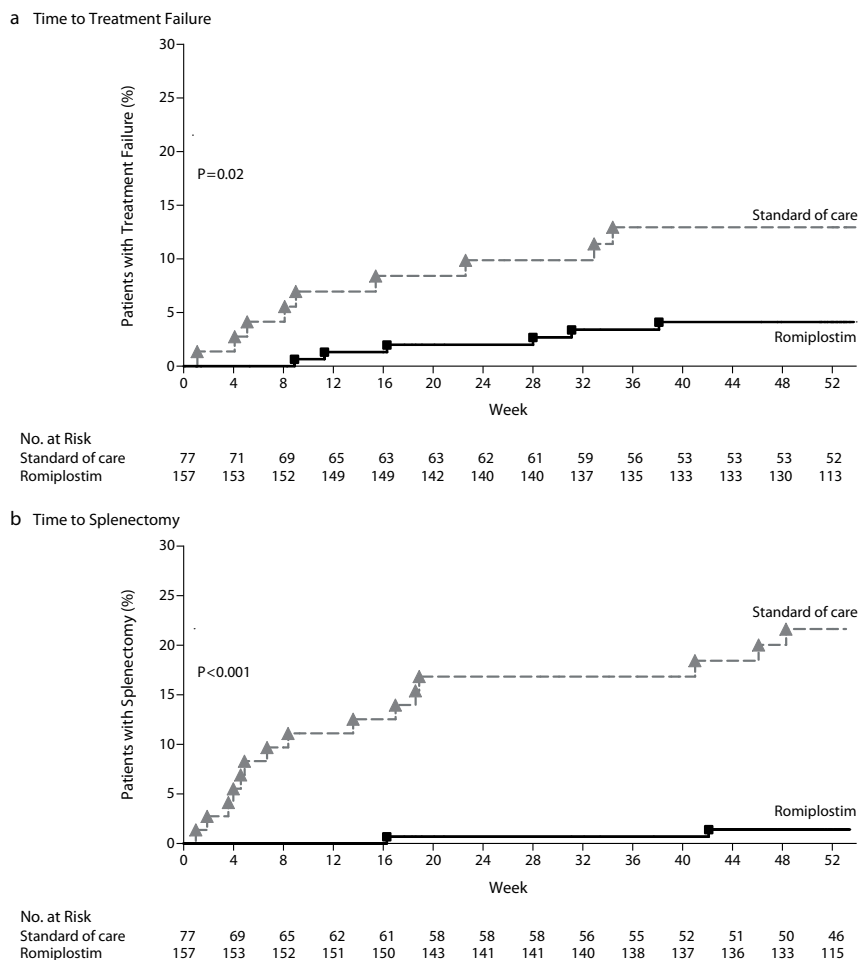


FIGURE 1 Time to treatment failure (a) and splenectomy (b) in patients with immune thrombocytopenic purpura receiving romiplostim or standard of care. Reproduced, with permission, from Kuter et al.¹ © 2010 Massachusetts Medical Society. All rights reserved.

romiplostim group (Figure 1b).

Throughout the study, the mean platelet count was higher in the romiplostim group than in the standard-of-care group. The percentage of patients with a platelet response (defined as a platelet count $> 50 \times 10^9/L$ at any scheduled visit) between weeks 2 and 52 ranged from 71% to 92% in the romiplostim group (median platelet count of $108\text{--}176 \times 10^9/L$) and from 26% to 51% in the standard-of-care group (median platelet count of $35\text{--}52 \times 10^9/L$).

On the whole, romiplostim patients were 2.3 times more likely to achieve a platelet response than patients receiving standard of care (95%

confidence interval, 2.0–2.6; $P < 0.001$). The romiplostim dose needed to maintain the platelet count within the target range was stable over time, particularly after the first 12 weeks of treatment; overall, the mean weekly dose of romiplostim was $3.9 \mu\text{g}/\text{kg}$.

Adverse events

Serious adverse events occurred in 23% of the romiplostim group and in 37% of the standard-of-care group (5% and 8% of these events, respectively, were considered treatment related). Headache and fatigue were the most common adverse events observed overall. Adverse events of interest with thrombopoietin mimetics

include bleeding, thrombosis, hematologic cancer or myelodysplastic syndromes, and increased bone marrow reticulin.

After adjustment for duration of study-drug exposure, the romiplostim group had significantly fewer incidences of overall bleeding ($P = 0.001$) and grade 3 or higher bleeding ($P = 0.02$); no significant difference between the two treatment groups was observed for less severe bleeding. Overall, 260 bleeding events occurred in 80 patients (52%) in the romiplostim group, for a bleeding rate of 3.56 events/100 patient-weeks; 153 events occurred in 40 patients (53%) in the standard-of-care group, for a rate of 5.02 events/100 patient-weeks. Eight grade 3 or higher bleeding events occurred in five romiplostim-treated patients (3%), a rate of 0.11 events/100 patient weeks; 10 events occurred in five patients (7%) in the standard-of-care group, a rate of 0.33 events/100 patient-weeks.

A total of 41 blood transfusions were given to 12 patients (8%) in the romiplostim group, whereas a total of 76 transfusions were given to 13 patients (17%) in the standard-of-care group. There was no significant difference between the two groups with regard to the occurrence of thrombotic events. A total of 11 thrombotic events occurred in six patients (4%) in the romiplostim group, yielding a rate of 0.15 events/100 patient-weeks, whereas two events occurred in two patients (3%) in the standard-of-care group, yielding a rate of 0.07 events/100 patient-weeks.

Two cases of hematologic cancer were observed, consisting of lymphoma and myelodysplastic syndrome in one patient each in the standard-of-care group. Bone marrow reticulin was found in one romiplostim-treated patient during 6 months posttreatment follow up, with the level being within the normal range (grade 2).

Three deaths occurred during the study treatment period, including

one death due to pneumonia in one romiplostim-treated patient and two deaths due to hepatic failure and cardiorespiratory arrest, respectively, in two patients in the standard-of-care group. Three additional deaths due to metastatic lung cancer, left ventricular failure, and hepatic neoplasm occurred in the standard-of-care group during the 6-month posttreatment follow up. None of the deaths was attributed to study treatment. No neutralizing antibodies to romiplostim or thrombopoietin were detected.

