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Late Effects of Treatment for Wilms Tumor

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Advances in multimodality treatment have significantly improved the survival rates of patients with Wilms tumor. The current 8-year survival rate for most patients who have favorable-histology tumors is 80–98% [1,2-6]. Large multi-institutional cooperative groups in their trials have designated treatment according to well-defined risk categories in order to improve cure rates and decrease the frequency and severity of acute and late toxicities. Depending on tumor histology and disease stage, treatment usually includes nephrectomy and various combinations of chemotherapeutic agents (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide) with or without radiotherapy. However, treatment success comes at a price as cancer treatment is not cell specific. Some adverse effects, such as those related to radiation therapy, may become apparent only after a latent period; on the other hand, adverse effects related to chemotherapeutic agents are often immediate and transient, but occasionally, as for anthracyclines, may be permanent.

Studies on survivors of childhood cancer have shown that at least 60% of young adults develop chronic health problems [7,8]. Generally, late complications are a consequence of treatment type and intensity. Currently, the use of nephrectomy followed by two-drug chemotherapy with vincristine and actinomycin D for low-stage disease has helped minimize late effects [9]. In contrast, patients with higher-stage or relapsed disease often require anthracyclines in addition to radiotherapy, thereby increasing the risk of late sequelae.

This commentary highlights some clinically significant late sequelae in survivors of Wilms tumor – musculoskeletal effects, cardiac toxicity, reproductive problems, renal dysfunction, and the development of second malignant neoplasms (SMNs).

Musculoskeletal Effects

Radiation treatment in young children may be particularly damaging to growth and development of normal tissues. The degree of damage depends on the total dose, fractionation, and field of radiation. Treating only part of the vertebral column, as used in flank irradiation before 1960, resulted in differential growth of the spine and subsequent development of spinal deformities [10], but using an altered technique in which the entire vertebral body is irradiated prevented some of the severe deformities. However, studies continued to report occurrence rates of kyphosis and scoliosis between 10% and 70% [11-13], the wide range reflecting the difference between clinical and radiological evaluation. Most patients, however, remain asymptomatic, requiring neither bracing nor surgery.

Cardiac Toxicity

Anthracyclines, primarily doxorubicin, have been used to treat stage III and IV disease despite knowledge of their preferential cardiomyocyte toxicity [14]. Reports of cardiac failure in previously well long-term survivors have raised concerns [2,14]. The most important risk factor appears to be the total cumulative dose, although all dose levels cause some degree of cardiomyocyte damage [15]. In the National Wilms Tumor Studies (NWTs)-1, -2, -3, and -4, the frequency of congestive heart failure 20 years after diagnosis was 4.4% for patients treated with doxorubicin at initial diagnosis and 17.4% for those treated with doxorubicin at relapse [16]. The relative risk (RR) of congestive heart failure was increased in females (RR = 4.5) and by cumulative doxorubicin dose (RR = 3.2/100 mg/m²), lung irradiation (RR = 1.6/10 Gy), and left abdominal irradiation (RR = 1.8/10 Gy) [16,1]. In addition, subclinical cardiac abnormalities such as increased end systolic wall stress (a measure of afterload) or decreased contractility were found in 24 of 97 (25%) survivors of Wilms tumor whose treatment included doxorubicin (mean cumulative dose, 303 mg/m²) at a mean follow-up of approximately 7 years [17]. Total dose and intensity of dose were risk factors for increased left ventricular afterload. In contrast, cardiac function was reduced in only 4 of 157 (2.5%) patients treated in Societe Internationale D'oncologie Pediatrique (SIOP)9 and SIOP 93-01 trials after a shorter median follow-up of 2.9 years [15]. Other studies have suggested that the damage progresses gradually, particularly in patients given a total doxorubicin dose of more than 250 mg/m², leading to a persistent risk of clinical cardiac dysfunction and a possible cardiac transplant in the future [18-20]. An additive effect may occur with radiation involving the heart, as in patients with lung metastases. Long-term monitoring of survivors and efforts to reduce the total anthracycline dose on the basis of risk of disease recurrence are warranted.

