A COMPARISON OF JOHNS HOPKINS CURRENT CLINICAL PRACTICES IN ANEMIA AND NEUTROPENIA WITH THE ASCO/ASH AND NCCN GUIDELINES

Interview with Jerry L. Spivak, MD, and Stephen J. Noga, MD, PhD

Dr. Spivak is Professor of Medicine and Oncology at the Johns Hopkins University School of Medicine and a member of the active staff of the Johns Hopkins Hospital. He earned his medical degree from Cornell University Medical College and received his training in internal medicine, hematology, and oncology at the Johns Hopkins Hospital and the National Cancer Institute. He is board certified in Internal Medicine and Hematology. Dr. Spivak was Director of the Hematology Division at Johns Hopkins from 1980 to 1992 and is currently the Director of the Center for the Chronic Myeloproliferative Disorders at Johns Hopkins. He is an author of 195 publications and the recipient of a merit award from the National Institutes of Health. Dr. Spivak's research and clinical interests include the physiology of erythropoiesis and erythropoietin and the pathogenesis of the chronic myeloproliferative disorder, polycythemia vera.

Dr. Noga is the Director of the Division of Hematology and Medical Oncology and the Director of the Bone Marrow Transplantation/Cellular Therapeutics Program at the Alvin and Lois Lapidus Cancer Institute of Sinai Hospital in Baltimore, Maryland. He is also an Associate Professor of Oncology and Pathology at Johns Hopkins University. He received his bachelor of science degree in medical technology from the University of Florida, Gainesville, in 1976, and his PhD in experimental pathology from the same university in 1983. He then pursued medical education at Johns Hopkins University, where he received his medical degree (1987) and completed his internship/residency (1989) and oncology fellowship (1991). He joined the faculty of Johns Hopkins in 1991 and was appointed Medical Director of the Graft Engineering Laboratory. In 1997, he became Co-Director of the Hematopoietic and Therapeutic Support (HATS) Service, which managed all marrow and stem-cell harvesting/processing, platelet apheresis/transfusion, therapeutic apheresis and autologous blood donations for The Johns Hopkins Medical Institutions. In 2001, he assumed the directorship of the Division of Hematology and Medical Oncology at Sinai Hospital. Dr. Noga's major research and clinical interests include stem-cell mobilization and hematopoietic graft manipulation, elutriation, stem-cell heterogeneity, multiple myeloma, and lymphoma. He is on the Editorial Board of 2 journals and is President of the International Society for Cellular Therapy (ISCT). He has authored more than 70 peer-reviewed papers, 15 book chapters, and numerous abstracts. He is a member of numerous organizations, including the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Hematology Association, Transplantation Society, American Society of Blood and Marrow Transplantation, ISCT, and the Bone Marrow Transplantation Scientists of Australasia.

A senior clinical editor for Advanced Studies in Medicine (ASIM) interviewed Dr. Spivak and Dr. Noga to discuss the Johns Hopkins current clinical practices in anemia and neutropenia in patients with cancer and how these practices compare with the ASCO/ASH and National Cancer Care Network guidelines.
Over the past 4 years, new therapies have emerged for—and new studies have illuminated—the treatment of anemia and neutropenia in patients with cancer. In response, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) issued joint clinical practice guidelines for the treatment of anemia, ASCO updated its guidelines on the treatment of neutropenia in cancer patients, and the National Comprehensive Cancer Network (NCCN) has issued its own guidelines for both conditions, which it updates annually.

These guidelines are a valuable aid, but because they demand consensus among experts as well as Level I data, they do not always reflect common clinical practice. Following a summary of these guidelines is an interview with Jerry L. Spivak, MD, and Stephen J. Noga, MD, PhD, in which they discuss the ways in which their own practice habits at Johns Hopkins differ from the guidelines.

SUMMARY OF THE NATIONAL GUIDELINES

SUMMARY OF ASCO/ASH RECOMMENDATIONS FOR THE TREATMENT OF ANEMIA

• The use of epoetin is recommended for patients with chemotherapy-associated anemia and a hemoglobin concentration of 10 g/dL or below. Red blood cell transfusion is also an option depending upon the severity of anemia or clinical circumstances.

• For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration <12 g/dL but whose levels have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels decrease to closer to 10 g/dL should be determined based on clinical circumstances. Red blood cell transfusion is also a therapeutic option when warranted by severe clinical conditions.

