The impact of treatment on the risk of second malignancy after Hodgkin's disease

In the last several decades, there has been a steady improvement in the cure rate of patients diagnosed with Hodgkin’s disease as more effective treatment and more accurate staging techniques become available [1]. With the growing number of patients surviving Hodgkin’s disease, various delayed complications are being increasingly recognized. Second malignancy after Hodgkin’s disease, first reported in the early 1970s [2], is one of the most serious late effects and is the leading cause of death in long-term survivors of Hodgkin’s disease [3, 4]. The elevated risk has largely been attributed to leukemogenic or carcinogenic effects of the treatments for Hodgkin’s disease. There are likely other contributing factors, however, including an impaired immune system related to treatments or the disease itself and genetic susceptibility in some of the patients.

The identification of risk factors for the development of second malignancy after Hodgkin’s disease can be helpful in guiding practice. For patients with risk factors that are modifiable (e.g. tobacco use, sun exposure, dietary habits), counseling and behavioral modification both at the time of Hodgkin’s disease diagnosis and during follow-up can serve to lower the risk. Patients with risk factors that cannot be modified (e.g. gender, young age at treatment, family history) can be targeted for more vigilant follow-up and perhaps more intensive cancer screening. Treatment-related risk factors can fall into either of these two categories. They are modifiable in patients with newly diagnosed Hodgkin’s disease, and data on the contribution of the various treatment exposures to the risk of second malignancy have motivated clinical investigators to design trials that aim at reducing or eliminating specific treatments. For survivors who have already completed therapy, with known exposure to high-risk treatments, they may be candidates for more rigorous follow-up and screening programs. Understanding treatment-related risk factors for second malignancy risk after Hodgkin’s disease is therefore crucial as it can have management implications in both newly diagnosed Hodgkin’s disease patients and in survivors of the disease.

The majority of studies analyzing second malignancy risk after Hodgkin’s disease and the associated risk factors are in the form of retrospective cohort or case–control studies [5–13]. In evaluating second malignancy risk with respect to treatment exposure, the main limitation of a retrospective study design is the varying follow-up time of the different treatments as therapeutic approaches for Hodgkin’s disease evolve over time. This is especially problematic when evaluating solid tumor risk, which typically arises after a long latency. Prospective randomized trials provide an ideal setting to evaluate treatment-related risk factors for developing second malignancies. In addition to similar length of follow-up time between the treatment arms, the patient and disease characteristics should also be evenly distributed. A number of prospective randomized trials on Hodgkin’s disease have reported on cases of second malignancies after treatment [14–20]. In trials with shorter follow-up time and in which alkylating agent-based chemotherapy was used, the data were mostly on leukemia risk, but in trials with longer follow-up time, solid tumor data are emerging. Because of the small number of events within each individual trial, however, the available information is largely descriptive in nature.

In the article by Franklin et al. [21] in this issue of *Annals of Oncology*, the investigators collected information from randomized trials on Hodgkin’s disease, selected on the basis of the availability of individual patient information, and carried out a meta-analysis to compare the second malignancy risks after different treatment modalities. Meta-analysis as a research tool improves the power to detect differences in treatment outcome, but operates under a number of important assumptions, such as the inclusion of all relevant research studies, both published and unpublished, and the inclusion of studies of comparable quality with the study quality being weighed in the computation [22, 23]. The analysis should also be on the basis of the studies with similar treatment arms and relatively homogeneous patient populations. These issues need to be taken into consideration when interpreting the results and in judging the reliability of the conclusions of a meta-analysis.

In the meta-analysis conducted by Franklin et al. [21], when results of trials that compared radiation therapy alone versus combined modality therapy were considered, the latter approach was found to be associated with a lower risk of second malignancy. The authors attributed this finding to the cumulative effect of salvage therapy in patients who relapsed after radiation therapy alone. Another potential explanation is that the radiation therapy alone arms in 13 of the 15 trials used extended-field or total nodal irradiation, whereas about half of the patients were treated with a more limited radiation field in the combined modality therapy arms of the included trials, and the differences in radiation field size could have contributed to the difference. The authors also reviewed trials that compared chemotherapy alone versus combined modality therapy, and the addition of radiation therapy was found to be associated with an increased second malignancy risk. While this is not a surprising finding, the results need to be viewed in the context that the majority of the trials included in the analysis were on advanced-stage patients, in whom a more extensive radiation treatment field would have been used, and that over half of the trials mandated use of subtotal or total nodal irradiation in the
combined modality therapy arms. Radiation therapy alone versus chemotherapy alone was also compared, although it was on the basis of the results of only three trials. The use of chemotherapy alone was found to be associated with a higher second malignancy risk compared with radiation therapy. This finding may be driven by the leukemia and/or lung cancer risk with the use of alkylating agent-based chemotherapy. As in combining trials with different radiation fields, it is difficult to draw conclusions with the grouping together of trials that used different chemotherapy regimens, given that different chemotherapeutic agents can have different leukemogenic or carcinogenic potentials. Perhaps, the most relevant comparison in this study is that of involved-field versus extended-field radiation therapy. The current standard in combined modality therapy uses involved-field radiation therapy, but there is a paucity of reliable documentation of lower risk of late effects with the use of smaller radiation fields. Although the authors were not able to show a lower second malignancy risk with limited-field radiation therapy, it should be noted that 85% of the patients included in the analysis were from trials conducted in the 1990s, and the follow-up is likely too short to see differences, especially with respect to solid tumor risks.

Despite the inherent limitations associated with meta-analysis, which have been acknowledged in detail in the article, this international collaborative effort of combining randomized trial results is a remarkable accomplishment, and leads the way of using this research tool to specifically assess second malignancy risk in relation to treatment exposure. Currently, there are a number of ongoing or recently completed randomized trials on Hodgkin’s disease, with the focus being on treatment reduction in patients with early-stage, favorable prognosis Hodgkin’s disease, while the role of more aggressive chemotherapy regimen is being addressed in patients with unfavorable prognosis and/or advanced-stage disease. The increasing movement towards treatment reduction among patients with early-stage disease may come at the expense of a higher relapse rate, with one prime example being the use of chemotherapy alone [19, 24, 25]. As emphasized by the authors, continued data collection after relapses is crucial in order to capture the contribution of additional salvage therapy, which may involve high-dose therapy, to the overall second malignancy risk. For patients with unfavorable prognosis and/or advanced-stage disease, the foremost goal is improving the Hodgkin’s disease cure rate. The late toxicity profile of the newer and more intensive chemotherapy regimen needs to be carefully documented as more of these patients become successfully cured [15, 26]. The availability of mature results from trials conducted in the 1990s, and the follow-up is likely too short to see differences, especially with respect to solid tumor risks.

References