Dr Bensinger is a clinician and researcher at the Fred Hutchinson Cancer Research Center in Seattle, Washington; he is also Professor of Medicine in the Department of Medicine at the University of Washington. Dr Noga is 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 Associate Professor of Oncology and Pathology at Johns Hopkins University.

A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr Bensinger and Dr Noga to get their reactions to recently published Multinational Association of Supportive Care in Cancer (MASCC)/International Society for Oral Oncology (ISOO) mucositis guidelines and also to talk more generally about the role of guidelines and protocols in improving the management of mucositis in the setting of bone marrow transplantation (BMT)/hematopoietic stem cell transplantation (HSCT).

Most patients undergoing high-dose myeloablative chemotherapy and/or radiotherapy as conditioning for BMT or HSCT are affected by oral and gastrointestinal mucositis. In this special setting, the oral mucositis is often so severe that patients require parenteral narcotics for pain relief. This mouth pain and other therapy-related morbidities, such as diarrhea, malnutrition, dehydration, and infection, make mucositis the most debilitating complication of transplantation.

A variety of clinical strategies have been developed to prevent or treat mucositis in patients undergoing BMT or HSCT. For example, at most major transplant centers, teams of clinicians, nurses, dentists, and pharmacists have established protocols for oral care, pain control, and total parenteral nutrition. However, most of these homegrown treatment schemes have evolved empirically and the sheer variety of transplantation regimens for BMT or HSCT, patient types, mucositis therapy combinations, and mucositis scoring systems have hampered the development of any basis for truly evidence-based guidelines. Previous efforts in this area, many developed by the nurse and nurse practitioner professionals who provide the bulk of the transplantation support care (see Semin Oncol Nurs. 2004;20:1-66), have focused on single aspects of the problem (eg, nutrition or analgesia) in patients having standard-dose cancer chemotherapy rather than those patients undergoing BMT or HSCT.

In an attempt to create comprehensive evidence-based guidelines on preventing, evaluating, and treating mucositis, a panel of 36 experts was recently convened. These experts from the MASCC and ISOO performed a methodologically vigorous review of the mucositis literature and then drafted clinical practice guidelines. The goal was to establish a benchmark for clinicians to use in the routine care of patients with cancer and to identify the key areas of need for future research.

As highlighted in the following summary, these MASCC/ISOO guidelines still fall short of the long-term goal, mainly because of the methodologic deficiencies of the clinical trials that have evaluated...
mucositis over the past 36 years. This quality gap is reflected in the lack of grade A recommendations in this publication. But do these new MASCC/ISOO guidelines have any value for the BMT/HSCT community? What can be learned from this latest attempt to rationalize supportive care? Are there lessons for clinicians who manage patients undergoing BMT/HSCT today? Should anything be done differently?

background

- Developed by Mucositis Study Section of the MASCC and ISOO.
- Created recommendations that were graded A, B, C, or D based on study design. For example, grade A for evidence from a meta-analysis of well-designed controlled studies or multiple well-designed studies, and grade B for evidence from generally consistent findings derived from separate well-designed studies.
- Plan to reconvene every 3 years.