Quality of life

Quality of life was assessed by the ITP Patient Assessment Questionnaire, consisting of 44 ITP-specific items on each of 10 scales ranging from 0 to 100 points each (with higher scores indicating better quality of life). Scores on two scales (Women's Reproductive Health and Work Quality of Life) could not be assessed due to inadequacies of the statistical model used in the analysis. Of the eight scales assessed, clinically significant increases of 8–15 points were observed for both treatment groups on all but the Fatigue scale. The romiplostim treatment group showed statistically greater improvements on the Symptoms ($P = 0.01$), Bother ($P = 0.008$), Activity ($P = 0.02$), Psychological ($P = 0.049$), Fear ($P < 0.001$), Social Quality of Life ($P = 0.002$), and Overall Quality of Life ($P = 0.02$) scales compared with the standard-of-care group, although the between-group differences of 2–8 points on these scales are of uncertain clinical significance.

Romiplostim in children with chronic refractory ITP

Few data exist on the effects of romiplostim therapy in pediatric ITP patients. In a recent single-blind, placebo-controlled trial,² 18 patients aged 2.5 to 16 years with chronic refractory ITP (baseline platelet count $< 20 \times 10^9/L$) who had not under-

Thrombopoietin mimetics challenge the conventional wisdom about controlling ITP

Chronic immune thrombocytopenic purpura (ITP) affects 60,000 adults in the United States and is associated with the risk of life-threatening hemorrhage. For decades, the standard treatments included glucocorticoids and splenectomy.

The advent and subsequent regulatory approval of the thrombopoietin mimetics romiplostim (Nplate) and eltrombopag (Promacta) have not only added to the therapeutic arsenal for this orphan disease but also successfully challenged the conventional wisdom that the key to controlling ITP is to reduce platelet destruction. Instead, these agents work by increasing intramedullary platelet production and are thus able to outpace the rate of peripheral destruction.

As reported by Kuter and colleagues last November in *The New England Journal of Medicine*, romiplostim is safe, well tolerated, and highly effective in the adult population with chronic ITP, including individuals with an intact spleen. Among the remaining questions regarding its use are: Where in the sequence of treatments for ITP do thrombopoietin mimetics belong? What is the long-term safety of these agents, given the changes to the bone marrow microenvironment that they induce? And, what will the cost impact be of a treatment that is designed for disease maintenance as opposed to providing a cure.

Thrombopoietin mimetics have not been widely tested for the treatment of pediatric ITP. Two small trials have shown that in children with disease that has been refractory to all standard approaches (with the exception of splenectomy), romiplostim is well tolerated, effective, and results in a meaningful reduction of clinically significant bleeding episodes. These data are preliminary but nevertheless provocative, and they offer the potential for new hope to children with chronic refractory ITP. Additional experience will be required to prove long-term safety and tolerability in the pediatric population before these new agents will be adopted into standard practice.

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gone splenectomy were randomized to receive weekly SC injections of romiplostim ($n = 12$) or placebo ($n = 6$) for 12 weeks. Romiplostim was started at a dose of $1 \mu\text{g}/\text{kg}$, escalated to $5 \mu\text{g}/\text{kg}$ at 5 weeks, and tapered afterward.

All patients had either no response or failed to maintain a response to at least two prior treatment modalities for ITP. All had received prior steroid treatment; 44% had received corticosteroids, IVIG, and anti-D immunoglobulin in combination or sequentially; and 22% had received cytotoxic or immune-modulating agents. All such treatments were stopped 2 weeks prior to the study.

For patients in the romiplostim

versus placebo group, mean age was 9.5 versus 7.0 years, 10 (83%) versus 3 (50%) were male, and median disease duration was 2.3 versus 3.0 years. Median baseline platelet counts were $10.5 \times 10^9/L$ in both groups.

The median platelet count in the romiplostim group was significantly higher ($P = 0.039$) than that in the placebo group within 1 week of the first dose of romiplostim ($1 \mu\text{g}/\text{kg}$) and remained so at 3 weeks after the end of treatment (15 weeks total; median platelet count of $47.5 \times 10^9/L$ vs $19.0 \times 10^9/L$; $P = 0.001$). Changes in platelet count in the romiplostim group were dose-dependent, with a median peak platelet count of $73.5 \times 10^9/L$ reached after 5 weeks, when

How I treat ITP

Immune thrombocytopenic purpura (ITP) and its associated problems are frequently encountered by the practicing hematologist. When it comes treatment, there are several options:

- If the platelet count is at least 30,000/ μ L and there is no active bleeding, close observation is the most prudent approach. In anticipation of the possibility of splenectomy at some point in their course, patients are offered immunization against *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis*. In addition, I screen for exposure to hepatitis B virus (HBV), because patients may at some point receive treatment with rituximab (Rituxan), which is associated with HBV reactivation.
- For patients with a platelet count below 30,000/ μ L, evidence of impending bleeding (such as wet purpura), or frank bleeding, treatment is indicated. Typically, this involves the use of glucocorticoids, often in combination with IV gamma globulin (IVIG) or, occasionally, anti-D immunoglobulin.
- For a platelet count below 10,000/ μ L, I give methylprednisolone, 1,000 mg/d IV, for 5 consecutive days with IVIG, 1 g/kg daily, for 2 consecutive days. I then shift the patient to oral prednisone, 1 mg/kg daily, for 1 week, followed by tapering the dose by 10 mg/wk, as allowed by the platelet count, which should remain at \geq 30,000/ μ L. Failure of this approach, or the inability to reduce the prednisone dose to 10 mg/d or less, would raise the options of either giving rituximab, 375 mg/m² per week, for 4 weeks or performing a therapeutic, laparoscopic-assisted splenectomy, the single intervention still the most likely to provide meaningful, long-lasting benefit.
- In the setting of asplenia (including the absence of accessory splenic tissue), I favor a trial of a thrombopoietin mimetic, either romiplostim (Nplate) or eltrombopag (Promacta). In the truly refractory patient, other options include calcineurin inhibitors, cytotoxic agents, danazol, tumor necrosis factor-alpha inhibitors, and staphylococcal A column immunoadsorption.

—David M.J. Hoffman, MD, FACP

the dose was 5 μ g/kg. Eleven of the 12 patients in the romiplostim group (93%) reached the target range of greater than 50×10^9 /L by the fifth week. At week 12 (end of treatment), 10 romiplostim patients (83%) versus no placebo patients were at target levels. Six romiplostim-treated patients (50%) maintained target platelet count levels at 3 weeks after treatment.