• The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by weaker evidence, an alternative weekly dosing regimen (40 000 U weekly), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice-weekly regimens.

• Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, <1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing medication.

• Hemoglobin levels can be raised to (or near) 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the “normalization” of hemoglobin levels to above 12 g/dL.

• Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated might be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.

• Evidence from one well-designed, placebo-controlled, randomized trial supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but no published high-quality studies support its use in anemic myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia in the absence of chemotherapy. Treatment with epoetin for patients with myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia and chemotherapy-associated anemia should follow the above recommendations.

• Clinicians caring for patients with myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.
SUMMARY OF NCCN GUIDELINES FOR THE TREATMENT OF ANEMIA

The NCCN guidelines recommend that when patient evaluation reveals hemoglobin levels below 11 g/dL, the first step is to rule out noncancer or non-treatment-related causes. Once these causes have been excluded, if the problem requires immediate correction, transfusion is the preferred treatment. If immediate correction is not required, the clinician should determine if the patient is symptomatic or has risk factors. If the patient is symptomatic or if compelling risk factors are discovered, erythropoietic therapy should be considered. If the hemoglobin levels are below 10 g/dL, the NCCN strongly recommends erythropoietic therapy. At the same time, the NCCN recommends performing iron studies. If serum ferritin levels are below 100 and transferrin saturation is less than 20%, the NCCN recommends iron supplementation as indicated.

The NCCN lists several options for erythropoietic therapy (Figure). First, it lists package doses for epoetin alfa (10 000 U 3 times weekly by subcutaneous injection) and darbepoetin (2.25 µg/kg weekly by subcutaneous injection). If there is no response at 4 weeks, the suggested titration is to increase the dose of epoetin alfa to 20 000 U 3 times weekly. For darbepoetin, if the patient is nonresponsive after 6 weeks, the suggested titration is to 4.5 µg/kg weekly.

Commonly used regimens are also reviewed in the NCCN guidelines. For epoetin alfa, the regimen is as follows: 40 000 U weekly by subcutaneous injection; if there is no response after 4 weeks, the dose is titrated to 60 000 U weekly. For darbepoetin, the guidelines note 3 µg/kg biweekly by subcutaneous injection; if there is no response after 6 weeks, the dose is titrated to 5 µg/kg biweekly. Again for darbepoetin, NCCN notes a 200-µg fixed dose biweekly by subcutaneous injection; if there is no response after 6 weeks, the dose is titrated to 300-µg fixed dose biweekly. In all cases, if there is no response after 6 to 8 weeks, NCCN recommends discontinuing therapy. The NCCN recommends titration to achieve a hemoglobin level of 12 g/dL, at which point clinicians should check symptom response to determine if there are other concerns.

SUMMARY OF ASCO RECOMMENDATIONS FOR THE USE OF CYTOKINES FOR NEUTROPENIA

In 2000, ASCO updated its 1996 guidelines for the use of cytokines in patients with cancer. It is recommended that primary administration of colony-stimulating factor (CSF) be reserved for patients with a risk of febrile neutropenia of 40% or greater. ASCO makes note of special populations in whom CSF might also be appropriate, including those with AIDS, those with non-Hodgkin's lymphoma, elderly patients, and possibly patients with testicular or nonseminomatous germ-cell tumors.

In adults, the recommended CSF doses are 5 µg/kg daily for granulocyte colony-stimulating factor (G-CSF; filgrastim) and 250 µg/m² daily for granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) for all clinical settings other than peripheral-blood progenitor cell (PBPC) mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 µg/kg daily seems preferable. Outside of this indication, CSF dose escalation is not advised. The preferred route of CSF administration is subcutaneous. Existing clinical data suggest that starting G-CSF or GM-CSF between 24 and 72 hours following chemotherapy may provide optimal neutrophil recovery. Continuing the CSF until the occurrence of an absolute neutrophil count (ANC) of 10 000/mm³ after the neutrophil nadir, as specified in the G-CSF package insert, is known to be safe and effective; however, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

Clinicians occasionally encounter patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for febrile neutropenia or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at high risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive.