key points

- A summary of the MASCC/ISOO guidelines is reprinted in the Table.
- Overall, the expert panel concluded that although many of the agents studied are potentially useful, shortcomings in trial design prevent any comprehensive guidelines for mucositis. The panelists identified many gaps in the evidence that made it impossible to recommend definitively for or against specific agents, even agents that have long been used to combat mucositis.
- The only grade A recommendations for use included the following: use patient-controlled analgesia with morphine as the treatment of choice for pain in patients undergoing HSCT; use 30 minutes of oral cryotherapy in patients receiving bolus 5-fluorouracil (5-FU) chemotherapy; use ranitidine or omeprazole to prevent epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or after treatment with 5-FU with or without folic acid chemotherapy; use octreotide subcutaneously (at least 100 µg twice daily) when loperamide fails to control diarrhea induced by standard- or high-dose chemotherapy associated with HSCT.
- The guidelines also made grade A recommendations against use of specific agents, such as not using chlorhexidine, to treat established oral mucositis in standard-dose chemotherapy; not using oral sucralfate to prevent acute diarrhea in patients with pelvic malignancies who are undergoing external-beam radiotherapy; and not using 5-aminosalicylic acid (5-ASA), mesalazine, or olsalazine to prevent gastrointestinal (GI) mucositis.
- In a special section on preventing mucositis in patients receiving high-dose chemotherapy with or without total body irradiation plus HSCT, the only specific guidelines were as follows: do not use pentoxifylline to prevent mucositis in patients undergoing HSCT (grade B) and, in those centers capable of supporting the necessary technology, use low-level laser therapy to reduce the incidence of oral mucositis-associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT (grade B).
- The guidelines acknowledged several post-2001 publications with potential significance for future updates of these guidelines, including studies involving recombinant human keratinocyte growth factor (KGF)-2 and recombinant human KGF-1; L-glutamine; iseganan and oral triclosan; and the bioadherent oral gel (Gelclair; OSI Pharmaceuticals, Inc, Melville, NY) that contains polyvinylpyrrolidone, sodium hyaluronate, and glycyrrhetinic acid.
- Although the panel states that the evidence base currently does not allow for the creation of a specific oral care protocol, it acknowledges the importance of ubiquitous practices such as brushing, flossing, and the use of topical fluoride in maintaining mucosal health, integrity, and function in patients with cancer. Use of oral care protocols that emphasize feasibility, adherence, and comprehensive patient education are recommended for grade B. Use of specific agents in these protocols are not recommended.
Table. Summary of Clinical Practice Guidelines for Care of Patients with Oral and Gastrointestinal Mucositis

I. Oral mucositis

Foundations of care
1. The panel suggests the use of oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiation therapy.
2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT.

Radiotherapy: prevention
3. To reduce mucosal injury, the panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment.
4. The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy.

Standard-dose chemotherapy: prevention
5. The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30-min oral cryotherapy to prevent oral mucositis.
6. The panel suggests using 20- to 30-min oral cryotherapy in an attempt to decrease mucositis in patients treated with bolus doses of edatrexate.
7. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis.

Standard-dose chemotherapy: treatment
8. The panel recommends that chlorhexidine not be used to treat established oral mucositis.

High-dose chemotherapy with or without TBI plus HSCT: prevention
9. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HSCT.
10. LLLT requires expensive equipment and specialized training. Because of interoperator variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence in support of LLLT. For centers capable of supporting the necessary technology and training, the panel suggests the use of LLLT in an attempt to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT.

II. Gastrointestinal mucositis

Radiotherapy: prevention
1. The panel suggests using 500-mg oral sulfasalazine twice daily to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external-beam radiotherapy to the pelvis.
2. Oral sucralfate does not prevent acute diarrhea in patients with pelvic malignancies undergoing external-beam radiotherapy and, compared with placebo, it is associated with more gastrointestinal side effects, including rectal bleeding. Consequently, the panel recommends that oral sucralfate not be used.
3. The panel recommends that 5-aminosalicylic acid and its related compounds mesalazine and olsalazine not be used to prevent gastrointestinal mucositis.

Radiotherapy: treatment
4. The panel suggests the use of sucralfate enemas to help manage chronic, radiation-induced proctitis in patients with rectal bleeding.

Standard-dose and high-dose chemotherapy: prevention
5. The panel recommends ranitidine or omeprazole for the prevention of epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or treatment with 5-FU with or without folinic acid chemotherapy.

Standard-dose and high-dose chemotherapy: treatment
6. When loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose of at least 100 µg administered subcutaneously twice daily.

Combined chemotherapy and radiotherapy: prevention
7. The panel suggests the use of amifostine to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with non-small cell lung cancer.

5-FU = 5-fluorouracil; HSCT = hematopoietic stem cell transplantation; LLLT = low-level laser therapy; TBI = total body irradiation.
AS/M: Describe the range of mucositis you see every day in patients.