Adverse events occurred in 50% of patients in each group. The most frequent adverse events were headache, epistaxis, cough, and vomiting, which occurred in one patient each in the romiplostim group (8%) and placebo group (17%). Two romiplostim-treated patients (17%) developed a skin rash.

None of the patients had thrombocytosis or rebound thrombocytopenia, and none of the romiplostim-treated patients developed bone marrow fibrosis by week 18 of follow up.

Rescue medication, consisting of IVIG 1 g/kg for two doses, was given to one romiplostim-treated patient (8%) due to head trauma and loss of consciousness and two placebo-treated patients (33%) during the 12-week study period, with no interruption of study drug being required. The number of romiplostim-treated patients with grade 3 bleeding decreased from four (33%) prior to the study to none during the study, and the number with grade 2 bleeding decreased from six (50%) to two (17%; $P = 0.002$).

These findings are similar to results observed in another small study of romiplostim in children with ITP.^{3,4} An open-label phase III study designed to study the long-term safety of romiplostim and the durability of platelet responses to the drug in pediatric patients currently is in the recruitment stage.⁵ In this extension trial, approximately 20 patients aged 1 to 18 years with ITP are to receive weekly SC injections of romiplostim, starting at 1 μ g/kg (or prior dose) and escalated to 10 μ g/kg (based on the platelet count) over a period of 3 years. The primary outcome measure is the incidence of adverse events, including significant changes in laboratory values and the incidence of antibody formation. Secondary outcome measures include the platelet response ($> 50 \times 10^9$ /L) in the absence of rescue medication and the need for concurrent ITP medication (corticosteroids, danazol, or azathioprine) over the duration of the study.

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Rare case of renal cell carcinoma presenting as a cutaneous horn

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Cutaneous metastases are a rare and generally late manifestation of renal cell carcinoma (RCC). Because they can mimic other dermatologic lesions, they may pose a diagnostic challenge if there is not a high degree of suspicion of their underlying cause.

Case presentation

A 61-year-old man presented with a right leg mass initially noted as a pimple-like lesion that enlarged rapidly over 2 weeks. This lesion was extremely painful to touch, and the patient had also noticed the appearance of adjacent leg varicosities. He denied any recent trauma or insect bites. Review of systems revealed an unintentional 30-lb weight loss in the past 6 months as well as progressive dyspnea on exertion and intermittent chest pain for 4 months prior to presentation. The patient had a history of smoking half a pack of cigarettes a day for 12 years; however, he quit 10 years ago.

Physical examination showed a large, 3.7 cm × 3.5 cm × 2 cm, malodorous, moist, exophytic friable mass located on the lateral aspect of his right lower extremity, 5 inches above the lateral malleolus (Figure 1). The lesion was smooth yet firm, yellow-tan to purplish-black without any surrounding erythema. It was slightly gelatinous and bled easily with minor trauma. Prominent dilated veins spanned the length of the patient's right leg, from his groin to his foot. There was no appreciable lymphadenopathy or abdominal mass.

Laboratory data were significant for anemia, with a hemoglobin level of 5.8 g/dL and hematocrit of 18.9%; thrombocytosis, with a platelet count of 447,000 cells/mm³; and hypercalcemia, with a corrected serum calcium level of 11.5 mg/dL. The patient was hospitalized for packed red blood cell transfusions and further workup of his leg mass.

A biopsy revealed the mass to be metastatic clear cell RCC (Figure 2). A CT scan of the chest, abdomen, and pelvis showed a large, 9.2 cm ×



FIGURE 1 A 3.7 cm × 3.5 cm × 2 cm exophytic, violaceous, friable mass on the lateral aspect of the lower extremity.

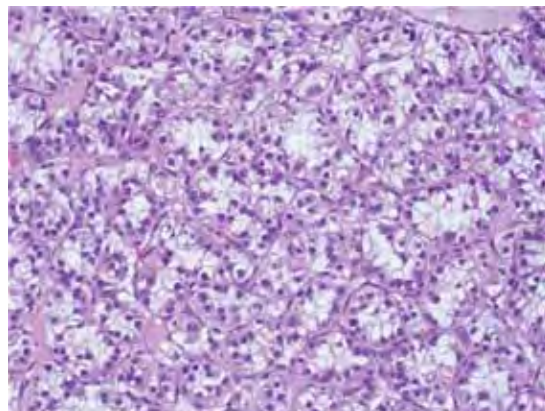


FIGURE 2 Photomicrograph of a skin biopsy reveals classic histology for clear cell renal cell carcinoma.

11 cm, heterogeneously enhancing mass with necrotic components arising from the mid and inferior poles of the right kidney (Figure 3). Multiple necrotic mediastinal and bilateral hilar lymph nodes; numerous scattered pulmonary nodules; innumerable enhancing hepatic masses; and lytic lesions in the thoracic, lumbar, and iliac bones

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were also noted. A CT scan of the brain was negative.

The patient's hospital course was subsequently complicated by the onset of persistent hematuria, despite continuous bladder irrigation. He was started on sorafenib (Nexavar), and a follow-up appointment was scheduled with oncology upon discharge; however, the patient decided to enroll in inpatient hospice instead.

Discussion

RCC comprises 90% of primary renal neoplasms, and 85% of them are clear cell type.¹ RCC represents 2%–3% of all cancer diagnoses; however, rates have steadily increased by 2% each year in the past 65 years, with unknown cause.² Smoking and obesity are known risk factors. As the use of imaging modalities, such as ultrasonography and CT scans of the abdomen and pelvis, has become more prevalent, the frequency of incidental detection of RCC has increased also. Fewer than 9% of patients with RCC present with the classic triad of hematuria, flank pain, and palpable abdominal mass.³ Indeed, its presentation can be so varied and nonspecific that it is deservedly called the internist's tumor.

Cutaneous metastases

Most RCCs are clinically silent in their natural course, and their presence may not be discovered until the disease is either locally advanced and unresectable or metastatic. The most common sites of metastasis are the lungs, liver, brain, bones, and adrenal gland.³ Cutaneous metastases are relatively rare, with an incidence of 3.4%.⁴ The most common sites for cutaneous metastases are the head and neck region followed by the trunk, whereas in our patient, the lesion was located more distally on the leg.

