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Supportive Care in Pediatric Cancer: New Options, but More Research Needed

By Michelle Hogan

While the aggressive, intense treatment regimens administered to children with cancer give these young patients their best shot at cure, it is well known that the treatments also leave patients vulnerable to side effects, such as nausea and vomiting, infections.

These consequences of therapy are not only debilitating, but also life-threatening in and of themselves and not only debilitating, but also life-threatening in and of themselves and threaten in and of themselves and are challenging.

In spite of this barrier, new agents approved over the past 15 years, such as the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists, have proven quite successful in managing nausea and vomiting in children, said Dr. Amy Louise Billett, MD, noted that although there are currently no published clinical trials of aprepitant in children, the treatment is being used off-label in children and more.

“We’ve definitely used it in lots of teenagers. We’re sneaking down in age, like everyone else I talked to is, and the sense is that it clearly helps with delayed symptoms, as we expected, and it has some effect on acute symptoms as well, which is also what you’d expect from the published adult literature.”

Questions remain about how to optimally dose the drug in children, Dr. Billett said. “It’s very challenging to figure out how to apply an astounding good set of clinical trials in the adult world to our pediatric world.”

The few pharmacokinetic studies of antiemetics in children, such as those of ondansetron, have revealed that children metabolize these drugs more quickly than adults do.

“It’s been very traditional to just give it [ondansetron] every eight hours no matter what, and based on the pharmacokinetic analysis, the doses need to be given more frequently, and the dosing itself probably doesn’t need to be as high as originally thought to...” (continued on page 38)
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MRSA, particularly community-acquired, is emerging in the population of pediatric oncology patients, but there are few agents that are effective against the bacteria. “Our worry now is that it will soon become more prevalent in the pediatric oncology population, and with that we look more toward therapeutic agents that can help these patients.”

“I think 10 years from now we’re going to laugh that this is all we had, which is good, and a great sign of progress. But I think looking down the pike that we’re understanding a lot more about the brain biochemistry particularly of nausea and vomiting, and so all of those therapies are going to change in terms of how we can affect them.”

Nonchemical approaches like biofeedback also should not be underestimated or discounted, Dr. Gore added.

“There’s such a psychological component to nausea and vomiting with chemotherapy that there is a lot of work and research now on understanding some of those implications and how we can better anticipate people’s needs for those types of supports, so I think that’s also going to come out as being a big quality-of-life issue.”

The medical community is also better understanding how to recognize nausea and vomiting in young cancer patients, Dr. Gore said.

“We not only have better agents, but I think people have actually paid attention to the fact that nausea and vomiting, particularly even in younger children, is often perceived differently by those kids, and so when we may have thought they weren’t having nausea and vomiting before they really were; they just didn’t know how to describe it very well.”

**Colony-Stimulating Factors: Use Rising, but Not Universal**

The aggressiveness of the chemotherapies given to children and teenagers with cancer makes febrile neutropenia common.


These risk factors included non-white race; age younger than one or older than 12; fungal infection; bacteremia, sepsis, or other bacterial infection; pneumonia; hypotension; and a diagnosis of acute myeloid leukemia or multiple cancers. The mortality rate was 3%.

The study’s senior author, Gary H. Lyman, MD, MPH, Professor of Medicine and Oncology at the University of Rochester School of Medicine and Dentistry, said, “It was more of a descriptive study demonstrating that this is a real problem in children, that a lot of children are still hospitalized for febrile neutropenia at universities in the United States, and that children are still dying of febrile neutropenia, and hopefully starting to better define what risk factors that the pediatric hematologist-oncologist can use to assess the individual child’s risk.”

More and more, colony-stimulating factors are being used in pediatric oncology patients to boost neutrophil counts, Dr. Lyman said. “Increasingly, certainly data around the country would suggest that growth factors are playing an important role—not universally, but in children receiving the more intensive treatments and where they are at risk for serious toxicities.” Most of the pivotal work in colony-stimulating factors was done in adults, he added, and the studies in children have been small and their results varied.