In the setting of many tumors exclusive of curable tumors (eg, germ-cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose intensity, chemotherapy dose reduction should be considered after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

Current evidence supports the recommendation that CSF should not be routinely used for patients with neutropenia who are afebrile. In addition, CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia.
fever and neutropenia are defined as follows: fever of less
than or equal to 10 days in duration; no evidence of
pneumonia, cellulitis, abscess, sinusitis, hypotension,
multiorgan dysfunction, or invasive fungal infection;
and no uncontrolled malignancies. In the absence of
more trials demonstrating a favorable effect on overall
survival, disease-free survival, quality of life, or toxicity,
there is no justification for the use of CSF to increase
chemotherapy dose intensity, chemotherapy schedule, or
both outside of a clinical trial.

CSF is recommended to help mobilize PBPC and
after PBPC infusion. CSF use can be considered for
patients with acute myeloid leukemia if possible ben-
etits, such as shortened hospitalization, outweigh the
costs of CSF use. CSF can increase the ANC in neu-
tropenic patients with myelodysplastic syndromes. Data
supporting the routine, long-term, continuous use of
CSF in these patients are lacking, but intermittent
administration of CSF may be considered in a subset of
patients with severe neutropenia and recurrent infec-

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**Figure. NCCN Practice Guidelines for Erythropoietic Therapy—Dosing and Titration**

<table>
<thead>
<tr>
<th>Initial Dosing</th>
<th>Titration for No Response</th>
<th>Titration for Response</th>
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<tbody>
<tr>
<td><strong>Package Insert Dosing Schedule</strong></td>
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<tr>
<td>Epoetin alfa 10 000 U tiw by subcutaneous injection or Darbepoetin 2.25 mcg/kg weekly by subcutaneous injection</td>
<td>Increase dose of epoetin alfa to 20 000 U tiw by subcutaneous injection</td>
<td>Increase darbepoetin up to 4.5 mcg/kg weekly by subcutaneous injection</td>
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<tr>
<td><strong>Commonly Used Regimens</strong></td>
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<tr>
<td>Epoetin alfa 40 000 U weekly by subcutaneous injection or Darbepoetin 3 mcg/kg every 2 weeks by subcutaneous injection or Darbepoetin 200 mcg fixed dose every 2 weeks by subcutaneous injection</td>
<td>Increase dose of epoetin alfa to 60 000 U weekly by subcutaneous injection</td>
<td>Increase darbepoetin to 5 mcg/kg every 2 weeks by subcutaneous injection</td>
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<tr>
<td><strong>New Regimens Being Used in Clinical Trials</strong></td>
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<tr>
<td>Epoetin alfa 60 000 U loading dose subcutaneously then 120 000 U every 3 weeks maintenance subcutaneously or Darbepoetin 4.5 mcg/kg weekly loading dose subcutaneously, then 4.5 mcg/kg every 3 weeks maintenance subcutaneously*</td>
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*There has been no head-to-head comparison of regimens; †Studies evaluating loading-dose regimens and less frequent administration schedules are currently being investi-
gated; ‡Less frequent dosing regimens have not yet been determined; ¶Less frequent dosing regimens are under investigation, and could be considered as an alternative to dose

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: The NCCN believes that the best management of any cancer patient is in a
clinical trial. Participation in clinical trials is especially encouraged.

Reprinted with permission from the National Comprehensive Cancer Network. Cancer and treatment-related anemia. The Complete Library of NCCN Clinical Practice Guidelines in Oncology [CD-ROM]. Rockledge, Pa: National Comprehensive Cancer Network; March 2004. To view the most recent version of the guide-
line, go to www.nccn.org.
tion. The data also are sufficient to recommend beginning G-CSF administration after completion of the first few days of chemotherapy of the initial induction for acute lymphocytic leukemia (ALL) or first postremission course, thus shortening the duration of neutropenia of less than 1000/mm³ by approximately 1 week. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy.

CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of CSF may be considered if prolonged delays secondary to neutropenia are expected. In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group.

NCCN Guidelines for Fever and Neutropenia

The NCCN begins its recommendations with the initial evaluation for febrile neutropenia. The guidelines identify a single temperature of above 38°C or 38.5°C, a neutrophil count of less than 500/mm³, or a neutrophil count of less than 1000/mm³ and a predicted decline to 500/mm³ within 48 hours as the factors in determining treatment.