Given the high vascularity of RCC, distant skin metastasis is believed to occur via hematogenous spread. Cutaneous lesions can be flesh-colored

but may also appear erythematous to violaceous, due to hemosiderin deposits in the dermis from its high vascularity. Lesions can be multiple but may infrequently present as solitary masses. Histologically, these lesions involve the dermis, with occasional extension into the subcutis. A *grenz zone*, a thin layer of superficial dermis separating the lesion from the epidermis, is usually present.

Due to the depth of invasion seen in these lesions, it is preferable to do an excisional or punch biopsy over a superficial shave biopsy so that dermal involvement is not missed. Cutaneous metastases are highly vascular, and a significant amount of bleeding may occur during biopsy. Most RCC cutaneous metastases are histologically consistent in appearance with clear cell adenocarcinoma. Other diagnostic techniques include immunohistochemical staining for vimentin and keratin.

The presence of cutaneous metastasis is a late manifestation of disseminated disease. Prognosis is poor, with a mean survival of about 6–9 months after cutaneous lesions are found.^{4–6} Prognostic indicators of short survival in RCC include a serum lactate dehydrogenase level higher than 1.5 times the upper limits of normal and paraneoplastic syndromes (anemia, hypercalcemia with corrected serum calcium levels higher than 10 mg/dL, hepatic dysfunction). Karnofsky performance score of 70 or less, two or more metastases, and less than 1 year from the time of diagnosis to the start of therapy also portend poor outcomes.⁷ Thrombocytosis, if present, is also a rare but ominous sign of poor prognosis in RCC.^{8,9}

Treatment

Treatment options include surgical resection of early localized disease, with radical nephrectomy of primary renal tumors and metastasectomy of isolated oligometastatic sites. There are ongoing studies to deter-



FIGURE 3 A CT scan of the chest, abdomen, and pelvis shows a large, heterogeneously enhancing mass in the mid and inferior poles of the right kidney, borderline prominent spleen, and peripherally enhancing lesions in the liver, consistent with metastatic disease.

mine whether neoadjuvant systemic therapy prior to radical nephrectomy in patients with advanced RCC improves overall survival; however, data using older regimens have not shown this effect. In patients who have undergone a complete resection of their tumor, neither adjuvant chemotherapy nor radiotherapy has shown any benefit in terms of decrease in relapse or improvement in survival.² With nonresectable disease, treatment options are limited to systemic therapy and supportive care.

Clear cell type RCC overexpresses receptors related to angiogenesis, and this has been the main therapeutic target. First-line systemic therapy includes multikinase inhibitors (MKIs), such as sorafenib, pazopanib (Votrient), and sunitinib (Sutent), which inhibit tumor invasion and metastasis by decreasing tumor vascularity and inducing tumor necrosis. MKIs target tyrosine kinase receptors, including vascular endothelial growth factor (VEGF) receptor-2 and platelet-derived growth factor receptor.

Other agents such as everolimus

(Afinitor) and temsirolimus (Torisel), which are specific mTOR (mammalian target of rapamycin) inhibitors, also inhibit angiogenesis and are used in patients with a poor prognosis. Biologic agents, such as interferon- α (INF- α) and interleukin-2 (aldesleukin, Proleukin), were frontline treatment options in the past; however, with the development of the MKIs and mTOR inhibitors, they have fallen out of favor as first-line therapy.

It has been shown that patients with metastatic RCC treated with sunitinib versus INF- α have a better quality of life, longer progression-free survival (11 months vs 5 months), and a higher objective response rate (31% vs 6%).¹⁰ A subsequent follow-up study showed that patients who were on sunitinib had longer overall survival (26.4 months vs 21.8 months).¹⁰

The AVOREN (Avastin and Rofenon in Renal Cell Carcinoma) trial also showed that the addition of bevacizumab (Avastin), a VEGF inhibitor, to INF- α improved progression-free survival by 89%, although there was no statistically significant increase in overall survival.¹¹ This combination is currently recommended as another treatment option for patients with relapsed or medically unresectable stage IV clear

cell type RCC.¹¹ Although the combination of MKIs with VEGF inhibitors is a promising option in phase I studies, it has shown no synergistic effect and has significantly more toxicity. However, all available agents have various toxicity profiles and, at most, prolong survival for a few months. Supportive care, including palliative radiation, metastasectomy, and bisphosphonates for metastatic bone disease, is still an integral part of treatment.

Conclusion

Cutaneous metastases from RCC can pose a diagnostic dilemma, as they can mimic other dermatologic lesions. Renal malignancies should be included in the differential diagnosis, since cutaneous lesions may be the first manifestations of disease. A high index of suspicion and a confirmatory biopsy are crucial to the diagnosis.

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A case of lung cancer and hypercoagulability, complicated by suspected heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a life-threatening disorder that follows exposure to unfractionated heparin or (less commonly) low-molecular-weight heparin (LMWH). Patients classically present with a low platelet count ($< 150,000$ cells/mm³) or a relative decrease of 50% or more from baseline, although the fall may be less (eg, 30%–40%) in some patients. Thrombotic complications develop in approximately 20%–50% of patients.

HIT is caused by antibodies against complexes of platelet factor 4 and heparin. These antibodies are present in nearly all patients who receive a clinical diagnosis of the disorder and are also known to cause disease in animals. However, they are also present in many patients who have been exposed to heparin in various clinical settings but who do not develop clinical manifestations. It is uncertain why complications occur in some patients but not in others.¹ We present a 73-year-old man who developed thrombocytopenia after starting LMWH and who has newly diagnosed adenocarcinoma of the lungs with extensive arterial and venous thrombosis and a negative serology for HIT.

Case presentation

A 73-year-old man presented to the emergency department after waking up in the morning with right-sided vague weakness and an inability to get out of bed. He had a history of right parietal stroke 1 month before the current presentation, when he was diagnosed with an aortic arch atheroma and started on warfarin. (At that time, CT scan of the head showed a right posterior temporoparietal lobe infarct in the posterior right middle cerebral artery distribution, and MRI of the brain and magnetic resonance angiography

showed acute or subacute infarction in the distribution of the posterior division of the right middle cerebral artery, likely embolic, and tiny acute infarctions in the left frontal lobe.) This patient had been admitted 5 days prior to the current presentation for right lower extremity deep vein thrombosis (DVT) and was discharged after being prescribed enoxaparin (60 mg subcutaneously every 12 hours) and warfarin as per international normalized ratio (INR) daily.