As a result, Brenda Wittman, MD, formerly a fellow at the University of Rochester and now Assistant Professor at the University of Arizona College of Medicine; John Horan, MD, MPH, of Emory University; and Dr. Lyman conducted a meta-analysis of 16 randomized, controlled trials of prophylactic colony-stimulating factors in pediatric cancer patients, which was published this year in Cancer Treatment Reviews (2006;32:289-303).

“When one pulls all this data together, the growth factors do seem to reduce the risk of febrile neutropenia approximately in half. They shorten the hospitalization that’s associated with febrile neutropenia by a couple of days, and the hope is that they enable children to complete their treatment pretty much on schedule and on time, and with the optimal long-term results.”

The study also showed that colony-stimulating factors reduced the duration of neutropenia by an average of 3.40 days and the duration of reported antibiotic use by two days, but did not significantly decrease documented infections.

In terms of using filgrastim or pegfilgrastim in pediatric patients, Dr. Lyman said pegfilgrastim looks to be as effective and safe as filgrastim, with the convenience of once-per-cycle dosing.

For hospitalized patients, “I know some institutions still use filgrastim because there’s perceived not to be a whole lot of advantage to using the long-acting form, but for ambulatory treatment—or when kids go home, if they still need a growth factor, using the long-acting form is attractive to the children and parents and caregivers.”

**Platelet Growth Factors Being Investigated**

A number of candidate platelet growth factors are currently being studied, but it probably will be at least a few more years before any of them are approved by the Food and Drug Administration, said Gary H. Lyman, MD, MPH, Professor of Medicine and Oncology at the University of Rochester School of Medicine and Dentistry.

“We really need new agents for platelet counts because obviously as we support more and more children getting effective cancer treatment, supporting their white count as needed and their red count as needed, and they continue to get full-dose schedules, we’re seeing thrombocytopenia increasingly as a problem.”

And of course they can get platelet transfusions when severe bleeding ensues, but even that is not without its potential complications, and refractoriness may develop,” he continued. “So having an agent—oral or injectable—that could be used to reduce the risk of that would be of tremendous help to both adult and pediatric oncologists.”

Currently, the Food and Drug Administration recommended that secondary prophylaxis or therapeutic use of colony-stimulating factors be limited to high-risk pediatric patients and that the use of these factors in children with acute lymphoblastic leukemia “be considered with caution” because of the associated potential risk for secondary myeloid leukemia or myelodysplastic syndrome.

While concerns over the safety of using growth factors in the pediatric population limited their use in the past, data have shown that they are safe, Dr. Lyman said.

“The use now long-term follow-up data in both younger adults and children that they are not experiencing higher than expected rates of leukemia and other blood disorders that one might tie back to something like hematopoietic growth factors, so the safety issues seem, in most oncologists’ eyes, to pretty much have been set aside.”

Still, he agreed that the medical community needs to be on the lookout for any delayed or long-term consequences of the growth factors, and of course it’s often hard to separate the effects of the chemotherapy, which we know can unfortunately in some instances cause another cancer in adulthood, but as we gather more and more data that seems to be sorting out.”

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Nita Seibel, MD, Director of Outreach Services in the Department of Hematology/Oncology at Children’s National Medical Center.

Some physicians may prescribe a combination regimen, such as an aminoglycoside with a cephalosporin, she added.

“There’s not one antibiotic or combination that is superior to all others. It depends on how often you see resistant organisms at your institution and just what your general preference is. Generally I think physicians feel they [antibiotics] work pretty well, but we’re starting to see some resistant organisms grow out or emerge.”

For example, said Thomas Walsh, MD, Head of the Immunocompromised Host Section of the Pediatric Oncology Branch in the Center for Cancer Research at the National Cancer Institute, methicillin-resistant Staphylococcus aureus (MRSA), particularly community-acquired MRSA, is emerging in the population of pediatric oncology patients, but there are few agents that are effective against it.

“Our worry now is that it will soon become more prevalent in the pediatric oncology population,” he said, “and with that we look more toward therapeutic agents that can help these patients, and certainly daptomycin has a novel mechanism of action in that it appears to be non-cross-resistant with vancomycin.”

