



The Field of Childhood Cancer Survivorship Gains Momentum

Anna T. Meadows, MD, a Professor of Pediatrics and Director of the Childhood Cancer Survivor Program at the Children's Hospital of Philadelphia, delivered the 2006 ASCO Pediatric Oncology Award Lecture at a Special Session on Saturday afternoon. As a pioneer in the field of the late effects of cancer treatment, Dr. Meadows' groundbreaking research has greatly illuminated the long-term physical and emotional difficulties that childhood patients with cancer face, thereby enabling safer and more effective therapies to be designed. Her lecture, "Cancer Survivors: Childhood and Beyond," focused on several late complications of childhood cancer and the landmark achievements made in pediatric oncology that have greatly enhanced childhood survivorship.

"When my fellowship began in 1972, the promise of curing childhood cancer was just a blip on the radar screen, but it was there," Dr. Meadows said. During the next three decades, marked improvements in the long-term survival of children with cancer were made, resulting in more than 250,000 childhood cancer survivors in the United States. "You must recognize that only 3% of lifetime cancer occurs in children or adolescents, but with 70 potential years ahead, it makes a big difference if you are able to cure that many children," she noted. Advances in survivorship came about through several astute observations in conjunction with innovative experimentation in pediatric oncology.

Dr. Meadows noted that survivorship research began with a trickle of anecdotal reports and case series but soon blossomed to include prospective studies and multivariate analyses. Several key areas of childhood survivorship — growth and development, reproduction, vital organ function, second neoplasms, and psychosocial adjustment — now engage a growing pool of survivorship researchers. Today, the field is so far advanced that research investigating mathematical modeling, surveillance and counseling, and interventions for improving survivorship are routine. Given the wide recognition the field has now attained, Dr. Meadows thanked ASCO "for making survivorship an important focus over the past several years."

In the early 1980s, Dr. Meadows led the survivorship research charge by helping to publish an influential prospective study documenting the late neurocognitive effects of radiation therapy. The results revealed that young children who received cranial radiation for leukemia showed a deterioration of intelligence following treatment; one-third of the children in the study exhibited developmental delay, and only one-half achieved an average level of intelligence. These critical findings revolutionized the practice of cranial radiation for childhood leukemia patients. "One of the things that we have learned in pediatrics is that if we can reduce the dose [of radiation] or eliminate it altogether by substituting something that's equally effective, we do better for our patients," explained Dr. Meadows.

Dr. Meadows has also been involved in several studies assessing the late cardiac effects of treatment. This research has shown that females and young children age 18 months to 5 years are at increased risk of cardiac events with the use of anthracyclines, especially at higher doses. Spinal radiation also correlates with an increased risk of adverse cardiac effects, including lower cardiac output, higher cardiac wall stress, and asymmetrical heart growth. Based on these findings, pediatric oncologists now limit the total dose of anthracyclines administered, infuse anthracyclines for longer periods, regularly evaluate cardiac function during treatment, and avoid concomitant radiotherapy in children.

In the area of infertility, Dr. Meadows participated in a study implicating the procarbazine component of chemotherapy as the culprit in infertility in young men who were treated for Hodgkin's lymphoma as children. Avoiding or reducing the total dose of alkylating agents is now warranted in males to prevent gonadal toxicity. Dr. Meadows also advocates sperm banking to enable any regimen to be administered without the worry of preserving fertility.

Perhaps one of the greatest advances in which Dr. Meadows has been involved concerns a nonradiotherapy approach to the treatment of retinoblastoma. Patients with hereditary retinoblastoma have a 3-fold greater risk of developing secondary cancer when treated with radiation therapy compared with another form of therapy. "Radiation...is the gift that keeps on giving, especially for children whose second tumors connected with radiation occur later in life," said Dr. Meadows. To explore other treatment options, 12 years ago, Dr. Meadows and colleagues at the Children's Hospital of Philadelphia began administering carboplatin, etoposide, and vincristine (CEV) to patients with bilateral retinoblastoma. The results were striking: more

than 90% of eyes were saved in children with mild disease, and nearly 60% of eyes were saved in those with moderate disease. CEV dose intensification proved successful for improving the proportion of eyes saved from enucleation in patients with moderate and more advanced disease. Moreover, the chemotherapy proved to be a good preventive agent against the development of secondary pineal tumors.

Both the Late Effects Study Group (LESG), which Dr. Meadows helped to initiate in the early 1970s, and the National Cancer Institute-supported Childhood Cancer Survivor Study (CCSS), which began in 1993 and in which Dr. Meadows has been active, have carefully assessed the development of secondary neoplasms in childhood cancer survivors. Among the nearly 1,400 patients followed in the LESG cohort, more than 150 second neoplasms were observed between 7 years of follow-up and 17 years of follow-up. The CCSS found that among more than 14,000 participants, the 20-year cumulative incidence of secondary malignant neoplasms for 5-year survivors is 5.2%. As Dr. Meadows' work has consistently shown, radiotherapy emerged as the prime risk factor for the development of second cancers. With regard to late mortality, many patients who died succumbed to disease relapse, but many also died from treatment-related second malignancies, thus emphasizing the importance of survivorship research.

Although much of the innovative work generated by Dr. Meadows and her colleagues has revolutionized how childhood cancer is treated and has enabled the creation of guidelines for counseling and surveillance of long-term survivors, Dr. Meadows is still concerned by several shortcomings in care and research. With more young patients transitioning to adulthood, greater efforts must be made to educate providers about the late effects of treatment, reconcile insurance problems, and gather more information about the late-late effects for patients age 40 and older. In addition, resources must be secured to ensure continuous follow-up of patients, and survivor interventions such as education, reproductive counseling, and psychosocial support must be developed to encourage patient participation in follow-up studies.

In concluding her talk, Dr. Meadows noted that "there are many lessons the oncology world has learned from pediatrics...and our adult colleagues are now paying attention to us." Dr. Meadows stated that researchers in childhood cancer survivorship — herself included — will continue to strive to improve cure rates and reduce late complications of treatment. Perfecting the ability to predict late effects, ensuring a seamless transition to adult-based follow-up care, and devising better interventions for both primary and secondary malignancies remain sought-after goals, which are closer to becoming clinical realities.