Also included in the medical history was supraventricular tachycardia status post ablation, non-ST elevation myocardial infarction (NSTEMI), hypertension, hyperlipidemia, and macular degeneration. He had no surgical history. The patient had a family history of coronary artery disease. He had an extensive smoking history up until the day of admission. His medications on admission included atorvastatin (Lipitor; 20 mg daily), warfarin daily as per INR, enoxaparin (60 mg subcutaneously every 12 hours), amlodipine (5 mg daily), and aspirin (81 mg daily).

Pertinent initial laboratory results on admission were as follows: hemoglobin, 12.9 g/dL; white blood cell count, 8.6×10^9 /L; platelet count, 183,000 cells/mm³; INR, 1.2; and initial troponin level, negative. His admission chest x-ray showed a 4.5 cm \times 5.5 cm lobulated density in the right hilum, suspicious for a hilar or subcarinal mass. Initial peripheral blood smear showed an isolated platelet decrease with increased size and no schistocytes. Initial CT of the head on admission showed no evidence of acute

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transcortical infarction and no definite evidence of acute intracranial hemorrhage but did show interval evolution of the right middle cerebral artery and left watershed distribution infarctions, with a probable small region of laminar necrosis in the right parietal lobe.

Clinical course

The patient was initially thought to have had a transient ischemic attack causing aphasia, confusion, and right-sided weakness. He was started on therapeutic anticoagulation with dalteparin (Fragmin; 12,000 U subcutaneously daily), and enoxaparin was discontinued. The following day, his platelet count was 86,000 cells/mm³, down from an admission platelet count of 183,000 cells/mm³. A subsequent MRI of the brain showed a new hemorrhagic area in the right parietal infarct (Figure 1). The decision was made to stop anticoagulation, even though he had an embolic source from his aortic arch atheroma and lower extremity DVT.

The patient then underwent inferior vena cava (IVC) filter placement to prevent pulmonary thromboembolism and was transferred to the medical service due to low platelet count and an episode of nine beats of ventricular tachycardia. Subsequently, his troponin level was found to be elevated > 12 ng/mL, without significant electrocardiographic changes. He was diagnosed as having NSTEMI. Given his conversion from an ischemic to hemorrhagic CNS infarct and decrease in platelet count after LMWH exposure, HIT became a concern, and both anticoagulation and antiplatelet agents were held. The patient's platelet count continued to trend downward over the next 3 days to a low of 27,000 cells/mm³. An HIT panel was negative by both immunologic and functional assays.

A CT scan of the brain 3 days after admission to monitor the hemorrhagic infarct showed multiple evolving infarcts and a new left occipital hemorrhagic infarct. The following day, a repeat CT scan of the head showed mul-

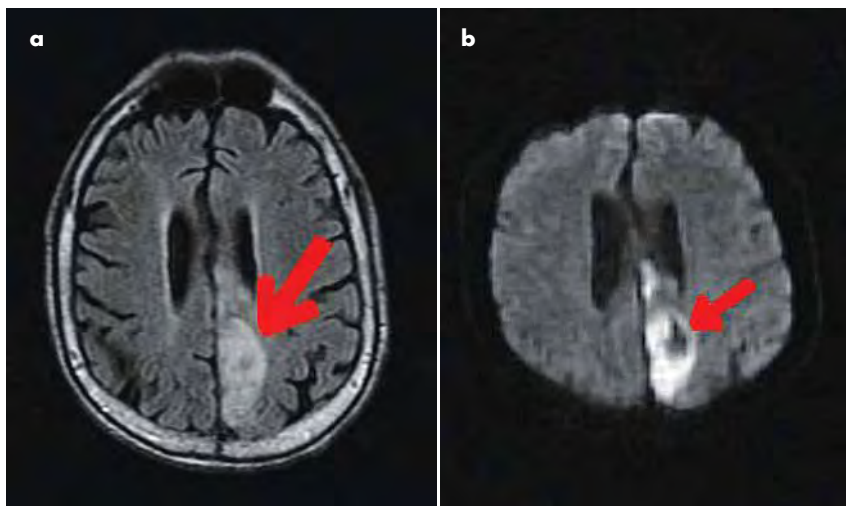


FIGURE 1 MRI of the brain T2 image (a) and diffuse-weighted image (b) showing acute infarct.

multiple evolving infarcts of varying ages, some with hemorrhage, and a mild interval increase in the previously described left medial parietal and left occipital lobe infarcts.

With worsening of his hemorrhagic infarct, along with his low platelet count and negative HIT panel, the decision was made to transfuse 2 units of platelets. His platelet count increased to 64,000 cells/mm³ after transfusion, subsequently dropping to 44,000 cells/mm³. However, during this time, the patient began to have worsening right lower extremity pain and left upper quadrant abdominal pain.

A CT scan of the thorax showed multifocal right hilar adenopathy suspicious for malignancy, either metastatic or representing a central lung carcinoma. It also showed nonocclusive segmental and possibly subsegmental pulmonary emboli in the right lower and middle lobes, as well as hypodense areas in the spleen, suggestive of areas of splenic infarction. Echocardiography showed an ejection fraction of 60%–70%, diastolic dysfunction, mildly elevated pulmonary artery pressure, and no evidence of patent foramen ovale. A cardiac stress test showed no reversible defects and an ejection fraction of 63%.

Risk of further bleeding into the brain was thought to be too great to

initiate anticoagulation despite the CT thorax findings. The neurologist recommended waiting 2 weeks post hemorrhagic infarction before beginning anticoagulation. Antiphospholipid antibody syndrome was ruled out, with a negative lupus anticoagulant and anticardiolipin antibody. Also, negative blood cultures, normal fibrinogen levels, and normal haptoglobin levels ruled out disseminated intravascular coagulation. D-dimer was elevated but nonspecific, secondary to malignancy and multiple infarcts. He was started on aspirin (81 mg daily) 9 days after admission.

The patient had a repeat CT scan of the thorax and CT scan of the abdomen and pelvis due to continued abdominal pain. The CT scans showed multiple subsegmental pulmonary emboli, greatest in the right lower lobe, some of which were new since the prior study (Figure 2); continued evidence of multifocal splenic infarction (Figure 3); and multiple right and left kidney infarcts (Figure 3).

