Perspectives in Febrile Neutropenia: Q&A with Gary Lyman, MD, MPH

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***AJMC®*: What is the importance of febrile neutropenia (FN) in oncology?**

LYMAN: Fundamentally, those who work in the field consider febrile neutropenia to be either one of the most, if not the most important dose-limiting toxicity of conventional cancer chemotherapy. It not only greatly increases the risk of sepsis and life-threatening infection, but also often leads to reductions in chemotherapy intensity through early termination or reductions in dose or delays that can have a direct impact on the effectiveness of chemotherapy in patients with cancer. It has a dual impact: first, in terms of the risk of infection, which increases as neutrophil counts go down, and second, in terms of the delivery of chemotherapy at safe, effective, or even curative levels. Before the availability of the myeloid growth factors [granulocyte colony-stimulating factors; G-CSFs] for prevention and aggressive treatment strategies, FN was often fatal and severely limited effective cancer chemotherapy. Even now, the risk of life-threatening infection and delivery of full-dose chemotherapy remains a challenge in cancer patients who are often older with other serious medical conditions. There continues to be a lot of research in this area, particularly looking at adherence to guidelines, and what can be done to improve on quality of cancer care by ensuring that the patients who are at risk for these complications get the right supportive care, as well as prompt, effective treatment for infection if they develop FN.

***AJMC®*: In 55% to 95% of cases, G-CSFs as primary prophylaxis are used inconsistently with guidelines. What, in your opinion, accounts for the inconsistency in use of G-CSFs as primary prophylaxis?**

LYMAN: There are probably multiple factors, and part of our ongoing Pragmatic Trial Assessing CSF Prescribing Effectiveness and Risk (TrACER) study is to identify the main drivers. There is clearly both underuse and overuse of G-CSFs. Certainly, from a cost perspective, the overuse is of high concern because these are expensive drugs, and if they are not needed, it drives up healthcare costs.

From a clinician standpoint, we may be even more concerned about underuse: that is, not providing prophylaxis or prevention of these life-threatening complications leading to costly hospitalizations in patients getting high-risk chemotherapy. These patients may end up with serious infections and hospitalizations that could be avoided with the appropriate use of these agents that are costly in their own right. In terms of why there is both underuse and overuse, I think it is complicated and multifactorial. We have seen in our survey data that a lot of growth factor use is either automatic, meaning some practices administer growth factors to almost everyone getting chemotherapy, and other practices give very little if any growth factor, and that may stem out of how individuals are trained or constraints in terms of costs that have been imposed on them.

The 3 major guidelines from ASCO, NCCN, and EORTC are consistent, and they recommend G-CSF use based on the level of risk. The guidelines are all in sync, and recommend the routine use of myeloid growth factor support if »

the risk is in the range of 20% or more. If the risk is less than 10%, the benefits and risks may not favor using these drugs routinely, unless the patient has other high-risk conditions. A remaining big challenge, however, is that there are a large proportion of chemotherapy regimens that fall in a gray zone that we call "intermediate risk," where the risk of FN is somewhere between 10% and 20%. That may account for upwards of half to two-thirds of chemotherapy regimens. Of course, those risks are generally estimated from clinical trials that led to the approval of those drugs or regimens. It is complicated because the clinical trials are often very selective of which patients they allow to participate. These trials do not allow patients with important comorbid medical conditions to participate. Often the trials are conducted in younger patient populations. The patients in those trials are a more favorable risk population that may not be representative of patients in a real-world setting where patients are often older or have other health problems, where complications like FN can be much more serious or life-threatening. For that reason, this gray area where the regimens are associated with a 10% to 20% risk of FN based on clinical trials, the guidelines are somewhat ambiguous. However, the guidelines recommend that if, in addition to the chemotherapy, a patient has other risk factors either for developing FN or having a bad outcome if they were to get FN, then one should consider using G-CSF support. This represents more personalized supportive care that goes beyond the guidelines based on patients eligible for clinical trials.

Our own data suggest that approximately half of patients receiving chemotherapy who are considered intermediate risk for FN are actually at high risk for FN because of other medical conditions, such as heart disease, lung disease, liver disease, and so forth. Presence of these comorbidities, in addition to the cancer, progressively increases the risk of FN, and the potential for complicated hospitalizations or even dying from febrile neutropenia. Although the guidelines do not give strict prescription of when to give growth factor support and when not to give growth factor support, treating clinicians should consider other risk factors in addition to the chemotherapy regimen when making a decision whether to utilize G-CSF support.