Dr Bensinger: Some degree of mucositis occurs in all patients undergoing stem cell transplantation and becomes severe in certain settings. For example, regimens for autologous transplants involve intensive chemotherapy and often cause moderately severe mucositis. In an autograft performed in an outpatient setting, mucositis is by far the most common reason for a patient’s hospital admission. These patients are in pain and cannot swallow liquids, foods, or even their pain pills. Therefore, they are admitted to the hospital to receive fluids and intravenous feeding and parenteral pain management. The cost of hospitalization is significant and is an immense issue for our program. In allogeneic transplants, the high-dose therapy makes mucositis an issue for most patients, but then these patients also develop GI complications related to graft-versus-host disease (GVHD). These patients require a different assessment and treatment. Finally, significant mucositis is relatively uncommon in patients receiving less intensive or nonmyeloablative chemotherapy as preparation for allogeneic transplant. These patients still have to deal with GVHD, but the mucositis issues are reduced markedly.

AS/M: Before publication of the MASCC/ISOO guidelines, what recommendations on preventing or treating mucositis were available to specialists in BMT/H SCT?

Dr Bensinger: There has been no standardization among transplantation centers regarding how to prevent or treat mucositis. There is information on mucositis in general, such as the 1990 National Institutes of Health consensus panel on the oral complications of cancer therapy, but nothing specifically on mucositis as it relates to transplantation. The Cochrane Group has also reviewed mucositis but, almost without exception, there are no studies that have evaluated mucositis in the context of H SCT. Therefore, much of what is done clinically is still based on tradition, on “what we’ve always done.” Nurses and doctors use various proprietary therapies, such as saline rinses and mouthwashes with antibiotics or local anesthetics, to relieve the pain.

Dr Noga: I agree. There has been little discussion in the scientific literature on this topic. Most mucositis treatment information has been developed by individual centers and passed from person-to-person. In fact, in the past, known effective preparative treatments often were avoided because clinicians didn’t know how to manage the mucositis. For example, a protocol developed several years ago for transplantation used hyperfractionated radiation, cyclophosphamide, and etoposide, which was effective in terms of disease survival and remission rate. However, the mucositis rate was so severe that most centers shied away from it, even though the protocol had the potential for cure. Only recently, as these adverse effects have been addressed, have we returned to using these protocols.

AS/M: Why the paucity of literature on mucositis?

Dr Bensinger: I don’t have a good answer. It may be partly because hematologists and oncologists traditionally have focused more on treating the cancer and less on supportive care or quality-of-life-issues. This is changing as centers recognize the high patient morbidity. For example, at our center, we have a group of oral care specialists with dental training who take special interest in our patients who are undergoing transplantation. Ten years ago this was the exception, but it’s changing.

Dr Noga: Yes. Initially, we were most concerned about delivering chemotherapy regimens that were effective and improved survival, even if the patient had adverse effects from the treatment. You heard the phrase “a cure in a wheelchair is still a cure.” In this new millennium, mucositis is evaluated differently. The cure, with its significant morbidity and pain, sometimes can be worse than the disease. A patient’s quality of life is a major issue now and should be discussed with the patient. A treatment with adverse effects may not fit in with their plans.

AS/M: Has the lack of a standard treatment approach to mucositis led to a wide variation in how it’s managed?

Dr Bensinger: Yes, each center has its own approach, and this leads to inconsistencies in care. At the Hutchinson Cancer Center, we are lucky to have an extremely talented oral care group led by a dentist who has been on staff for 15 years. He has led our efforts in mouth care, and his group has developed our tools for assessing mucositis. Our Standard Practice Manual with specific instructions for oral care is available online to any practitioners in our center via the Intranet.

Dr Noga: To a large degree, the various center protocols are based on special regimens or “magic cock-
tails” that the nurses and pharmacists have developed. These homegrown treatments or recipes move from center to center as the staff are trained and then move on. Still, even if there’s some variation in strategies at the large institutions where so many transplants are done, the standards for managing mucositis are usually quite high. For example, as Dr Bensinger mentioned, often an oral pathologist will examine the patient’s mouth. In fact, if a center was not actively trying to limit mucositis, it would have a hard time retaining staff. The nursing staff always has been proactive in this area, especially in pain management. Many patients say that mucositis pain feels like they “were chewing on and swallowing broken glass.” Therefore, if a center didn’t include pain management in their treatment protocol, nurses simply would be reluctant to work in that unit.