The guidelines focus on thoroughly evaluating the sites of infection and the causative organisms. NCCN recommends that initial therapy be a choice between intravenous (IV) monotherapy, IV antibiotic combination therapy, monotherapy combined with an appropriate vancomycin, or an oral antibiotic combination therapy. This therapy should be site specific and, depending on site and cause, may be a combination of antibiotic, antifungal, and antiviral therapies. For high-risk patients, therapy should be conducted in the hospital. For low-risk patients, clinicians must decide on hospitalization, outpatient treatment, or home care. In the case of infection around vascular access devices, clinicians must carefully weigh treatment with antibiotics such as vancomycin versus removal of the catheter. Cytokines (G-CSF and GM-CSF) are only mentioned as a possible adjunct therapy.

Interview with Dr Spivak and Dr Noga

ASiM: Please describe the strengths and weaknesses of the ASCO/ASH and NCCN guidelines for treatment of anemia.

Dr Spivak: The real strength of ASCO/ASH is that it’s a rigorous review of all of the data on the use of erythropoietin for the treatment of anemia associated with cancer since the very first studies—there had not been this type of analysis previously. The problem is, there wasn't as much of the high-level evidence that people doing this type of analysis are used to seeing. This creates a conflict between the analysts and the evidence, because the evidence was initially derived to show safety and efficacy sufficient for FDA [US Food and Drug Administration] approval and not to go any further than that. Therefore, in terms of the highest quality studies with randomized controls, adequate power, consideration for dropout rates, details as to type of chemotherapy given, and so on, a lot was missing.

Sometimes the evidence-based approach is not necessarily the practical or clinically applicable approach, however. Where this comes up most strongly is in the recommendations of how erythropoietin should be administered. We know in the clinic—and from the pharmacokinetics—that the standard recombinant form needs to be administered only once per week; the newer genetically engineered forms can be administered every 2 weeks. ASCO/ASH couldn't find Level I evidence to prove that, but we all know unequivocally in the clinic that it works.

The NCCN builds on the ASCO/ASH guidelines but reflects a more real-world perspective. For example, ASCO/ASH considers hemoglobin increase, transfusion reduction, and quality of life as 3 separate concerns and examines the data for each, but the reality is, all of these need to be considered together; NCCN does that. NCCN also makes the important point that clinicians should look for the other correctable causes of anemia. When those causes are separated out, you’re left with cancer-associated anemia, which is not going to go away unless the cancer is treated or you pharmacologically correct the anemia by giving erythropoietin, so that part is highly appropriate.

The NCCN also looks at quality of life; they suggest a complete symptom assessment, which is a plus. Looking at quality of life is an important thing that peo-
people did not used to do, but it is so important to patients, who have a different perspective from clinicians. We tend to consider pain first, which might be appropriate during chemotherapy, but after that, fatigue is the most important thing. There might not be Level I data on quality of life, but there has been a consistent trend in “inadequate” study after “inadequate” study in the right direction; it’s really hard to ignore that patients feel consistently better if their hemoglobin levels increase.

One concern I have with the NCCN guidelines for anemia is the lack of gender specificity. The guidelines use the National Cancer Institute scale, which is similar to the World Health Organization scale of anemia. This has its positives (it is always important to quantify the degree of anemia), but this is not the scale I would use because it is not gender specific. Mild anemia is considered as a hemoglobin level from 10 g/dL to 12 g/dL, but no one would consider a hemoglobin level of 11 g/dL to be normal—a man would be symptomatic. Suppose the patient is a man with lung cancer who is a smoker—already the patient has impaired oxygen transport. I think the guidelines are starting from the wrong point; if treatment is delayed until the hemoglobin level is that low, it takes more work to get it to where it needs to be. I think that needs to be hammered home because anemia is so prevalent.

Dr Noga: ASCO should be applauded for putting out guidelines on fever and neutropenia, but they have crippled many of us somewhat because managed care providers and pharmacists have interpreted those guidelines as the Holy Grail. Also, the ASCO guidelines are immensely outdated in terms of the use of cytokines. Maybe in 2000 (or prior to 2000 when the guidelines were actually written) this may have been the thinking, but now that thinking has changed significantly. I know that the guidelines are already being updated with some of the newer thinking. The guidelines contain some helpful cost analysis, indicating that use of cytokines is cost effective when the risk of febrile neutropenia is greater than 40%, but I guarantee this will come down to a 30% or 20% risk to show a cost advantage.

