patients treated with CHOP-14 and 5 of 22 (22.7%) patients treated with R-CHOP-14 had an isolated CNS relapse. One of the 7 patients treated with CHOP-14 and 2 of 5 treated with R-CHOP-14 had received intrathecal MTX.

With regard to the frequency and severity of toxicities occurring in patients who received or did not receive intrathecal MTX during the first 2 courses of therapy we performed a multivariate analysis (logistic regression) adjusting for International Prognostic Index factors except age and sex (for hematotoxicity only). We observed significantly more leukopenia of grades 3 or 4 with an odds ratio (OR) of 1.6 (95% confidence interval [CI] 1.7-3.2, \( P = .012 \)). Thrombocytopenia of grades 3 or 4 was not significantly increased in patients receiving intrathecal MTX (OR 2.2, CI 0.8-5.9, \( P = .138 \)). Mucositis of grades 3 or 4 occurred in significantly more patients if intrathecal MTX had been given (OR 2.8, CI 1.8-8.1, \( P = .001 \)). No differences were seen for other toxicities including severe or life-threatening infections. Taken together, these additional analyses show that very few patients with aggressive lymphoma (< 1%), treated with modern therapy experience an isolated CNS relapse. Although the low number of such patients in our trial precluded a statistical analysis of whether at least these patients may have benefited from intrathecal MTX we agree with Brugière et al that intrathecal MTX was of limited value in the population at large and should no longer be administered, particularly if the side effects are taken into account. Alternative strategies like early systemic MTX (which should be able to prevent not only CSF but also parenchymal CNS involvement) and intrathecal liposomal cytarabine (Depocyte) are under evaluation in adults. It remains to be determined if these strategies administered to a “high-risk” population will be more successful than intrathecal MTX or whether patients with leptomeningeal and/or parenchymal disease detected with more sensitive methods (FACS analysis) should be treated on protocols for primary CNS lymphoma.

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Reference


To the editor:

Consistency and synergy

We have read with interest the study by De Bruin et al\(^1\) reporting an increased mesothelioma risk among irradiated Hodgkin lymphoma (HL) survivors in The Netherlands. Their almost 30-fold increased risk is similar to that reported by Hodgson et al\(^2\) (relative risk = 20), who used 9 NCI SEER registries and other registries in Europe. The association seen in these studies is consistent with our work using the SEER database only, although the magnitude of our increase for males treated with radiation was much smaller (standardized incidence ratio [SIR] = 6.59).\(^3\)

There are several possible explanations for this difference. Both of the European studies restricted their cohorts to those who had survived HL for more than 5 years, and De Bruin et al restricted HL cases to those diagnosed before age 51. We had only a 2-month survivor restriction and no age restrictions, yet all of our male cases of mesothelioma treated with radiation survived more than 5 years, and all but one were less than 51 years of age at HL diagnosis. If we had applied the same exclusion criteria as De Bruin et al, our person-years of observation would have been fewer, while only one case of mesothelioma would have been excluded. The rate of mesothelioma among those treated with radiation (and, therefore, our SIR) would have been greater. Furthermore, we may have missed mesothelioma cases diagnosed in geographic regions not covered by SEER, whereas the study by De Bruin et al actively followed patients for second cancers nationwide,\(^4\) and nearly half the cohort in Hodgson et al was from national cancer registries, where loss to follow-up is less of a problem.

We disagree, however, that the data “suggest potential synergy” between radiotherapy and asbestos. Asbestos exposure is presented only for those diagnosed with mesothelioma. It is, therefore, impossible to assess separate or joint effects. Rather, the authors compare mesothelioma cases with past asbestos exposure (54%) to an expected prevalence of less than 50% in the Dutch population. The reference cited to support a 50% prevalence in the general Dutch population is inappropriate; the estimate was taken from a review paper by Peterson et al,\(^5\) who cite this percentage from a publication of Canadian and North American male mesothelioma cases.\(^6\) Even if this were a valid comparison, the limited data suggest an independent effect of asbestos, not synergy. All 7 of the mesothelioma cases with reported asbestos exposure are men. The cases of mesothelioma in females, none of whom had reported asbestos exposure, have a SIR of 85.2, much higher than that for males (17.9). The authors cite 2 experimental studies as providing support for this hypothesis. The in vitro study did not address mesothelioma, but the effect on biomarkers of oncogenic transformation in a cell model, and the in vivo study reported the frequency of mesothelioma in mice after asbestos exposure only.
Response

Malignant mesothelioma after irradiation: consistency and synergy

We thank Drs Teta and Wagner for their comments. We agree with their remark that the relative risk for mesothelioma differs between different cohorts and with different inclusion criteria. Within our own population, we noted that all mesothelioma cases were from the 2 hospitals from the highly industrialized areas, whereas no mesothelioma cases were observed in the populations from the other hospitals.1

This heterogeneity, in combination with the unexpectedly high proportion of patients who had been exposed to asbestos, prompted us to state that a potential synergy might exist between radiation and asbestos.

Precisely because we had no data on asbestos exposure in Hodgkin lymphoma patients who did not develop mesothelioma, we very carefully worded our suggestion on the potential interaction between asbestos and irradiation. Similarly, we suggested a potential synergy between chemotherapy and radiotherapy, because the standardized incidence ratio (SIR) for patients treated with both chemotherapy and radiotherapy was considerably higher that for those who had been treated with chemotherapy alone.

In conclusion, we think our data might add to the scarce preclinical evidence for the synergistic action of asbestos and radiation in the pathogenesis of mesotheliomas, but our data certainly do not prove such synergy. Hardly any clinical, or even preclinical, data have been published on this topic. Determining whether or not an interaction exists between radiation and asbestos requires data from larger studies examining the etiology of mesothelioma as a second malignancy. The collection of valid exposure data on asbestos will not be a trivial task in such research.

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Reference

To the editor:

Selective accumulation of virus-specific CD8+ T cells within the peripheral blood stem cell compartment

The absence of cellular immunity is central to the pathogenesis of herpesvirus-mediated diseases after allogeneic hematopoietic stem cell transplantation (HSCT).1,2 For both bone marrow (BM)– and granulocyte-colony stimulating factor–mobilized peripheral blood stem cells (PBSCs) HSCT, donor-derived Epstein-Barr virus (EBV) and cytomegalovirus (CMV) peptide–specific CD8+ T cells clones undergo early expansion and persist long-term, with additional diversification arising from novel antigen-specific clones.

References

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