The patient then underwent endobronchial ultrasound (EBUS)-guided biopsy of his right hilar adenopathy to confirm the diagnosis of suspected malignancy. After the procedure, he developed right upper quadrant pleuritic pain with a low-grade fever. A repeat CT scan of the thorax showed a marked increase in the extent of the

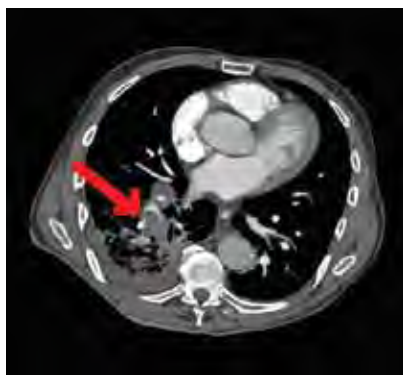


FIGURE 2 CT scan of the thorax showing pulmonary emboli.

right lower lobe pulmonary emboli, with a new small embolus noted in the anterior segment of the right upper lobe. There was a thrombus inferior to the IVC filter, with probable mild extension of a thrombus superior to the filter as well, and again multiple splenic and bilateral renal infarcts.

With progression of thrombosis and now post EBUS, anticoagulation was initiated with argatroban and warfarin. His D-dimer was followed daily and remained high, despite therapeutic anticoagulation with warfarin. Given the persistently elevated D-dimer, the hematologist recommended discontinuing warfarin and starting fondaparinux (Arixtra) subcutaneously. His platelet count improved to a range of 156,000 cells/mm³ to 181,000 cells/mm³, even before the initiation of chemotherapy.

Follow-up

HIT was suspected clinically by classic drop in platelet count but was negative on enzyme-linked immunosorbent assay (ELISA) and serotonin release assay (SRA). The patient has been maintained on fondaparinux for anticoagulation, avoiding heparin. Factor V Leiden and lupus anticoagulant were negative.

Fondaparinux was discontinued after 3 months, and the patient presented again with swelling of his right lower extremity. Ultrasonography of the right lower extremity redemonstrated an occlusive thrombus in the peripheral portion of the right femo-



FIGURE 3 CT scans of the abdomen (a) and pelvis (b) showing splenic and renal infarcts.

ral vein and throughout the right peroneal vein. The patient was restarted on fondaparinux (7.5 mg subcutaneously daily). During this follow-up, his platelet count ranged from 134,000 cells/mm³ to 193,000 cells/mm³.

Regarding management of non-small cell lung carcinoma of the left upper lobe (stains positive for TTF-1 [thyroid transcription factor-1], CK7, and CK20; weakly positive for CK5/6; and negative for P63) with metastasis to bone and adrenal glands, he received 4 cycles of paclitaxel/carboplatin, with improved disease. A repeat CT of the chest, abdomen, and pelvis after chemotherapy showed improvement in mediastinal and hilar lymphadenopathy, resolution of extensive right lower lobe pulmonary consolidation, resolution of right-sided effusion, and no evidence of metastatic malignancy in the abdomen or pelvis and no osseous metastasis.

He was started on maintenance therapy with pemetrexed (Alimta), which was continued for 4 months, until repeat CT revealed progressive disease. He then received 4 cycles of vinorelbine. He had progression-free survival of 7 months from first-line chemotherapy and stable disease for 7 months after 4 cycles of vinorelbine.

Discussion

In summary, we have a 73-year-old man admitted with a hemorrhag-

ic infarct, NSTEMI, and recently diagnosed right lower extremity DVT with a decreasing platelet count in the setting of LMWH. Throughout the hospital course, he had worsening hemorrhagic infarcts, preventing proper anticoagulation for his progressive thromboembolic events in the lungs, spleen, kidneys, and legs. Incidentally, he was also found to have a mass on a chest x-ray, later identified by biopsy as adenocarcinoma.

Given that the 4T scoring system for HIT showed a high probability with 8 points—identified by a platelet count fall > 50%, a platelet nadir > 20,000 cells/mm³, clear onset between days 5 and 14 with exposure to heparin/LMWH, new thrombosis, and no apparent cause of thrombocytopenia—suspicion for HIT remained high. Both functional and immunologic assays were negative for HIT, when repeated 2 weeks apart. The assays for laboratory diagnosis of HIT are immunologic, done by ELISA with a sensitivity of > 95% and a specificity of 50%–89%, and functional, done by SRA with a sensitivity > 90% and a specificity > 90%.² As neither assay is 100% sensitive and specific, we still had a high clinical suspicion for HIT.

The HIT diagnostics in the presence of other comorbid states that may also induce thrombocytopenia represent a specific clinical problem.³

Despite increasing awareness of the clinical features of HIT, laboratory detection of the pathogenic HIT antibodies remains central to diagnosis.⁴⁻⁶ This is because thrombocytopenia during heparin anticoagulation does not necessarily indicate HIT. Indeed, several other disorders complicated by thrombosis and thrombocytopenia during or shortly following heparin treatment strongly resemble HIT. These “pseudo-HIT” disorders^{7,8} (eg, cancer, sepsis, disseminated intravascular coagulation, pulmonary embolism, antiphospholipid syndrome) can reliably be distinguished from HIT by negative results using sensitive tests for HIT antibodies.

Thrombosis is strongly associated with HIT, with an incidence of 50%–67%.^{9,10} The most common complication of HIT is venous thrombosis (DVT being the most frequent, followed by pulmonary embolism).^{9,11} Arterial thrombosis commonly presents as limb ischemia followed by cerebral vascular accident and myocardial infarction. Our patient had DVT followed by NSTEMI, cerebral vascular accident, and pulmonary embolism. He also had splenic and renal infarctions, which are rare in HIT. A literature review revealed, in abstract form, a retrospective study from a single institution showing a high incidence of thrombosis in a patient with a high 4T score and negative SRAs.¹²

The most common causes of thrombocytopenia in cancer are related to cancer treatment and bone marrow invasion by tumor cells. Chemotherapy and radiation therapy are damaging to the bone marrow and can cause severe myelosuppression, which results in lowering of platelet counts as well as white and red blood cell counts. It commonly occurs in patients with leukemia and lymphoma, but there are many other cancer types that can spread to bone marrow. Other causes of thrombocytopenia in cancer include the syndrome of disseminated intra-

vascular coagulation and thrombotic microangiopathy.¹³

Nonbacterial thrombotic endocarditis (NBTE) is a disease characterized by the presence of vegetations on cardiac valves, consisting of fibrin and platelet aggregates devoid of inflammation or bacteria. NBTE has increasingly been recognized as a condition associated with numerous diseases and a potentially life-threatening source of thromboembolism. NBTE is not a common entity; however, it is frequently underestimated, probably due to underlying diseases (cancer, autoimmune disorders, HIV). NBTE is difficult to diagnose and relies on strong clinical suspicion. NBTE is also difficult to manage, and each case should be individually managed by identifying and treating the underlying pathology.¹⁴ Even though our patient had thromboembolism, there was no evidence of vegetations on cardiac valves by transthoracic or transesophageal echocardiography.