Here are some key points arguing in favor of the use of cytokines. Cancer is becoming a geriatric disease. It sounds like a bland statement, but it is important because the number of cases of cancer in people aged 65 years and older will double between 2000 and 2030. Today, because their health and functional status is so much better, we offer chemotherapy to older people who 10 years ago we might have approached with hospice. Also, our supportive care options (cytokines, antiemetics) are so much better that chemotherapy becomes a realistic choice. The ASCO guidelines say that in most cases, cytokines are not needed, yet they mention that certain special populations might show benefit. One of those special populations is the elderly. We now have data showing that maintaining the chemotherapy schedule on time and at full dose is important. It is likely that someone aged 65 years or older will be admitted to the hospital with fever and neutropenia if they do not receive cytokines during the first round of chemotherapy. This will alter treatment—not to mention the direct mortality risk. Because of that, I think the mindset with this population has changed drastically.

Terms just barely mentioned here are dose intensity and, more importantly, dose density—the practice of giving standard chemotherapy over shorter intervals of time. In a couple of big clinical trials, cure rates—not only remission rates—were higher for patients with both breast cancer and non-Hodgkin’s lymphoma with dose-dense chemotherapy. On the dose-dense arms of this study, cytokines were absolutely required. A third important change is the introduction and FDA approval of pegylated filgrastim. Instead of the inconvenience for the patient of daily cytokine injections, we now have one treatment that can last throughout the treatment cycle. That has revolutionized what we do.

As for the NCCN guidelines, certainly it was a plus that, for the first time, they define fever and neutropenia, which puts everybody on the same playing field. This has implications for when patients arrive at the hospital—if a patient were admitted to the hospital for fever and neutropenia and these guidelines were not available, the admission might not be a paid admission.

The NCCN guidelines are on target. I saw no glaring errors; however, I found the guidelines to be very general. For academic cancer centers with high levels of expertise, I’m not sure they are of much use, and I don’t know if it is best for clinicians to merely follow these general guidelines instead of using them as a base and formulating their own guidelines. Also, I would have liked to have seen a section devoted to the use of cytokines; enough space was certainly devoted to how to treat infections that might occur with fever and neutropenia, but not enough was dedicated to being proactive and trying to prevent that condition with cytokines.
ASiM: Can you describe how your practice habits at Johns Hopkins differ from the guidelines?

Dr Spivak: As I said, for anemia the dose recommendations in the guidelines are outdated. They favor erythropoietin given 3 times per week, although they hedge a bit because they understand common practice. At Hopkins, we use 40,000 U once per week for recombinant erythropoietin. There is no therapeutic difference between administering erythropoietin 3 times per week and once per week. For darbepoetin, at Hopkins we give 200 µg every 2 weeks.

ASiM: Is there a preferred option between the 2 treatments?

Dr Spivak: Hopkins does not stipulate which erythropoietin should be given. The guidelines dictate that darbepoetin should be used for non-myeloid malignancies and epoetin for myeloid malignancies, but I think that is mostly because there are more data for darbepoetin on solid tumors. I don’t think there is a difference. There might be a convenience factor, because darbepoetin can be given less frequently, and some of the early studies show that it increases hematocrit levels more quickly, but in terms of the end result, it probably doesn’t make a difference.

The big question is: how does the clinician know that the agent will achieve a response? We know the odds are that someone with a very high transfusion requirement will not achieve a very good response. The same is true for someone with myelodysplasia and an erythropoietin level greater than 100 mm/mL. There are some data that show if the erythropoietin level is below 100 mm/mL, a response will likely be achieved. We do not usually measure erythropoietin levels in our patients, however, because a correlation has not been definitively shown between initial level and response—so, there is no real predictor of response.

A wait-and-see approach is appropriate. In 4 weeks, there should be at least a 1-g/dL increase in the hemoglobin level. If there has been no increase in 4 weeks, the dose might need to be escalated. I think everybody is mostly in agreement about that. With epoetin, dose should be increased 20,000 U; with darbepoetin, the dose is increased by 50%.

ASiM: What if there is no response in the subsequent 2 to 4 weeks?