Daptomycin is approved for treatment of MRSA, but currently there are no safety, tolerance, and pharmacokinetics studies of the antibiotic in the pediatric oncology population, Dr. Walsh said.

As is the case with antimet-

ics, a dearth of pharmacokinetic and clinical data for antibiotics in children is an issue. And even when studies in pediatrics are done, they often lag behind the adult studies, he said.

“So a compound may be approved for usage in adults, and we still have little or no information on how to use it in children. There is a need to do these studies in close tandem as we study compounds in adults, to often conduct them in synchrony.”

Determining proper dosing of antibiotics in pediatrics affects not only the treatment of individual patients, but also the potential emergence of resistant organisms, Dr. Walsh said.

“If you under-dose you will expose the bacteria to what we call sub-inhibitory concentrations—that is, concentrations that are below the intended dose. Bacteria can become resistant and start growing when they’re exposed to nonlethal or nontoxic dosages.”

Inpatient vs Outpatient Treatment of Febrile Neutropenia

Recent studies have examined the possibility of treating adults with cancer, fever, and neutropenia who have a low risk of developing an invasive bacterial infection as outpatients.

That tactic, however, is far from the standard of care in pediatrics, Dr. Seibel said. “That’s something that is not universally accepted in the pediatric realm. It is done in adults, but there hasn’t been a large study to look at this issue to the point that people feel comfortable taking that approach.

Pediatric oncologists will take the approach of trying to classify a patient as a low-risk patient versus a high-risk patient, and so maybe they don’t need to be in the hospital until their ANC [absolute neutrophil count] recovers; they only need to be there for 48 hours or so until you’re sure blood cultures are negative.

Erythropoietin Not Routinely Used in Pediatric Cancer Patients

While anemia is very common in pediatric cancer patients, occurring in almost every patient at some time during chemotherapy, erythropoietin is not routinely used, said Bassem I. Razzouk, MD, Associate Member in the Division of Leukemia/Lymphoma at St. Jude Children’s Research Hospital.

Until last year, there were no pediatric indications for epoetin alfa. The safety and efficacy of darbepoetin alfa has not been established in pediatric cancer patients, according to the prescribing information.

To assess the effects of weekly epoetin alfa on health-related quality of life, hemoglobin, transfusions, and tolerability in children with cancer, Dr. Razzouk and colleagues conducted the first large-scale, randomized, placebo-controlled study of epoetin alfa in this patient population, the researchers wrote.

The study, which was sponsored by Ortho Biotech, the drug’s manufacturer, found that the 111 patients treated with epoetin alfa had greater increases in hemoglobin overall and were more likely to be transfusion-free after four weeks compared with those in the placebo group, but there was no significant difference in health-related quality of life between the two groups.

There was a significant positive association between changes in hemoglobin and changes in health-related quality of life in the epoetin group, but not in the placebo group.

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LEARNING OBJECTIVES:

1. Outline the current approaches to managing stay and mortality among children with cancer and febrile neutropenia, one of which was a. hypotension. c. depression. b. asthma. d. anemia.

2. According to Gore, which drug, currently being studied in teenagers, is increasingly being used off-label in children? a. aprepitant. d. pegfilgrastim. b. a salicylate. c. an antibiotic.

3. If given to children in increasing doses, dexamethasone increases the risk of a. fungal infection. b. febrile neutropenia. c. chemotherapy resistance. d. MRSA infection.

4. According to Gore, which drug, currently being studied in teenagers, is increasingly being used off-label in children? a. aprepitant. d. pegfilgrastim. b. a salicylate. c. an antibiotic.

5. Based on the pharmacokinetic analysis, ondansetron for children a. is unsafe at any dosing regimen due to adverse effects. b. should be given more often than every eight hours. c. has no effect on acute chemotherapy-related symptoms. d. should be given in doses higher than originally thought.