In the TrACER trial that's under way, we're just being run through SWOG and through the community oncology sites affiliated with SWOG. We are randomizing sites, not patients. Some practices have agreed to embed the guidelines into their computer order entry system. This means that for patients getting high-risk chemotherapy, G-CSF support would be automatically given, even if, in the past, the physician might not have made that call. Of course, the physician can always opt out of that, but the default position is, if the patient is high risk they receive the support, if the patient is low risk they do not receive it, and these are built into the order systems for various chemotherapy regimens. The comparison groups at the other sites receive usual care. The physician selects the chemotherapy and they make the decision, presumably, how they always have, on whether to give growth factor support or not. Our hypothesis is, by having this built in automatically, and to somewhat enforce guideline adherence, we will see better outcomes. Again, patients who do not need growth factor are not getting it, and those who should get the support are getting it. We will follow and see if the rates of FN and complications from FN are altered and improved by building this into electronic order systems.

There is another element to this study. Again, there are not much data on G-CSF support in patients getting intermediate-risk chemotherapy, which accounts for half to two-thirds of chemotherapy regimens. The guidelines are ambiguous on this and simply call for the physicians to use their best judgment. So, in our trial, at the sites where growth factor support is built into the treatment regimen, if the patients receiving chemotherapy are at intermediate risk, the protocol calls for a second randomization, to either automatically give growth factor support or not, depending on the trial site. The purpose of this second randomization is to see if we can improve our understanding of the effectiveness and safety of G-CSF support in patients getting intermediate-risk chemotherapy, because data on this are limited. This is a 5-year study, and, so far, we have great engagement from the sites; the accrual is going well, but it's still going to be a couple of years before we begin to see results coming out of this, to see whether we can improve adherence to guidelines and how effective growth factor support is in intermediate-risk chemotherapy groups.

***AJMC®*: In many of your previous publications, you have mentioned financial toxicity as an important challenge in oncology care. How are the costs of G-CSFs affecting prescribing decisions, and how might those decisions be affected by lower-cost agents, such as biosimilars? What is the experience with these agents in Europe, and what could that mean for the United States?**

LYMAN: One of the reasons we do not give G-CSF to ev-

ery patient, if they don't need it, is to avoid the burden of injections, which are administered as frequently as once daily. The other reason to limit the use of G-CSF when the risk of FN is low is cost. These are very expensive drugs. Like with all of healthcare, the prices on these drugs have gone up over time, and certainly that has been true in the last 5 to 10 years. We have done economic analyses to suggest that, for high-risk patients, you either break even or save money by using these agents, based on their ability to prevent serious infections leading to hospitalization, and sometimes even death. The cost of hospitalization, like healthcare costs in general, has gone up greatly, and has exceeded the overall increase in healthcare costs. The cost of hospitalization with FN, if it is not prevented, is thousands of dollars a day in many institutions. It is true that the drug may be expensive, but comparing that cost with the preventable cost of hospitalization and intensive care unit stay and any other complication that may come with it, the net effect can be cost saving. So, all of these considerations are important.

Another concern that has gained considerable attention in recent years is that cost increasingly has become a barrier to a patient either getting appropriate and potentially curative treatment at all, or safely administered treatment. Patients who should be getting a chemotherapy regimen where growth factor support is necessary, or indicated, may simply be unable to afford treatment because they have no insurance, or because the associated out-of-pocket cost, which has also gone up, has become a barrier to access to care and appropriate treatment. And even when patients can and do get treated, they may be left with insurmountable bills, which we refer to as the "financial burden" or "financial toxicity" of treatment. We have shown that financial toxicity can double the rate of bankruptcies when a patient is diagnosed with cancer and goes through treatment. Financial toxicity may even increase mortality just by virtue of dealing with the cost associated with cancer care.

There are many solutions to this, but they are all difficult. One, of course, would be to improve insurance coverage. The Affordable Care Act attempted to do that by trying to help uninsured patients become insured. Another strategy lies in the G-CSF agents. These myeloid growth factors are biologic substances, not small chemicals like antibiotics or pain medications. They are synthesized in living cells and then purified and packaged and delivered. But, because they are made in living organisms, unlike small-molecule drugs, you cannot replicate them identically. To develop competitors as the patents expire on these biologic agents, one can't replicate the drug exactly. However, once the patent expires there's the capacity to develop very similar systems and synthesize biologic agents that are highly similar to the original drug, and that is called a biosimilar. Therefore, the biosimilar is not an exact copy of the originator, but it has to meet certain FDA criteria both in terms of its molecular makeup and structure, as well as how it behaves in animal and in human studies.