Dr Spivak: The NCCN suggests looking at iron levels and stipulates serum ferritin levels of less than 100 ng/mL and transferrin saturation of less than 20%. Hopkins does the same thing, but I would recommend doing only the ferritin rather than the transferrin saturation because that might not reflect reality. Of course, a ferritin less than 100 ng/mL is not typically the criterion for iron deficiency, but in these patients, iron might be sequestered or there might be a number of other reasons for the higher ferritin level.

I like to use oral iron supplements, taken with meals. Supplementation should begin with an iron phosphate preparation and gradually be built up. The clinician must remember to tell the patient what to expect. If the patient does not tolerate the oral iron—or has a large deficit—then IV iron might be a better choice. There are new formulations (iron saccharides) that might cause fewer side effects, in part because they’re given at a lower dose over a longer period of time. It is a convenient way to get iron into people who are either not compliant or cannot tolerate oral iron.

ASiM: Why not start iron supplementation from the beginning?

Dr Spivak: If there is no evidence of iron deficiency, I probably would not, because most patients are not iron deficient. If a patient had a gastrointestinal malignancy or was nonresponsive, that’s different. Iron is unpleasant to take; it causes constipation, it’s an irritant, and it turns the stool black.

ASiM: What about the differences between the guidelines and how you deal with neutropenia at Johns Hopkins?

Dr Noga: It really depends on the population we’re treating. Patients who have undergone bone marrow transplant and those with leukemia are very different from the standard patient with hematologic malignancy. They’ve already received a good bit of chemotherapy and have been immunosuppressed for a longer period of time, so they are treated differently. For them, our own critical pathways begin with the broad-spectrum antibiotics that are tailored to the organisms we know commonly infect our patients, as well as the resistance and sensitivity patterns of those organisms.
Patients with hematologic malignancies, in general, do not have infection at presentation. They may harbor organisms from the community, and that has to be considered because they might become susceptible to these organisms. Knowing this, the use of different antibiotics is important. There is some controversy here regarding initiation of empiric antibiotics. A lot depends on the regimen and the type of malignancy the patient has. For those with solid tumors, I generally do not use prophylactic treatment unless the patient has known infection, recent infection, or a history of fungal infection.

On the other hand, for patients with hematologic malignancy who will be undergoing aggressive regimens that I know will induce neutropenia, I initiate a quinolone and an antifungal drug (fluconazole) as well as an antiviral agent. For hematologic malignancies, the evidence isn’t as clear for doing this as it is with leukemia; however, in providing coverage in this way, preventing one serious infection is worth it.

Also, Hopkins is very forward thinking on the use of cytokines. Both G-CSF and GM-CSF are fairly equivalent for prophylaxis, but when it comes down to mobilizing stem cells, I think the data overwhelmingly favor G-CSF. I’ve had a problem with more side effects, in terms of people having more fevers and myalgias from the GM-CSF, but those who have used it a lot say it turns on more of the body's defenses and might be more effective against fungal infections.

I think the benefits with the development of pegfilgrastim—its convenience and the fact that it stays in the circulation for up to 14 days and is cleared quickly when neutrophil counts recover—outweigh any theoretical benefit of using GM-CSF, and there’s been an overwhelming shift to the use of pegfilgrastim. A lot of physicians in the community have been using this the same day as the treatment. That use is against the information on the product insert, but physicians do it for convenience and have not seen any problems. There are currently studies ongoing through the FDA about this subject. We’ll wait for the answer to this shortly.

**ASIM**: Are there good markers for neutropenia?

**Dr Noga**: Patients with leukemia are compromised anyway; they are at very high risk. Those with a hematologic malignancy that involves marrow are at increased risk. Patients with a pulmonary problem have a tendency to be colonized, such as you see with pulmonary disease from smoking; they also have reduced pulmonary reserve. People with any end-organ damage at all are also at higher risk. One damaged organ might be tolerable, but with more than 1 damaged organ, the ability to withstand infection is compromised. Every step should be taken to reduce the chance of infection because the risk of death is so high.

Patients with a previous fungal infection are of major concern. These patients need to be taking treatment doses of antifungal agents because it is very hard to clear a fungal infection in a patient who is already colonized; fungal infection will rapidly develop the moment neutrophils decrease below 500/mm³, and infection is then hard to overcome. Even using the best antifungals is like putting on a bandage; increasing neutrophils is the only way to adequately fight a fungal infection.