Trousseau's syndrome is a paraneoplastic syndrome characterized by hypercoagulability related to malignancy. Coagulation abnormalities may include disseminated intravascular coagulation, pulmonary embolism, various types of gangrene, thrombotic endocarditis, arterial thrombosis, and embolic stroke.¹⁵ We considered this with our patient; however, a literature review showed no cases of Trousseau's syndrome associated with thrombocytopenia, although concurrent Trousseau's syndrome and HIT could not be excluded.

In summary, we need to consider all the above differential diagnoses in a patient presenting with thrombocytopenia and thrombosis. Treatment relies on clinical correlation of all the findings and supporting data.

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Conflicts of interest: The authors have nothing to disclose.

Hydroxyurea-induced palmar-plantar erythrodysesthesia in an adult with sickle cell disease

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Sickle cell disease consists of hemolytic anemia and episodes of vaso-occlusion, which are caused by sickling of red blood cells (RBCs) precipitated by deoxygenation. The change in shape of the RBCs is what causes vascular occlusion, leading to acute sickle crisis.

Hydroxyurea has been approved by the US Food and Drug Administration for the treatment of adult patients with clinically severe disease. Hydroxyurea blocks DNA synthesis via enzymatic inhibition of ribonucleotide reductase.¹ Administration of hydroxyurea is associated with an increase in HbF (fetal hemoglobin) levels,² thereby reducing the severity of vaso-occlusive crises, acute pain, acute chest syndrome, transfusion requirements, and hospitalizations.³ As a cytotoxic, cell cycle-specific agent, hydroxyurea is associated with several adverse reactions, namely bone marrow suppression.⁴ Other side effects associated with hydroxyurea use include gastrointestinal upset, mild dermatologic reactions, alopecia, and leg ulcers.

The case study presented here focuses on an adult with sickle cell disease who complained of painful discoloration and edema of his hands and feet with blisters about 1 week after starting hydroxyurea therapy.

Case presentation

A 50-year-old black man with a history of atrial fibrillation, avascular necrosis of the shoulder, and sickle cell disease had frequent hospitalizations for acute crises requiring multiple packed RBC transfusions. He had no known history of leukemia/lymphoma or exposure to other cytotoxic drugs. The patient was placed on hydroxyurea to reduce the frequency of sickle cell crises. Once hydroxyurea was begun, the patient noticed a decrease in acute pain and improvement in his general well-being.

Approximately 1 week after initiation of hydroxyurea therapy, the patient started noticing darkening of his hands. Two weeks later, hyperpigmentation

of the palmar creases was noted. Three weeks after hydroxyurea was started, the patient had edema and blisters of his hands and feet with associated desquamation. Symptoms were severe and painful and interfered with activities of daily living (Figure 1). The patient's fingers were so swollen that he was unable to make a fist. His feet were so edematous that it was difficult to walk. After these signs of hand-foot syndrome developed, his hematologist discontinued hydroxyurea, and the edema and pain gradually improved. Three months after hydroxyurea discontinuation, the edema and erythema had resolved, but the patient still had some hyperpigmentation.

Discussion

Palmar-plantar erythrodysesthesia, also known as hand-foot syndrome or acral erythema, is a known adverse reaction of several antineoplastic medications, although few published articles mention hand-foot syndrome as a common adverse effect of hydroxyurea therapy.³⁻⁵ The incidence of hand-foot syndrome in patients being treated with 5-fluorouracil, capecitabine (Xeloda), or liposomal doxorubicin (Doxil) ranges from 7% to 63%.⁶ It is a known adverse event of hydroxyurea therapy, although its exact frequency has not been established.

In a study examining mucocutaneous changes in 158 patients with chronic myeloid leukemia (CML) and long-term hydroxyurea therapy, 21 had severe changes and acral erythema.⁷ In these CML patients acral persistent erythema involved palmar, plantar, and facial areas, with less frequent involvement of the scrotum.⁷ Symptoms were described as a burning sensation associated with redness, scaling, and fissuring.⁷ Acral erythema was noted to disappear gradually after

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FIGURE 1 Hydroxyurea-induced palmar-plantar erythrodysesthesia. Painful darkening of the hands, hyperpigmentation of the palmar creases, and edema of the hands (**a, b**) and feet (**c**). Three weeks after hydroxyurea was started, severe edema and blisters of the hands and feet interfered with the patient's activities of daily living.

discontinuation of hydroxyurea.⁷ Hand-foot syndrome is known to occur in patients with CML being treated with hydroxyurea, but our case report describes a patient with hand-foot syndrome associated with hydroxyurea therapy and sickle cell disease.

Most cases of hand-foot syndrome improve, if not completely resolve, after cessation of the offending agent. Our patient did not require treatment

specifically for hand-foot syndrome, as termination of hydroxyurea resulted in resolution of edema and pain.

Among the most common therapeutic agents for hand-foot syndrome is pyridoxine (vitamin B₆). Pyridoxine has not been known to prevent the development of hand-foot syndrome, but observations suggest better symptom control with this vitamin, although randomized controlled stud-

ies are needed to further support this use.⁶ Another agent to consider for hand-foot syndrome is topical 99% dimethyl sulfoxide (DMSO). Case descriptions have reported improvement with DMSO in soft-tissue damage and edema in patients being treated with liposomal doxorubicin.⁸

In conclusion, hand-foot syndrome is a potentially reversible condition that is a common complication of certain chemotherapeutic drugs. However, it is not frequently reported with the use of hydroxyurea in adult patients with sickle cell disease.

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The House hears SGR alternatives, vows action

Frances Correa

A plan to finally replace Medicare's much-maligned sustainable growth rate (SGR) payment formula could be unveiled by this summer, federal lawmakers said at a committee hearing. "Here's the bottom line: If we get to December and we're doing an extension, that's a failure on our part," Rep. Michael Burgess (R-Tex) said at the hearing. "We need a permanent solution that's predictable, updatable, and reasonable for this year—and nothing else will do."

