Pediatric Oncology: “An Area of Great Change”

Stanford T. Shulman, MD, moderator: Pediatric oncology has been an area of great change over the years. Sharon B. Murphy, MD, has been right there, shepherding many of the changes.

Sharon B. Murphy, MD, Scholar-in-Residence at the Institute of Medicine: It’s very difficult to overstate the advances in the past 40 years, the most prominent of which, of course, is the development of curative treatment.

When I started as a fellow 40 years ago, most children who were diagnosed with cancer died. The survival and cure rate for pediatric cancer in the 1950s to early 1960s was about 10%. Currently, the cure rate for all stages and disease categories is about 80%. So this is a dramatic decrease in mortality, and it’s one of the outstanding achievements of biomedical advances, research, and treatment.

Along with this, there has been a development through a burgeoning of translational research: refinement of treatment, not just for cure, but for the development of risk factors. Stratification based on stage of disease as well as biological characteristics — mainly genetic characteristics, such as ploidy level, chromosomal translocations, and surface markers — have enabled oncologists to define patients who are at high risk and lesser risk for relapse. Not all kids with cancer are alike. We’ve been able to intensify treatment for cancers at high risk for relapse, and we’ve been able to reduce the intensity of treatment for cases that have a good prognosis.

I remember starting as a fellow seeing cases of pelvic rhabdomyosarcoma. You would see kids have life-changing, mutilating surgery from pelvic exenteration, ileal conduits for urinary diversion, and colostomies, and then receive high doses of radiation and prolonged chemotherapy. They would be cured, but the consequences were devastating. Now, that’s just not done.

With approaches like neoadjuvant treatment to shrink the tumors, more conformal doses of radiation in limited fields and lower doses, and chemotherapy to reduce tumor volumes, we can reduce treatment for patients with better prognosis in a nonmetastatic setting.

The reduction in radiation therapy is particularly significant. We used to use high doses and high volumes. Now, the use of radiation therapy for children with pediatric cancer has greatly diminished because of the recognition of adverse consequences. Even the techniques of radiation have changed a great deal to more conformal doses and modulated fields.

As far as the high-risk cancers where patients present with worse prognosis, high-risk leukemias, high counts, and advanced stages of neuroblastoma, we’ve been able to achieve tremendous increases in cure rates from practically nothing to substantial rates by intensifying doses of chemotherapy and combination regimens. This has been made possible by huge advances in supportive treatments. When I started practicing, we didn’t have venous access devices, Hickman lines, or Port-a-caths. We didn’t have platelet transfusions, hyperalimentation, or prophylaxis for Pneumocystis carinii. There was nothing that would enable us to dose-intensify the way we can now and adequately support patients through periods of prolonged marrow hypoplasia. This makes all of the difference.

I will give credit to colleagues in infectious disease also who have developed the vaccines for measles and chickenpox, so we never see disseminated varicella cases or fatal measles in immunocompromised cancer patients, as we used to routinely.

We also now have prophylaxis for Pneumocystis. When I started my career, we had 80 cases of P. carinii pneumonitis per year in our immunocompromised patients. There were so many on ventilators, we had to put the patients in the hallways. That’s a thing of the past. So the whole area of supportive care, antibiotics, antifungals, colony-stimulating factors to increase white blood cell counts, has been huge.

In the past 40 years, we’ve developed stem-cell transplants. For children with cancer, we now routinely do allogeneic transplants, autotransplants, matched un-
related transplants, cord blood transplants, peripheral blood stem cell transplants, all after high-dose chemotherapy, sometimes with total body radiation. There’s no question that stem cell transplantation has cured children who had otherwise fatal malignant disease. Also, for fatal, nonmalignant disorders, it’s been curative. So the whole field of transplantation has developed in this time.

Recently, the Centers for Disease Control and Prevention (CDC) issued a report that there are 12 million Americans surviving after treatment for cancer. Of course, most of those are adults who have either breast, colorectal, or prostate cancer, but the field started with pediatric cancer survivors, and we were the leaders in that. So in many ways, the past 40 years has established pediatric oncology as a model discipline: for multidisciplinary team care; for cooperative group clinical trials; and for rapid learning systems for adult oncology. It’s also been a model for AIDS treatment with AIDS clinical trials groups and combination antiretroviral treatments — some of the first antiretrovirals were anti-cancer drugs that were taken off the shelf.

Dr. Shulman: Sharon, can you speak about second malignancies?

Dr. Murphy: Of course, it is a concern because we know that alkylating agents, epipodophyllotoxins, radiation treatment, and anthracyclines in particular all are associated with increased risk of second malignancies. The risk tends to increase with longer duration of follow-up. There have been some studies of childhood cancer cohorts that point to something like a 10% to 12% rate. It varies, according to the underlying disease for which the patient was treated and the treatment regimen itself.

For some underlying malignancies, for example, retinoblastoma, which most patients survive, there is a genetic predisposition to get a second malignancy because of germline RB gene mutations. For Hodgkin’s disease, where historical-

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gently high doses of radiation and alkylating agents have been used, there has been a risk of second malignancies that may be up to 20% over 25 to 30 years.

This is kind of a shift because those estimates came from earlier eras of treatment where doses were higher. I’m not saying the risk has diminished totally, but it has gone down. It doesn’t change the fact that patients who survive childhood cancer and grow to adulthood need surveillance and lifelong medical checkups. I wouldn’t say their life is damaged forever, but some of the risks of long-term survivors aren’t in the area of second malignancies; they are in cardiopulmonary problems, late congestive failure and coronary artery disease from mediastinal radiation, and anthracyclines and valvular disease are also emerging as major problems. But first you have to survive your first cancer to be at risk for late effects.

Ram Yogev, MD: Sharon, are there any major changes in the past 40 years in the types of infections and treatments given to those patients until they get to the cure or the induction time?

Dr. Murphy: Is there a difference in the patterns of infectious complications that the children have? I think so. In 1970s or early 1980s, the infectious complications were bacterial, and gram-negative infections were major causes of concern. That changed, and we experienced many more problems with *Staphylococcus epidermidis* causing central venous line infections. Prolonged periods of neutropenia would be managed with empiric antibiotics, and this led to emergence of fungal disease. So the spectrum of infectious complications changed. Now, most children get empiric antifungal treatment if they have prolonged neutropenia.

Dr. Shulman: They still do get fungal infections.

Dr. Murphy: Yes, but it’s not as bad. I used to think that if you got an established fungal infection or fungemia, it was a fatal situation, but there have been improvements in antifungals, liposome-encapsulated amphotericin, and other approaches that have made it possible even to survive disseminated fungal disease.

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