**ASiM:** Overall, what are the strengths and weaknesses of the MASCC/ISOO guidelines on mucositis?

**Dr Bensinger:** The guidelines were an excellent attempt to standardize a global approach to oral medicine and mucositis. The panel that established the guidelines tried to be comprehensive by evaluating radiation therapy, standard-dose chemotherapy, and high-dose chemotherapy, in addition to evaluating oral mucositis and gastrointestinal problems such as esophagitis, radiation proctitis, and epigastric pain. Although the panel had some helpful solid recommendations, I think they missed some relevant studies. For example, I could not find any reference to the efficacy of allopurinol mouthwashes for 5-FU stomatitis, but the Cochrane Review noted this 1994 Italian study. The Cochrane Review also commented on the use of human placental extract, and that treatment wasn’t addressed in these new guidelines. Therefore, a lack of comprehensiveness may be a shortcoming of the guidelines.

**Dr Noga:** I applaud this group for publishing the guidelines, which are valuable, even if we are working with a scant evidence base, as reflected in the lack of level 1 or grade A recommendations. Recommendations about what treatments not to use also are valuable. For example, when pentoxifylline first came on the market, everybody thought it was the cure for mucositis. Then the flaws in the studies were reported, and we no longer heard or read as much about pentoxifylline. This seems to be a typical practice—no mention about once-hyped treatments once they are discounted. Therefore, I was glad to see this in print finally. Also, because many physicians also treat patients with cancer who are scheduled for transplantation, some of the guideline sections on standard chemotherapy were interesting. For example, the guideline said that sucralfate (other than enemas) actually causes increased GI bleeding. In addition, the guidelines now recommend against the use of 5-ASA, mesalazine, and olsalazine to prevent GI mucositis. Proactively, because so many patients receive cyclophosphamide, the recommendation to use ranitidine and omeprazole is positive and important.

**ASiM:** Are the results of mucositis studies in patients not scheduled for transplantation applicable to your BMT/HSCT population?

**Dr Noga:** It depends on the situation. As I just mentioned, we often use high-dose cyclophosphamide in stem cell mobilization, for example, or with the preparation of patients with lymphoma for transplantation. Therefore, the omeprazole recommendation is quite applicable. In fact, many of my high-risk patients are receiving omeprazole in the first part of their chemotherapy and then remain on the drug if they are to undergo transplantation.

**Dr Bensinger:** Much of the information about treatment for mucositis in patients receiving standard-dose chemotherapy is in fact not directly relevant to patients receiving SCT. For example, the recommendation for use of sulfasalazine to prevent radiotherapy enteropathy has not been studied for high-dose therapy for SCT. The evidence of efficacy in this other patient population may convince a researcher to study sulfasalazine in a different population, such as the patient undergoing transplantation. However, based on the current evidence of efficacy in the larger population of patients with cancer, you can’t assume a drug will be more effective in the BMT/HSCT population.

**ASiM:** Specifically, what are the most significant or surprising new recommendations in these guidelines?

**Dr Bensinger:** I was surprised by the recommendation for use of low-level laser therapy. Although a couple of randomized studies are positive, including one we did in 1995 to 1997, I’m not aware of any ongoing work in this area at our center or at other centers. This may be because the laser therapy machines are expensive (approximately $25,000) and require special maintenance and staff training. Also, the equipment
manufacturers apparently cannot afford to conduct the studies. The guideline’s statement on pentoxifylline also was interesting. This agent was once thought to be a miracle agent for preventing mucositis and a host of other cancer treatment toxicities. Now it’s largely been disproved as a useful agent. However, some of the negative studies were poorly designed, and subsequent, better-designed studies should be initiated. However, the current level of evidence confirms that pentoxifylline is not a useful drug.

