Editorial Commentary

Late health outcome among survivors of Wilms tumor

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It is a pleasure to write the editorial commentary on a landmark paper by Weil and colleagues recently published in the *Journal of Clinical Oncology* (1). The improvement in Wilms tumor (WT) survival, with 85–90% 5-year survivals, can be attributed to risk adjusted standardization of therapy based on protocols developed by the Children's Oncology Group (COG) in the United States (USA) and SIOP (Societie International Oncology Pediatrique) in Europe over the last half century. The focus has now rightly shifted to understanding long-term health consequences in WT survivors of current treatment protocols.

The paper was very well designed to study the long-term health related disease burden and suggest potential changes to treatment paradigms by understanding the consequences of risk adjusted multimodal therapy. It evaluated the incidence of long-term morbidity after treatment for unilateral nonsyndromic WT in a cohort of 2,008 survivors by studying the 35-year cumulative incidence of death and development of any grade 3–5 chronic health condition (CHC) to a matched cohort (2:1) of siblings of cancer survivors. WT patients in the cohort were treated between 1970 and 1999. The use of the Childhood Cancer Survivor Study (CCSS) and linking it to the National Death Index helped establish late mortality (beyond 5 years of therapy) and cause of death in the study. The authors proceed to further classify late deaths as due to WT relapse, other health related causes (including late effects of therapy), or external causes. Subsequent Malignant Neoplasm (SMN) incidence was ascertained by self-reporting and medical record review. CHCs were graded according to Common Technology Criteria for Adverse Events (CTCAE) as mild (Grade 1); moderate (Grade 2); disabling (Grade 3); life threatening (Grade 4); and fatal (Grade 5). In selecting grade 3–5 CHCs for further study the authors have rightly focused on the most commonly known causes of morbidity after WT surgery including intestinal obstruction needing operative intervention, kidney failure requiring dialysis or transplant, heart failure, and Premature Ovarian Insufficiency (POI) before age 40 years in females. Standardized Short Form-36 answers dichotomized to impaired/non impaired was used to subjectively measure health related quality of life (HRQOL).

Covariates included demographic data and treatment exposure. Chemotherapy (CT) exposure was evaluated based on established WT regimens while radiotherapy (RT) exposure was subdivided to (I) ipsilateral flank RT; (II) whole abdominal RT (WART); and (III) whole lung RT (WLRT). Further exposure was evaluated by RT site and RT dose. Survivors were stratified for two field categories [WLRT and abdominal radiotherapy (ART)] and dose was categorized as ≥20 or ≤20 Gy. The authors have included all variables that affect risk for CHCs after WT treatment and develop treatment attributable risk based on exposure.

Median age of survivor cohort at diagnosis and follow-up were 3.2 years (range, 0–20.2 years) and 27.8 years (range, 6.4–57.5 years). The true merit of this study lies in the length of follow-up that has been obtained. All survivors in cohort had undergone nephrectomy and nearly all (98.1%) received CT with vincristine (93.8%) and actinomycin D (93.5%) while doxorubicin was used in

44.8%. Use of other agents (etoposide, cyclophosphamide, and platinum agents) was more common after the 1990's as compared to those treated in the 70's and 80's. As would be expected, with greater disease burden, treatment group with >4 medications had the greatest proportion of survivors experiencing early relapse (23.2%). Doxorubicin use was also more common over time but cumulative dose exposure (≥250 mg/m^2) decreased over time. Fifty-five percent of survivors received RT with most common fields being flank (27.8%); WART (13.8%) and WLRT (13.4%). There were 142 late deaths (7.8%). Most importantly health related mortality (4.7%) was nearly three times relapse-related mortality (1.6%). This I believe is going to be important in making treatment decisions in the future.

Most frequent causes of death were SMN (n=42), WT relapse (n=30), and cardiac. (n=9). Breast cancer was the most commonly reported SMN [standardized incidence ratio (SIR) of 4.1] and was highest in the group that received VAD (vincristine + actinomycin D + doxorubicin) + ART. The VAD + ART group also had the highest SIR of intestinal/colorectal malignancy and soft tissue sarcomas. Thyroid neoplasm was more common in the group receiving WLRT and greater than four drugs with any RT.

Survivors treated with VA (vincristine + actinomycin D) had all cause and health-related mortality comparable to the general population. However, when all survivors were studied, both all-cause mortality [standardized mortality rate (SMR) 2.9] and health-related mortality (SMR 5.4) were elevated compared to the general population and this elevated mortality was seen in all groups VAD + RT; VAD + ART + WLRT; >4 drugs + any RT. Health-cause mortality included death due to cardiac, pulmonary, SMN, and other causes were all higher in WT survivors. This finding is one of the highlights of this paper and strongly supports the argument to deescalate treatment in stage 3 and 4 disease from current risk based therapy strategies.

The 35-year cumulative incidence of any grade 3–5 CHC was 34.1% [95% confidence interval (CI): 30.7–37.5%] among WT survivors and 14.8% (95% CI: 13.4–16.2%) among siblings. Intestinal obstruction had a 35-year cumulative incidence of 8.1% (95% CI: 6.6–9.6%) with a relative risk (RR) of 16.2 and like kidney failure (2.4% cumulative incidence and RR of 10.4) was seen in all treatment groups albeit lower in the VA group. Heart failure was seen in 4% (RR of 10.4) and was more common in the group exposed to doxorubicin (VAD + ART and VAD + ART + WLRT) and >4 drugs with any RT. POI with a cumulative incidence of 7.3% and RR of 11.8 was also seen in the same exposure group as heart failure. Both WART and WLRT were associated with increased risk of SMN, heart failure and bowel obstruction while WART specifically increased RR of POI. Flank RT <20 Gy was not associated with SMN any other CHC.

I completely agree with the authors that risk-based screening should be life long for long-term survivors of WT. VA survivors have a very low burden of late effects. Kidney failure incidence was significantly higher than sibling survivors and even when the early recurrence group (who had a higher risk of kidney failure) was excluded, the higher risk persisted in the WT cohort. Importance of screening and management of comorbidities such as diabetes and hypertension will be important, as survivor cohort grows older. More importantly as our recent research showed, Nephron Sparing Surgery (NSS) in carefully chosen patients does not impair WT survival (2,3), and should be considered in all patients in future prospective trials. Recent developments in 3D imaging technology aided by the metaverse may improve NSS patient selection and outcomes (4). Decreasing adhesions due to surgery will likely impact the incidence of bowel obstruction. Minimally Invasive Surgery or retroperitoneal approaches should be considered wherever tumor morphology and patient anatomy permits (5). The study also pointed out the additive risk of flank and ART to the development of bowel obstruction. Limiting flank radiation to <20 Gy will also be important towards this goal.

Another important aspect of this paper was the finding of a five-fold higher incidence of heart failure in those exposed to high doses of doxorubicin (≥250 mg/m^2) as compared to no exposure. Limiting doxorubicin to lower doses and developing alternatives will be important in future studies. Interestingly, there was a lower self-reporting of gonadal dysfunction in males as compared to POI in females. The authors rightly point out to the greater resistance of Leydig cells to the effects of RT as compared to the more actively dividing spermatogonia. Infertility may be undiagnosed or under-reported. External causes such as accident and injury were not elevated in WT survivors.

Many WT survivors suffer from poor general health, poor physical functioning, and have increased impairments in mental domain and it is important for society and governmental organizations to ensure that there is a greater investment in appropriate support structures as current treatment regimens will likely see even greater survival than that reported in the current study.

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