**ASIM**: Can you explain your target goals in treating anemia?

**Dr Spivak**: The first target is to be sure the patient is responding. In the literature, responsiveness is defined as an increase in hemoglobin of 2 g/dL or more. If a patient’s hemoglobin increases from 7 to 9 g/dL, I’m sure he or she would feel better but would still be anemic. The ultimate goal is to increase hemoglobin levels to the appropriate endpoint, which varies.

The NCCN calls for increasing hemoglobin to 12 g/dL; at Hopkins, it is similar, but we like to aim for 12 or 13 g/dL. There are no studies to support going higher. The big risk in patients with cancer is that they are prone to thrombosis; in a patient with bad arteries, there is an issue of how high to increase the hemoglobin level. We say 12 or 13 g/dL because no data support higher levels, but I think this is an area for more research. I have seen men who are anemic with low-grade renal disease, who tell me they need erythropoietin. Their hemoglobin levels are at 13 g/dL, but when the levels increase to 14 g/dL, they say they feel better. You can say it is a placebo effect—these are very soft data—but I think it’s something that has to be dealt with. Can you prove the benefit at higher levels, and will Medicare pay for treatment in these patients? On the other hand, people are understandably afraid of the clotting issue. In patients with comorbidities, there’s always the issue that the higher the hematocrit, the bigger the infarct or stroke size.

The other thing to consider is that if a man is symptomatic at 12 g/dL of hemoglobin, I would first get an electrocardiogram to make sure there isn’t something...
wrong with the heart before I start therapy to raise hemoglobin levels. With a woman, I would immediately check the heart, because at 12 g/dL, she is not anemic.

**ASiM**: What about the blood pressure issues?

**Dr Spivak**: What was learned about erythropoietin therapy in patients with renal disease was that there were increases in blood pressure in the first 6 to 8 weeks, before hemoglobin levels increased. In normal volunteers, however, who were likely iron deficient from donating blood at the local blood bank and whose hematocrit did not increase despite erythropoietin therapy, blood pressure did not change. In a normal individual—even if anemic—erythropoietin does not, per se, cause high blood pressure.

It does under other circumstances—now we’re talking about pharmacologic doses—mainly in patients with renal disease and prior hypertension. Also, anyone with renal disease who gets erythropoietin can develop de novo hypertension (about 40%). This is seen less frequently in patients who do not have renal anemia. Still, it makes me want to monitor blood pressure in patients for the first 4 weeks to see if they develop hypertension, especially if they have a history of hypertension. It’s not common, but you don’t want to miss it when it happens.

**ASiM**: What about red blood cell aplasia issues?

**Dr Spivak**: This is a very complex issue, because there are many reasons patients can develop red blood cell aplasia. With a particular recombinant human erythropoietin formulation in Europe—only in patients with renal disease—red blood cell aplasia occurred in association with antibodies that cross-reacted with every erythropoietin known, including the body’s endogenous erythropoietin. This drove the body’s red blood cell production to zero. That was a highly specific situation; this has been a limited issue with patients who have not received that particular formulation, and as far as I know, it occurred only in patients with renal disease.

**ASiM**: What are your targets for patients with fever and neutropenia?

**Dr Noga**: I give fairly intense chemotherapy in a lot of my patients with hematologic malignancies, and I do not expect the cytokines will totally abrogate neutropenia fever. What I expect to see is a shortened duration, and I think we’ve seen that in the literature. This is quite important for me, because if I have a patient that might be colonized with an organism because of previous treatment or a disease they have, the shorter they are neutropenic, the better. Even if they do become ill, increasing their white blood cell count is the most important thing for protecting them from dying or from having serious complications. It also keeps their treatment on track.

Another point has to do with overall quality of life. A lot of times the patients on these regimens are also taking antibiotics, antivirals, and antifungals. Even if their counts are low, if they are reliable, I do not bring them into the hospital for neutropenia; I see them in the outpatient clinic. We check their laboratory values, they keep a body temperature log, and if they become febrile, they call me. If the patient is 93 years of age, they should be in the hospital, of course; however, if the patient is a 30-year-old mother of 2 who wants to be home as much as possible, we weigh that against whether those children are both sick. It is a very individual decision. Such situations call for reliance on physician extenders who know these patients very well—typically a lot better than the doctors.