Dr Noga: One important and practical recommendation was the use of patient-controlled morphine for analgesia. The recommendation for ice therapy with 5-FU also was interesting, although we don’t use this agent in transplantation. I was always curious about this recommendation because some nurses use ice therapy and others don’t. I am surprised about the laser treatments, too. I’m not familiar with the references because this is used in only a few centers with that special equipment.

AS/M: Will these guidelines change the way you treat mucositis?

Dr Noga: Yes, but only if staff who treat mucositis daily are educated. We can give them copies of the guidelines or, even more effectively, have symposia to stimulate a discussion led by a pharmacist or nurse or nurse practitioner. This is the type of education that can lead to the development of critical pathways, which are crucial to ensure that supportive care protocols will be effective. Also, patients can never receive enough education about mucositis. Nurses constantly talking to the patient about oral hygiene and their level of mucositis is important. In fact, most patients benefit from writing their daily medical history in a notebook, which allows them to participate in their care.

Dr Bensinger: I like the idea of having regular educational sessions and of planning nursing meetings devoted to this issue. After all, for the patient who has received a stem cell transplant, mucositis and the related pain and nausea is the most difficult part of the treatment. Until recently there were no effective tools for dealing with this adverse effect.

Dr Noga: I think the key to improving how we treat mucositis is to encourage the consistent use of the best-known therapy. Guidelines can be a tool to develop that consistency. We recently developed a BMT antiemetic protocol at Johns Hopkins that was based on NCCN (National Comprehensive Cancer Network) guidelines. These guidelines, by the way, did not discuss patients undergoing BMT who were receiving high-dose myeloablative therapy—the group that actually has the highest rates of nausea and emesis of any treatment group. These patients who were undergoing transplantation were too far off the scale of severity to include. We wrote our own critical pathway that included a modified Rhodes score from 0 to 8 to measure nausea and vomiting. Retrospectively, we were running scores higher than 4 with our standard antiemetic regimens. We did a study comparing antiemetics alone with antiemetics plus the addition of acupressure, and found that both arms reduced the Rhodes score to 2.5. We think the reduction was more because of the adherence to a guideline than to the treatment in either arm of the study. Importantly, the antiemetic algorithm included standing orders, meaning that the nurses could rate the patient’s level of nausea and emesis and then make rapid decisions to treat based on physician-approved standing orders. This highlights the power of pathways to improve care—but you need the guidelines as a starting point to design critical pathways.

AS/M: However, the evidence to build the guidelines is also needed. Do we have sufficient evidence about preventing mucositis in patients undergoing BMT/HSC?

Dr Noga: I think the evidence supports centers developing a basic critical pathway on mucositis. These guidelines, along with a good scale of mucositis, would allow clinicians to at least begin data collection. Basic pathways for recommending agents, such as omeprazole or patient-controlled analgesia with morphine, can be developed by using the WHO (World Health Organization) scale. Today, a patient may spend the night in severe pain because they didn’t want to wake the doctor. A protocol may allow analgesia to be started automatically and consistently. I think enough evidence exists that this pathway can be included in the scientific literature.

Dr Bensinger: Clearly, there are few studies that address mucositis in SCT. Some randomized studies have examined various drug or radiation combinations, but often these studies are small and underpowered, and the tools for assessing mucositis and the degree of patient discomfort are inconsistent. However, the need for better studies should encourage researchers to keep trying. Even incomplete guidelines are better than nothing, and these new guidelines are a worthy initial effort. As data from new therapies become available, the guidelines will require revision.
**ASiM: Are mucositis scales widely used?**

*Dr Noga:* As in many disease areas, there were no approved scales for rating mucositis until new treatments were developed and the US Food and Drug Administration (FDA) required quantitative rating systems. The WHO scale is an incredibly simple system, rating mucositis from 0 to 4. The Radiation Therapy Oncology Group and others have published more complex scales, and the FDA requires a combination of scales for the current mucositis clinical trials. But, even the simplest WHO scale could provide the basis for critical pathways in transplant centers today. Certainly, I would surmise that all transplant centers previously involved in the multicenter trials of the 2 major KGF products in development are continuing to rate mucositis in all of their patients. Our nurses and physicians have found it useful to have an objective measure. Previously, we would look at the patient's mouth and write a descriptor in the chart. A fellow or resident may call me to say that a patient's “mouth looks like hamburger,” which isn't helpful in making a treatment decision. However, if I hear that a patient has a [WHO] grade 2 mucositis, then I can make informed decisions even when I'm not at the bedside.

