Comment on van Eggermond et al, page 319

Triple jeopardy for Hodgkin lymphoma survivors?

Lindsay M. Morton  NATIONAL INSTITUTES OF HEALTH  NATIONAL CANCER INSTITUTE

In this issue of Blood, van Eggermond et al demonstrate that Hodgkin lymphoma survivors who develop a second malignancy have increased risk of developing yet a third malignancy.1

With major advances in treatment over the last several decades, Hodgkin lymphoma (HL) has become one of the most curable malignancies, with a 5-year relative survival following HL diagnosis now exceeding 85%.2 However, HL survivors also have some of the highest risks for developing second cancers, which are a major cause of morbidity and mortality.3

van Eggermond et al reveal that consideration of “second” cancer risks provides an incomplete picture of the long-term health of HL survivors because a proportion will go on to develop a third or even fourth malignancy. They systematically collected data on subsequent malignancies in >3000 Dutch patients, who were originally diagnosed with HL by age 50 during 1965 to 1995, survived at least 5 years, and were followed through 2012. Such long-term follow-up is critical, because the median time from HL to second malignancy was 19 years and from second to third malignancy was another 4 years.

The persistently increased cancer risk for decades after HL diagnosis and the distribution of second and third malignancies by type (see figure) focuses our attention on several key issues: the major role of HL treatments—particularly radiotherapy—in subsequent malignancies, the question of whether some survivors may be more susceptible to subsequent malignancies than others, and how these results inform HL treatment and long-term follow-up practices.

Radiotherapy clearly is the dominant contributor to both second and third malignancies. Female breast, lung, and gastrointestinal tract cancers were the most frequently observed malignancies after HL in the Dutch cohort, and previous studies have demonstrated that risks for these malignancies are strongly related to the radiation dose these organs receive during HL treatment.4-6 Ninety percent of patients in the Dutch cohort received radiotherapy, typically with extended fields because the majority of patients were treated before the introduction of involved field irradiation around 1990. The impact of supra-diaphragmatic, extended field radiotherapy on subsequent malignancy risk is particularly evident from the substantial proportion of subsequent breast cancers among female HL survivors (44% of second malignancies and 55% of third malignancies) and subsequent lung cancers among male HL survivors (25% of second malignancies and 27% of third malignancies). The impact of changes in radiotherapy for HL (eg, lower doses, smaller field sizes, novel techniques) on subsequent malignancy risk remains unclear because most radiation-related malignancies occur 1 to 2 decades or more after exposure.7

HL chemotherapy plays a smaller role in subsequent malignancy risks. In the Dutch cohort, about 40% of patients received chemotherapy, typically a MOPP (methloretamine, vincristine, procarbazine, 5-fluorouracil, and prednisolone).
explain excesses of non-Hodgkin lymphoma malignancies could merely rehigher risk for developing third and additional patients who develop a second malignancy have cohort, which was restricted to 5-year survivors. following exposure, and thus they accounted for few second or third malignancies in the Dutch myeloid leukemia are well established, these striking chemotherapy-related risks of acute subsequent malignancy risks among survivors who developed non-melanoma skin cancer.10 Unfortunately, cancer registry–based studies such as the current Dutch study do not systematically ascertain the occurrence of nonmelanoma skin cancer and thus cannot confirm that finding. Plausibly, a non-neoplastic adverse outcome also could serve as a marker for identifying patients at high risk of developing subsequent malignancies if the outcomes share an underlying pathogenesis (eg, skin erythema or subcutaneous fibrosis, which could reflect underlying susceptibility to radiation-induced tissue damage). Future research should consider a range of adverse outcomes to further explore this possibility.

Because of their favorable prognosis, frequent diagnosis at a young age, and common receipt of cytotoxic chemotherapy and/or radiotherapy, HL survivors have long been harbingers of the late effects of treatments that also may affect other cancer survivors. The data from van Eggermond et al are a valuable addition to the sparse literature on the occurrence of multiple subsequent neoplasms, and their findings remind us of the importance of continued efforts to reduce the late effects of treatment so that cancer survivors are not faced with double—or triple—jeopardy.

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REFERENCES
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