Reproductive Health Problems

Long-term reproductive health effects, including fertility and successful pregnancy outcomes, are significant issues for survivors, especially because reproductive organs are sensitive to radiation. The majority of survivors of Wilms tumor are not at risk, but females who have undergone abdominal radiation wherein both ovaries or the uterus are within the radiation field are at significant risk of poor fertility outcomes [21-26]. High incidences of infertility, spontaneous miscarriages, and restricted fetal growth have been in part attributed to the radiation-induced damage of the uterine vasculature and ovaries [21-26]. Ultrasound imaging of female survivors of Wilms tumor has also shown small or absent ovaries within the radiation field; in some patients, the uterine volume remains low despite hormone replacement [27-29]. In a study, only 1 of 25 female survivors treated from 1940 to 1972 with whole abdominal radiation had normal ovarian function, with 20 experiencing primary ovarian failure and 4 developing premature menopause before 36 years of age [25]. Another study found that female patients of Wilms tumor who received abdominal radiation had a higher rate of spontaneous abortion (22%) than those who did not (6%) [21]. Also, at birth, infants of irradiated females weighed significantly less than those of nonirradiated females. Data from the Childhood Cancer Survivor Study have confirmed previously reported findings of increased rates of premature birth and low birth weight primarily among women who received pelvic irradiation [23,24,30-33]. In women with kidney cancers, primarily Wilms tumor, the risks of preterm birth, low birth weight, and small-for-gestational age among children of survivors were 41.5%, 25.6%, and 9.3%, respectively [30]. Preexisting genitourinary abnormalities such as Mullerian duct anomalies and septated or unicornate uterus occasionally contribute to adverse pregnancy outcomes in women treated for Wilms tumor [22,31,33-35].

Renal Dysfunction

Renal function remains an important consideration given that Wilms tumor arises from the kidney. Development of end stage renal disease (ESRD) is of particular concern in patients having progression of bilateral Wilms tumor or receiving irradiation in the opposite kidney in unilateral disease [36]. A recent study has shown that of 5910 patients enrolled in the NWTs, the cumulative incidence of ESRD 20 years after diagnosis of Wilms tumor in patients not having a mutation in the tumor suppressor gene *WT1* or genitourinary anomalies was 0.6% after unilateral disease and 12% after bilateral disease [36]. The cumulative incidence at 20 years after diagnosis of Wilms tumor was much higher for patients with the Denys-Drash syndrome (74%), Wilms tumor-aniridia syndrome (36%), and genitourinary anomalies (cryptorchidism or hypospadias) (7%) [36]. Fortunately, the risk of ESRD is remarkably low for most patients with unilateral Wilms tumor; however, a significant number of survivors have subclinical glomerular and tubular damage [37]. Chronic renal insufficiency has been reported in 19%–73% of survivors of Wilms tumor; nephrectomy, abdominal radiotherapy, and less compensatory renal hypertrophy are implicated factors [38]. Performing nephron-sparing surgery for bilateral disease, avoiding nephrotoxic chemotherapy, and optimizing radiation therapy are strategies used to decrease the risk of renal impairment [39].

Second Malignant Neoplasms

Secondary tumors – both benign and malignant – are well recognized late sequelae of therapy in survivors of childhood cancer. The NWTs Group reported 43 SMNs in 5278 patients diagnosed with Wilms tumor between 1969 and 1991, with a cumulative incidence of 1.6% at 15 years after diagnosis [40]. A European study reported 8 SMNs in 1988 patients with Wilms tumor treated on the SIOP trials 1, 2, 5 and 6, with a cumulative incidence of 0.65% at 15 years after diagnosis [41]. Various types of second cancers have been described, such as bone and soft-tissue sarcomas, breast cancer, lymphoma, gastrointestinal tumors, melanoma, and acute leukemias [40-44].

Radiation therapy remains an important contributory factor to the increased risk of secondary cancers observed in long-term survivors of all childhood malignancies [42,45-46]. In a cohort of survivors of Wilms tumor, 22 of 30 (73%) secondary solid tumors occurred within the radiation field [40]. Furthermore, several reports have suggested an interaction between radiotherapy and doxorubicin, a known radiation sensitizer [40-44]. Earlier reports by the NWTs Group showed that SMNs increase with the increase in radiation dose, and the use of doxorubicin potentiates the effect of radiation therapy [40]. In striking contrast to the expected 2.22 SMNs, 8 SMNs were seen in 234 patients who received both doxorubicin and more than 35 Gy of abdominal radiation [40].

Summary

The cure rates for children with Wilms tumor are improving. Careful medical and epidemiological monitoring of survivors along with efforts to minimize therapy-related long-term sequelae are required. Development of trials on an international level, focused on limiting cumulative chemotherapy doses, using low-intensity dose schedules, potentially using cardioprotective agents, and minimizing radiation exposure can help further reduce the late complications of treatment.

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