**ASiM: Is mucositis prevention or treatment of mucositis in the BMT/HSCT population different in a fundamental way from such therapy in other patients receiving standard-dose chemotherapy or radiotherapy?**

*Dr Noga:* As I mentioned previously, transplant specialists can learn about mucositis prevention and treatment from some studies in patients on standard-dose therapy. However, these are in fact quite separate groups that must be approached differently. By the time a patient requires HSCT, they usually have failed previous regimens or their disease is so severe that a standard regimen would not be effective. Therefore, these patients are in a special severe disease category. Most of these patients, with the possible exception of a patient with myeloma, will undergo transplantation only one time. Standard chemotherapy, by contrast, usually is administered repetitively, anywhere from 4 to 12 cycles depending on the disease and patient's situation. As such, there's more opportunity for mucositis to develop over a longer period of time, which is why mucositis should be approached differently in these groups. For example, for diseases such as breast cancer and lymphoma it's important for the patient to receive the full dose of therapy without delay to maximize the chance of cure. Those patients who have received a full dose in a timely manner have the highest cure rates. Patients do not benefit from being off chemotherapy for a week while the physician tries to treat a case of slight mucositis. When the guidelines recommend that ice chips with 5-FU can prevent mucositis, they're really implying that this simple step can keep the dosing on time and increase the chance of cure. For instance, in patients undergoing dose-dense chemotherapy, this translates to a more intensive therapy in a short time period. The chemotherapy is administered, and your plan to prevent or to treat mucositis must occur at the beginning or near the end of therapy because of close cycle lengths.

**ASiM: Does the potential for GVHD impact your management of mucositis?**

*Dr Noga:* GVHD is an inflammatory process, as is mucositis. Anything that is done to quell the mucositis also may improve the GVHD and vice versa. Some of the data reported by Bruce Blazer's lab in Minnesota show that, in addition to reducing oral mucositis, KGF also reduces the incidence of GVHD. In fact, this basic research finding was one of the reasons we at Johns Hopkins decided to become involved in the phase II trial with KGF, to gain some experience with a drug that may reduce mucositis in the transplant setting and, downstream, possibly prevent GVHD.

**ASiM: How does KGF reduce GVHD?**

*Dr Noga:* We don't know. This biological certainly reduces the inflammation. We do know that mice with GVHD usually die from sepsis, which is caused by the
invasion of bacteria through the GI tract. It’s a complex multifactorial process, but any substance that reduces GVHD—by reducing inflammation or maintaining the integrity of the intestine, perhaps, by limiting production of the cytokines produced during GVHD that cause inflammation—may be useful clinically to any center using allogeneic transplants.

ASiM: Isn’t there also the possibility that some of the existing or new antimucositis therapies will reduce the efficacy of the cancer therapy or transplant?

Dr Noga: Chemotherapy doesn’t work via inflammation, thus the general pathways are expected to be different. However, there are some mucositis regimens that may impinge on transplant outcomes. For example, there is some concern about the use of amifostine in standard radiation therapy and chemotherapy because it may actually protect tumor cells from exposure to the chemotherapy, which is why many clinicians don’t recommend amifostine. Also, we don’t know yet if mesodermally derived cytokines that stimulate the bone marrow can also stimulate tumor cells or protect them in some way. Of course, in the context of transplants and hematologic malignancies, the cytokines we’re investigating to limit mucositis are aimed at epithelial cells. Therefore, we are not too worried about these effects. However, our colleagues who are treating head and neck cancers and GI cancers are more concerned about the potential tumor-protective effects of these KGFs. Clinical trial data are needed. Clinicians may be willing to take a higher risk of treatment effects in patients undergoing transplant because this is the patient’s last chance for treatment, but there are still concerns.