The patents for these new biologic agents have begun to expire, so they are open to competition from biosimilar companies. In fact, there are biosimilars available in the United States that are G-CSF molecules. The first one that was an official biosimilar is filgrastim-sndz, but there's a whole line-up of companies that have applied to be approved by the FDA [with] biosimilar G-CSF forms. Therefore, we are very likely over the next year to have multiple potential agents. There's another drug that has approval as a biosimilar in Europe but received approval in the United States through the traditional pathway, tbo-filgrastim, and that's available now. Therefore, there are 3 forms of filgrastim available in the United States: the originator, which is Neupogen, and then 2 that are essentially biosimilars. The interesting thing about biosimilars, based on the FDA approval process, is that they don't need as much clinical trial data as the originator drug. The first biologic for a condition has to provide not only the preclinical data, but also the extensive clinical data demonstrating efficacy and safety. If we required the same amount of preclinical and clinical data of the next generation, the biosimilars, the development cost would be prohibitive, and we would not have companies pursuing that, or if they did, the pricing would be no less than what the originator required. The rules that have been promulgated and are now in place require much less clinical data, with the presumption that if the molecule has the same components and the same structure and behaves the same in preclinical studies, some limited clinical data should be sufficient to justify approval as being highly similar to the originator.

The other thing that makes clinicians uncomfortable is that the approval of that biosimilar based on the clinical data provided will be extended or extrapolated to all indications that the original drug has been approved for based on larger amounts of clinical data. So, this extrapolation beyond what the studies have previously justified makes some providers nervous; however, the experience in Europe is far ahead of the experience here in the United States. In Europe, where biosimilars have been approved for well over 5 years, no major safety concerns have emerged through »

this process of extrapolated approval. The hope is that with increased competition, prices will be driven down.

There are a couple of challenges, 1 of which is that these agents are still expensive to produce. They're biologics produced with a living organism. It's very sophisticated technology. There's that bottom-line cost that you can't go below in developing these drugs, and even with not requiring so much clinical trial data to get approval, the experience has been that you don't experience the huge price reduction that you see with generic drugs, which drops upwards of 80% of the cost of the brand name chemical agents. In the biologic area, because of the complexity and the high development cost of a biosimilar, it's expected that, and the European experience would suggest, we might see about a 20% drop in price, with no more than a 30% drop. Any reduction is good if we want to improve access, and the rising healthcare cost could go down because of competition; however, it will not be as dramatic as with generics.

There's 1 remaining issue around biosimilars, which is the proposed FDA criteria for approval as an interchangeable biosimilar, which providers and professional organizations as well as [individual US] states are trying to tackle. ASCO is representing the oncologist and the patient, and wants to make sure that everyone is educated about what is good and what is to be concerned about with the introduction of biosimilars in the oncology setting. Right now, there are some provisions in the draft guidance around the interchangeability of a biosimilar drug. If a drug is to be given the designation of interchangeable, you can switch from the brand name, or the originator, to the biosimilar, back and forth without any concern about safety and efficacy. It's a higher bar than just giving a designation as a biosimilar because you have to demonstrate through studies that you can go back and forth without any safety signals emerging or a loss of efficacy. This issue is discussed at length in a recent special issue of the *ASCO Journal of Oncology Practice* on biosimilars from September.

The regulations around interchangeability are out for public comment, and they have not been finalized yet. I think that among the concerns the clinicians have is a provision that the patient's treatment could be switched from the brand name agent that we've had for decades and that various oncologists are very comfortable with, to the biosimilar, without the physician or patient being aware of the change. In other words, the pharmacy could switch a drug to the lowest- costing agent, and this has been a concern for many people. In fact, we now have 35 US states that are attempting to preempt these rules through legislation that the prescribing physician needs to be notified if such a switch is going to occur. So, although the FDA approval and CMS may try to impose the switching without notification, these states have decided they want to make sure that patients and physicians know if a drug has been switched to a biosimilar. I think that's reasonable, and until we have more experience with these agents with longer-term follow-up, we want to make sure that there are not any rare or delayed [adverse] effects that didn't show up in the limited data provided. This is a work in progress, and the FDA hasn't issued the final ruling, but ASCO and others want to make sure that they're at the table during the discussions to ensure that these are best implemented in the coming years.

The next level of concern relates to biosimilars that are specifically cancer treatments and not supportive care, such as G-CSF, which helps enable patients to tolerate chemotherapy. The Oncology Drug Advisory Committee [ODAC] has recommended approval for trastuzumab, which is a biosimilar form of Herceptin, prescribed to women with breast cancer. The ODAC has also recommended and the FDA has recently approved bevacizumab, the biosimilar version of Avastin, which is used to treat several types of cancer. Therefore, we have, for the first time in the United States, a biosimilar approved for cancer treatment. That's why it's important to educate physicians and patients on how this will be done, what this means, what are the safety and efficacy issues, and how these will get integrated into guidelines.