6. According to Gore, nonchemical approaches like biofeedback a. are not practical for use with children. b. cannot help with nausea and vomiting. c. helps children to repress troublesome symptoms. d. should not be underestimated or discounted.

7. A recent study identified specific risk factors for longer length of stay and mortality among children with cancer and febrile neutropenia, one of which was a. hypotension. c. depression. b. asthma. d. anemia.

8. Wittman and colleagues’ meta-analysis of trials of prophylactic colony-stimulating factors in pediatric cancer patients indicated that this therapy reduces the risk of which complication approximately in half? a. fungal infection. b. febrile neutropenia. c. chemotherapy resistance. d. MRSA infection.


10. Walsh cited which antibiotic as having a novel mechanism of action in that it appears to be non-cross-resistant with vancomycin? a. imipenem. c. meropenem. b. daptomycin. d. ceftazidime.

11. Which drug is an example of the type that would be initiated when fever and neutropenia persist despite the use of broad-spectrum antibiotics? a. dexamethasone. c. filgrastim. b. ceftazidime. d. fluconazole.

12. Which drug appears to be active as salvage therapy in patients with Zygomycetes? a. posaconazole. c. voriconazole. b. caspofungin. d. amphotericin B.

13. An example of a cell-wall active antifungal agent is a. itraconazole. c. anidulafungin. b. voriconazole. d. posaconazole.
active agents, which include micafungin, caspofungin, and anidulafungin, Dr. Walsh said.

Studies have revealed the safety, tolerance, and pharmacokinetics (PK) of numerous antifungal treatments in pediatric oncology patients, including the echinocandins and voriconazole.

“That has been tremendous that we have so much pediatric PK data, but it’s really important, particularly with voriconazole—there’s a big difference between how adults and pediatric patients metabolize that drug,” Dr. Seibel said.

“The pediatric pharmacokinetic data has really been crucial to know the proper dosing for pediatric patients because they need a much higher dose than adults do.”

Emerging Fungal Pathogens

Still, even with all these treatment choices and pediatric pharmacokinetic data, some fungal infections are particularly difficult to cure. “It really depends on the situation. The mortality with invasive fungal infection varies anywhere between 60% and 70%, or even higher,” Dr. Seibel said.

For example, the hard-to-treat Zygomycetes class is emerging.

“The main concern is it’s not nearly as common as Candida and Aspergillus, but what we’re seeing—and this has been noticed particularly over the past few years—is that with better antifungal agents, particularly to treat Aspergillus, where patients were dying before, they’re living longer, and now we’re starting to see the Zygomycetes really emerging.”

Dr. Walsh noted that posaconazole, which was approved in September for Aspergillus and Candida in adults, appears to be active as salvage therapy in patients with Zygomycetes.

A study to determine the pharmacokinetics of posaconazole in pediatric patients is being planned, Dr. Seibel said, as is a randomized, controlled trial of posaconazole versus amphotericin B and/or its lipid formulations for the primary treatment of Zygomycetes, Dr. Walsh said.

Combination vs Monotherapy for Fungal Infection

Another area for investigation in treating fungal infections involves determining when to use monotherapy and when to use combination therapy. Dr. Seibel said.

“One of the big questions that has arisen because we have more choices in antifungal agents is the whole issue of whether combination therapy for invasive aspergillosis has a benefit. So far there have not been any prospective studies looking at the benefit of using one agent versus multiple agents.”

In an effort to fill that gap, a protocol has been developed for a Phase III randomized, controlled study of voriconazole plus micafungin versus voriconazole alone for the treatment of invasive aspergillosis in patients as young as two, Dr. Walsh said.

As is the case with antiemetics and colony-stimulating factors, while there is still a considerable need for more research into antibiotics and antifungals in pediatric cancer patients, supportive care in these areas has been transformed.

“There have been so many advances in pediatric oncology that have saved lives, and one of the most critical elements of the advances in pediatric oncology has been the advances in infectious disease supportive care that have enabled us to give curative-intent chemotherapy and bone marrow transplant—not only to save lives but to prevent infections as well,” Dr. Walsh said.