"Whatever virtues the SGR had when it was created 14 years ago..., it's clear that they have vanished," added Rep. Henry A. Waxman (D-Calif). He noted that in the past 2 years, Congress has had to pass legislation six times, blocking fee cuts of up to 21% or more.

About 30 medical associations, including the American Society of Clinical Oncology (ASCO), responded to the House subcommittee's request for suggestions and proposals in developing a new system. On May 5, 2011, House subcommittee members met with a five-person panel of experts from medical associations and health policy organizations to consider alternatives to the current SGR formula, which some participants labeled as anything but sustainable.

One size won't fit all

Although the details of ASCO's plan and others vary, they also show a consensus on several fronts: repealing the SGR, moving away from the traditional fee-for-services payment model, and providing a 4- to 5-year transition period during which pro-

viders can experiment with a variety of payment systems.

In a letter accompanying the ASCO recommendations, the president, Dr. George Sledge, and CEO, Dr. Allen Lichter, stressed that SGR reforms in general should be linked to existing "robust" systems that promote evidence-based medicine. For oncology in particular, that effort should leverage the Quality Oncology Practice Initiative (QOPI), a comprehensive, field-tested program that more than one-quarter of outpatient oncology practices in the United States already participate in. More than 80% of oncology care is provided in that setting.

"The current SGR system has created an uncertain and unstable environment—a situation that threatens the viability of practices and access to care for thousands of cancer patients," they concluded.

In its recommendations, ASCO asserted that evidence-based medicine is "both warranted and necessary" because:

- Medicare beneficiaries account for more than half of all new cancer diagnoses in the United States, and treatment and prevention of the disease comprise almost 10% of costs under fee-for-service Medicare;
- The care is complex, treatment can span many specialties, and treatment strategies change rapidly to keep pace with scientific advances; and
- These complexities would not be adequately addressed if a multispecialty system (such as the Physician Quality Reporting System) were to be applied in the oncology setting.

The recommendations also detailed why the QOPI should be in-

corporated as the primary quality measurement program: 25%–30% of a range of practices—urban, rural, community, and academic—participate in it; it is free; some private insurers have adopted incentives for participation in the program; the performance measures are field-tested and up-to-date; and participation promotes high-quality, high-value care and can help identify and address discrepancies in oncology care.

Moreover, QOPI "protects the best interests of patients, reduces exposure to unnecessary treatments and tests, minimizes the use of suboptimal treatment options, promotes the coordination of care, and protects the Medicare program from costs associated with poor-quality care," ASCO asserted in the recommendation.

Members of the expert panel also stressed the importance of avoiding a "one-size-fits-all" solution. "We should [be mindful] that what will work in one part of the country will not work in another part of the country, and that's why we have continued to talk about a variety of options," said Dr. Cecil Wilson, president of the American Medical Association (AMA). "There is a temptation to feel that we ought to figure out one rule...that solves it all."

Dr. Wilson pointed to the provisions in the Affordable Care Act that allow for a variety of models of accountable care organizations, embodying the concept of options in the medical system. In that spirit, he said that the AMA has formed a physician leadership group to evaluate the effectiveness of alternative payment methods.

Dr. Roland A. Goertz, president of the American Academy of Family Physicians (AAFP), noted in written testimony to the committee that “the evidence shows that to achieve the savings Congress is looking for, and to improve the quality of health care delivered to millions of patients in the country, reform must include investment in primary care.”

To strengthen primary care’s role in Medicare, the AAFP backs payment reforms that would boost primary care reimbursement and support the concept of the patient-centered medical home (PCMH). The AAFP’s proposal would create a blended reimbursement system for primary care delivered within a PCMH: fee-for-service payments and pay for performance, plus care management fees for PCMH-related activities that do not involve direct patient care.

To prepare for that new payment system, the AAFP has proposed a 5-year transition period with mandated pay increases for primary care physicians, an increase in the Primary Care Incentive Care payment from 10% to 20%, and a rule that Medicaid payments to primary care physicians will always be at least equal to Medicare payments.

Dr. David Hoyt, executive director of the American College of Surgeons, said the College is analyzing the use of bundled payments for surgery. Dr. M. Todd Williamson, of the

Coalition of State Medical and National Specialty Societies, introduced the option of private contracting, in which patients would be free to apply their benefits to a doctor of their choice, who would be free to opt out on a per-patient basis.

“Private contracting is a key principle of American freedom and liberty,” Dr. Williamson said. “[It] will help the federal government achieve fiscal stability while fulfilling its promise to Medicare beneficiaries.”

Harold Miller, executive director of the Center for Healthcare Quality and Payment Reform, suggested an episode-of-care payment plan through which hospitals and physicians jointly charge one price for all services included in a hospitalization. The model would also include a warranty stating that any infections or complications would be treated at no additional cost. Also, a physician practice would receive one payment for all patient needs associated with chronic diseases or other conditions.

Rep. Burgess, who is also a physician, said organizations should focus on ways to address patients with chronic conditions, adding that 80% of Medicare funding is spent by 20% of beneficiaries with chronic illnesses.

Is the IPAB the new SGR?

Rep. Fred Upton (R-Mich) raised concerns about the Independent Payment Advisory Board (IPAB), cre-

ated by the Affordable Care Act. The Board sets expenditure targets on which it bases spending cuts. In 2018, targets will be based on the gross domestic product. “Sounds a lot like the SGR, which we’re trying to get rid of,” Mr. Upton said. “Since hospitals are exempt from IPAB cuts through the rest of the decade, it seems that the IPAB has the potential to undermine any serious efforts at physician payment reform.”

Some panelists agreed. “It’s not impossible that [the IPAB] could serve a function,” Dr. Wilson said, “but as presently constituted, we see it [as] basically another target for physicians to meet, potential double jeopardy, with an SGR as well as the pronouncements from this body.”

The panelists also asserted their belief that whatever plan chosen should be physician led, with financial support of the government. “It would be very helpful if physicians could get better financial support in their own payment system to enable them to lead all of those efforts,” said Dr. Mark B. McClellan, director of the Engelberg Center for Health Care Reform and former administrator of the Centers for Medicare and Medicaid Services. “Right now, with fee-for-service staying the way it is, they’re staying behind.” Dr. McClellan added that physicians can be the best sources for innovative and cost-saving mechanisms.