Certainly, for G-CSF we have reviewed all the data with the ASCO guidelines and NCCN guidelines, and have recommended that the approved biosimilars can be used equally with the original G-CSF based on the data provided. However, the concern rises to another level when talking about cancer treatments and biosimilars for those treatments, and not just supportive-care drugs. A lot is happening and a lot will change in the coming months and years in the world of biologic agents. Clinicians and patients need to know as much as possible about what's coming.

AJMC®: What are some ways that insurers can partner with cancer institutions to enable more effective or more appropriate evidence-based treatments that adhere to guidelines for FN, and what would be the most important take-away for managed care?

LYMAN: I'm a strong proponent of clinical practice guidelines, and I believe that insurers and managed care

organizations should do what they can to improve adherence to guidelines. Having said that, as I mentioned earlier, there are some gray areas in the guidelines, where a decision on, for instance, G-CSF use is left to the discretion of the clinician, who knows the patient the best. I think it will be important to have the flexibility to allow the clinician to make a judgment call about whether a specific patient is high risk or not and to use growth factor support accordingly. However, our studies have demonstrated both underuse and overuse of these agents in actual practice. I think adherence to guidelines is important, and anything we can do to improve that adherence will be important not only to the quality of patient care, but also in terms of cost and making sure the value of care is optimal. When it comes to biosimilars, we hope there will be a lower price tag, and with competition, this may bring down the price of the brand name product, although, again, it will probably be more modest than what we see with generic chemical molecules. Nonetheless, I think the introduction to biosimilars is reasonable, and based on the FDA criteria for approval, it's reasonable to include those as options for physicians to use in supporting patients receiving cancer chemotherapy.

The next generation of G-CSF biosimilars that will be forthcoming will be for long-acting G-CSFs, so that the patient doesn't have to receive injections every day, but instead once per treatment cycle every couple of weeks. What's currently on the market is pegfilgrastim or Neulasta administered as an injection or using an on-body injector as a single injection each treatment cycle. Although this is currently the only option for the long-acting form, there are a couple of companies that have developed the long-acting competitor biosimilars going through the FDA process, but they probably won't be approved until next year. However, eventually there will be competitors for the long-acting product that patients prefer over the daily injections administered for 7 to 14 days. I think that for insurers and for managed care, cost is an issue, but patient adherence and satisfaction, and the full patient experience, have to be very strongly considered. There will still be pressure for patients to get these long-acting products. Of course, when the competitors come along, there will be more options available there and hopefully costs will come down.

Finally, I think the issue of interchangeability, and patient and physician notification, is important. Although at the federal level there may be rules that say that the brand name drug and the biosimilar can be switched without notifying the physician, I think clinicians and health systems and managed care organizations should still notify physicians if they build in the use of agents that mandate a switching from the brand name to a biosimilar. In other words, I think it would behoove us all to know what product the patient will actually be receiving and, if that has changed, there needs to be a notification of that change. I think we need to gain some experience over the next several years to make sure that the interchangeability is safe and that no unexpected or rare complications occur because of the switch from one agent to another. I think that's an area where transparency and accountability will be important, [but it won't] inhibit the introduction of biosimilars, which can reduce cost and improve access to treatment to patients who are desperately in need of treatment. But I think it will be important that we all be on the same page in terms of notification. The introduction of these new agents in the guidelines will lead to better-informed clinicians and patients. If we can ensure greater adherence to these guidelines, everyone will be better off.

***AJMC®*: What would be the No. 1 takeaway about FN for high-level individuals in a managed care company?**

LYMAN: Clearly, FN remains the most serious, life-threatening, and dose-limiting toxicity associated with cancer chemotherapy. We're all excited about the novel targeted cancer therapies that have come along. We'll now have biosimilars of those targeted therapies, and they do tend to have less effect on the bone marrow, in terms of FN. For the foreseeable future, in most instances, these new agents will not be given by themselves, but will be administered along with or in sequence with traditional chemotherapy, where FN remains the major limiting toxicity. So, FN is here for a long time to come. It is a big reason why patients end up in the hospital and the emergency department (ED), and there are considerable costs associated with these complications. While these drugs reduce the risk of hospitalization and ED visits, G-CSFs are also pricey, and that's why guidelines are so important, to find that appropriate point between not using expensive drugs unnecessarily, but using them to reduce complications, hospitalizations, and even mortality in patients who should be receiving these drugs. In addition, the introduction to biosimilars will, in the long run, improve access and our ability to tailor treatments to the right patients, when these agents are needed, improving long-term outcomes and the quality of life of patients receiving cancer treatment.