**ASiM**: What agents do you use when an infection does result?

**Dr Noga**: Ninety-nine percent of the time, it’s a presumed infection. The patient is neutropenic but has no organism identified—that is the most common situation, and that is the situation for which the guidelines were developed. Unless an organism can be identified, a broad-spectrum antibiotic should be used. We start hard, commonly with a fourth-generation cephalosporin. This is in patients who are already taking a form of quinolone, so they’re already getting some coverage; we take it to the next level.

The other consideration to remember is that almost all of these patients have vascular access devices—the most common source of infection. What might be missed is that a device was inserted 1 week previously, chemotherapy was given, and the patient comes in with a normal white blood cell count but with a pronounced infection around the device—most likely a Staphylococcus infection. It is difficult to determine whether vancomycin should be given, because we have the development of vancomycin-resistant strains, which are incredibly hard to treat; they mutate on vancomycin and can spread quickly through a hospital. Removing the device must also be considered; if the site
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is really infected and cannot be sterilized using antibiotics, it should be removed. That's not a light decision.

The other big issue in immunosuppressed patients occurs once they overcome the first fever. If they have subsequent fevers and an organism hasn't been isolated, a fungus must be considered—yeast or filamentous fungus. Candida and Aspergillus are the 2 biggest ones we deal with. Most of the time, we initiate empiric parenteral antifungals, whereas up to that point, we might have been using low-dose oral fluconazole.

**ASiM**: What is the impact of the anemia treatments on quality of life?

Dr Spivak: In the past, I tried to avoid transfusions despite the quality-of-life improvements, because of iron overload, risk of infection, allergic reactions, and so on. Recombinant erythropoietin has many of the benefits of blood transfusion without transfusing blood. It's a modern medical miracle; it truly is. We know from the literature that in patients with chronic renal failure, quality of life unequivocally improves reduced left ventricular volume and improved ability to withstand fatigue, even though renal disease hasn't improved.

The instruments for evaluating quality of life have improved, and I think the data are extremely compelling that erythropoietin improves quality of life in patients with cancer. We're no longer treating a number; we're treating the whole patient. If the patient is fatigued and tired, we are compelled to act. We have the tools to find out reasonably quickly if we're improving quality of life for reasonable expense. If the data do not meet all of the standards of evidence-based practice, they at least meet many of the standards. The trend is unmistakably in that direction.

I do think there is a difference between men and women. One study says there is a difference, another says there isn't, but I would say that it hasn't been studied enough because they haven't taken hemoglobin levels to where they might go in men. Whether anyone wants to do that is a different issue. Eleven or 12 g/dL is still 4 g/dL off in some men—25% of their blood volume.

**ASiM**: What is the transfusion threshold?

Dr Spivak: The threshold is historically based on the idea that a patient whose hemoglobin level was below 10 g/dL would not be eligible for surgery. In outpatient treatment, however, we don't really have a transfusion threshold. It's patient based. If a patient is comfortable with a hemoglobin level of 10 g/dL, then you might consider not doing a transfusion. On the other hand, if a patient wants to do things and is too fatigued to do them, even though the hemoglobin level is 10 g/dL, he or she should receive a transfusion. In patients who present breathless and anemic and who are symptomatic now, transfusion is necessary because erythropoietin takes 4 more weeks to take effect.

**ASiM**: What are the issues with white blood cell count and the impact on quality of life?

Dr Noga: The literature and NCCN identify neutrophil counts of less than 500/mm³ as making a patient susceptible to infection; counts below 100/mm³ place a patient at extremely high risk. We used to wait to achieve 500/mm³ to discharge patients from the hospital, but because of quality-of-life issues, we might be a little more lenient now if their counts are recovering and approaching 500/mm³. If levels are increasing and there have been no infections or fevers, it is likely that these patients will be discharged without waiting for that magic number. Quality of life used to enter into the decision more with cytokines, similar to insurance issues. Insurance carriers would require people to come into the hospital to get cytokines. Some patients did not want to do this, even if they knew it would result in morbidity or mortality, because it meant coming in every day for a shot of growth factor. They didn't want to give up a half-day, every day, to get a shot for a disease they felt was going to kill them. They might have other ways they want to spend their time. Now, with pegylated filgrastim, patients know they have to come in only once for each cycle of chemotherapy, so it's a win-win situation.

**REFERENCES**