ASiM: One of the main conclusions of the authors of these MASCC/ISOO guidelines was the need for better studies with more consistent methodologies to generate better evidence. Do you see this happening now?

Dr Noga: Absolutely. In looking at these guidelines, it was surprising to see the paucity of good evidence. Most of the studies are flawed, many are not randomized correctly, and there’s room for improvement in supportive care trials.

Dr Bensinger: Certainly the current studies involving agents, such as KGF, are rigorously designed with careful multiple measurements, adequate power, and double blinding. These company-driven studies of KGF are a good model for testing future agents.

ASiM: In looking ahead at some of the new interventions in development, do you think mucositis will ever become an avoidable adverse effect of BMT?

Dr Noga: We’re still pushing the envelope with aggressive cancer therapy, but we also are closer to attaining that goal of limiting mucositis risks. As we review the history of BMT, we know that several other toxicities such as infection, GVHD, and engraftment once had much higher priorities than did mucositis because people died from these toxicities at a much higher rate. However, clinicians learned to handle these toxicities with new growth factors, with more powerful antibiotics, and by using peripheral blood stem cell transplant instead of BMT. Therefore, engraftment was accelerated and the infection rate was reduced. In turn, this allowed the use of better transplant regimens, improved radiation therapy, and better chemotherapy regimens with optimized dosing. Now, mucositis remains as the key dose-limiting toxicity for patients. If this toxicity can be addressed, perhaps the transplant treatment can be further optimized to get better outcomes. At that point, there may be more mucositis, or there may be a rise of the next dose-limiting toxicity, but that’s the progression I expect toward better cures.

Dr Bensinger: We definitely are making progress, but I think mucositis will continue to present challenges for patients undergoing transplantation for many years. The studies with palifermin (KGF-1) are promising. Palifermin appears to be a useful agent leading to significant reductions in serious mucositis, but it doesn’t eliminate mucositis. Other agents in trials may work in synergy with palifermin or perhaps by different mechanisms. Fibroblast growth factor is a promising agent that has worked in animal models of inflammatory bowel disease; clinical trials are beginning. Fibroblast growth factor may have a better effect in the lower GI tract. Currently, palifermin may be effective in treating mucositis, but no clinical studies have been conducted to demonstrate if it is useful in areas below the level of the throat. If these new drugs can reduce mucositis risk, they may actually allow the use of even more intensive regimens, which potentially would translate into even more effective treatment of the cancer. Therefore, there is the potential for these new treatments to allow more effective treatment of cancer, as was shown in breast cancer and other cancers that allow greater dose intensity with the use of colony-stimulating factors, which translates to better outcomes.
ASiM: Will there be increasing or decreasing numbers of patients in need of BMT or HSCT and who are at risk for developing mucositis?

Dr Bensinger: There won’t be any major decrease in the mucositis risk because of the increased use of nonablative transplants. These special transplantation procedures with less intensive regimens are useful only for some patients, thus they will not necessarily replace high-dose therapy but will serve mostly to expand the whole population of patients eligible for transplants.

Dr Noga: The role of transplantation continues to change. The overall use of this procedure probably will remain about the same, but the techniques pioneered in this field will have wide applicability. In other words, transplantation techniques and research impact how other diseases are treated. For example, many of the supportive care regimens developed for transplantation now are used to help patients tolerate dose-dense chemotherapy with growth factors with high cure rates. Supportive care has advanced tremendously. I remember seeing young men with testicular cancer who, after the first cycle of chemotherapy, actually did not want to continue chemotherapy. The nausea and vomiting was so severe that, even though the patients knew there was a 90% chance of cure, they decided to take their chances without the chemotherapy. With the new antiemetics that fear has been erased, and now there are spokespeople such as Lance Armstrong who have helped to educate the population about testicular cancer. The same pattern will develop for mucositis. If a patient comes in for evaluation and sees patients undergoing transplantation who are struggling with mucositis, they may consider not going ahead with their own transplantation. However, if patients come in and see another patient who’s not experiencing adverse effects, this will be the deciding factor in going ahead with their treatment.

REFERENCE