More About Second Cancers After Retinoblastoma

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In 1973, Strong and Knudson (1) predicted that second cancers would occur at an increased rate in survivors of retinoblastoma, that only those with the genetic form of the tumor would be at risk, and that radiation therapy (RT) would increase the risk. Beginning with a report from the Late Effects Study Group in which retinoblastoma emerged as the most common primary cancer—it occurred in 52 of 292 children with more than one malignant disease (2)—many other cohort studies have confirmed this increased risk (3–8). The genetic form of the disease includes all children with bilateral disease (although the majority have a negative family history and are due to new germline mutations), patients with unilateral disease and a positive family history, and patients in whom genetic analysis has confirmed a mutation in RB1. Because genetic analysis of RB1 was performed in some members of the cohort described by Marees et al. (10) in this issue of the Journal, it would be interesting to know how many unilateral cases were added to the genetic list based on mutation analysis.

Marees et al. provide follow-up of the Dutch cohort in their earlier report with additional data (9,10). With almost 700 case subjects followed up for a median of 22 years, they report an elevated risk of second cancers in 298 hereditary cases: 38% at 50 years from diagnosis. This is similar to the 36% risk at 50 years reported by Kleinerman et al. (3) whose report was based on almost 1600 cases (of which 936 were hereditary). Both this study and that by Kleinerman et al. found a threefold increased risk for irradiated patients compared with nonirradiated patients with...
retinoblastoma and also found that the increased risk occurred only in those with the genetic form of the disease.

Because 85%–90% of children with the genetic form have tumors in both eyes, RT has been essential in preserving life and vision, the latter to assure normal development. In the study by Marees et al., 89% of the genetic cases were treated with RT, similar to the 88% in the Kleinerman cohort. Kleierneman et al. categorized RT doses to the tissues in which a second malignant neoplasm (SMN) arose as heavily irradiated (>1 Gy), moderately irradiated (0.4–1 Gy), or lightly irradiated (<0.4 Gy). In practice, the usual dose to the tumor and to the tissues surrounding the orbits (>40 Gy) was considerably more than the highest category, and Kleierneman’s highest dose category accounted for 67% of the SMNs. Marees et al. have used a more practical approach by considering only those SMNs that arose in the field of RT to be radiation related, and 63% were in this group. Marees et al. have found that risk of second tumor differs markedly at 40 years of follow-up—13.3% of irradiated patients developed SMNs without RT compared with 33.2% with RT. Kleierneman et al. also included pineal tumors as second cancers, but Marees et al. have recognized that pineal tumors are a manifestation of the same mutated gene in this light-sensitive organ (these neoplasms are designated as tri-lateral retinoblastomas) and do not include them.

It is only recently that chemotherapy in combination with intraretinal treatment has been found useful in eradicating tumor and avoiding RT. Since 1994, many children with bilateral disease in whom preservation of vision in at least one eye was attempted have received chemotherapy for “chemoreduction” with as few as one or as many as four drugs (11–14). Chemoreduction has been successful in avoiding RT by permitting focal treatment with laser or cryotherapy to eradicate tumor. The history of therapy for pediatric cancer is replete with examples documenting no loss of efficacy when RT was eliminated or reduced when effective chemotherapy was available (15–17). In children with retinoblastoma, even when chemotherapy is not completely successful and RT is needed for tumor control, the recommended doses of RT can be markedly reduced without compromising success. Furthermore, pineal tumors have occurred less frequently with the advent of chemoreduction, suggesting a prophylactic effect of these agents on microscopic disease (18).

Not surprisingly, there were no SMNs in 32 hereditary cases in the older cohort treated with surgery with or without RT. What occurred less frequently with the advent of chemoreduction, suggesting a prophylactic effect of these agents on microscopic disease (18).

This report by Marees et al. is important because, unlike some earlier ones, the study is based on a population selected without bias. Their proportions of hereditary (40%) and nonhereditary (60%) retinoblastomas conform to expectations in developed countries. Although the numbers are small, the authors were able to calculate the absolute excess risk (AER) per 1000 person-years for each of the important second cancers based on follow-up intervals into the fourth and fifth decades of life (Figure 1). This is important to individual survivors who carry the mutation. Sarcomas (AER = 7.29) begin in adolescence, melanomas (AER = 4.69) start in young adults, and epithelial tumors (AER = 13.3) occur in late adulthood and comprise the majority of the AER in 40-year survivors. These data now provide clinicians with information for targeted surveillance.

Studies of children with retinoblastoma provide a window into the interaction in carcinogenesis of a mutated tumor suppressor gene and environmental mutagens. There are still some unanswered questions: what can we expect to be the lifelong risk for new cancers in the older cohort treated with surgery with or without RT? What will be the second cancer incidence in the more recently treated cohort, many of whom received drugs—vincristine, carboplatin, and etoposide—commonly used in this disease? Are there specific RB1 mutations that confer susceptibility to SMN with or without RT? It is quite clear that the rarity of this neoplasm will necessitate a cooperative effort among institutions that treat such children with retinoblastoma and that resources need to be made available for the prolonged follow-up required to conduct the molecular epidemiological studies necessary to increase our knowledge.

References


