Other recently published studies have reported elevated mesothelioma rates associated with radiotherapy.[7-9] This study adds support to the conclusion that high-dose radiotherapy causes mesothelioma, although it does not provide evidence to evaluate whether there is synergy between asbestos and radiotherapy.

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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 ares, 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 chemo- 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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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 hemopoietic 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

Table 1. Patient characteristics

Characteristic	PBSC Median (range)	PBSC SE	PB Median (range)	PB SE	*P*	Findings of Moss in BM vs PB
Age, y	66 (22-70)	3.713	53 (24-72)	2.79	NS	
Sex, M/F	11/5	NA	13/13	NA	NS	
Diagnosis	7 myeloma, 8 lymphoma, 1 Ewing sarcoma	NA	Healthy	NA	NA	80% primary lung cancer, 20% secondary lung cancer
% $CD3^+CD8^+$	40.9	3.329	27	1.8	**	
CD4-CD8 ratio	1.288	0.213	2.358	0.2358	**	Increased $CD8^+$ (NS)
% $CD8^+CD45RA^{hi}CCR7^+$ (naive)	20.56	2.774	50.3	2.354	***	Lower in BM
% $CD8^+CD45RA^{lo}CCR7^+$ (CM)	20.96	3.54	10.2	1.11	*	Equivalent
$CD8^+CD45RA^{lo}CCR7^-$ (EM)	16	3.196	17.3	1.571	NS	Higher in BM
% $CD8^+CD45RA^{hi}CCR7^-$ (EMR)	19.2	2.589	20	1.16	NS	Lower in BM
% $CD8^+CD62L$	14.81	1.615	36.75	24.452	***	Higher in BM
% $CD8^+27^+28^+$	33.7	5.581	57.75	3.181	*	Higher in BM
% $CD8^+27^-28^+$	17.1	2.313	7.55	1.157	***	Equivalent
% $CD8^+27^+28^-$	10.19	1.187	18.8	1.862	***	Equivalent
% $CD8^+27^-28^-$	30.45	4.818	23.45	3.226	NS	Lower in BM
% $CD8^+CXCR3^+$	2.16	0.67	0.775	0.165	*	Lower in BM
% $CD8^+CCR5^+$	31	3.746	25.13	1.586	*	Higher in BM
% $CD8^+CXCR6^+$	4.745	0.92	2.55	0.53	NS	Higher in BM
% $FOXP3^+CD4^+$	5.35	0.87	6.772	0.54	NS	
% EBV latent peptide–specific IFN-γ $CD3^+CD8^+$	0.01	0.1114	0.2	0.5901	*	Equivalent
% EBV lytic peptide–specific IFN-γ $CD3^+CD8^+$	0.605	0.461	1.64	0.984	NS	Higher in BM
% CMV peptide–specific IFN-γ $CD3^+CD8^+$	0.25	0.123	0.59	0.6653	NS	Lower in BM
EBV-DNA copies/10^6 cells	0 (0-42)	2.871	2685 (0-3614)	251.9	**	Lower in BM

Herpesvirus peptide–specific IFN-γ producing $CD8^+$ T cells were detected by intracellular cytokine staining by stimulating PB or PBSCs with appropriate HLA class I–restricted viral peptide as previously described.[8] Intravenous cyclophosphamide (2 g/m^2) and subcutaneous G-CSF (10 mcg/kg) were used for PBSC mobilization. Leukapheresis was performed using a Cobe Spectra Gambro BCT continuous flow cell separator.

PBSC indicates peripheral blood stem cells; PB, peripheral blood; BM, bone marrow; NS, not significant; NA, not applicable; IFN-γ, interferon-γ; CM, central memory; EM, effector memory; and EMR, effector memory revertant.

*P = .05-.01; **P = .01-.001; ***P < .001.

from donor-derived progenitors.[3] Whether BM or PBSC is the superior source of antiviral $CD8^+$ T cells is unclear. Given that PBSC has largely replaced BM as a source of stem cells for HSCT, it is unlikely that herpesvirus effector T-cell reconstitution will ever be compared prospectively. PBSC grafts contain 10 to 30 times more T cells than BM[4] and a randomized study found proven viral infections were more frequent in BM than PBSC recipients,[5] suggesting viral-specific T-cell immunity is enhanced in PBSC. Recently Moss showed in lung cancer patients that herpesvirus-specific BM-derived $CD8^+$ T cells have unique homing properties relative to herpesvirus-specific $CD8^+$ T cells present in unmobilized peripheral blood (PB).[6] Immunodominant EBV-lytic peptide–specific $CD8^+$ T cells were enriched in BM but were reduced for CMV peptide–specific $CD8^+$ T cells relative to PB. EBV-latent peptide–specific $CD8^+$ T cells were equivalent, which has relevance in the context of posttransplantation lymphoproliferative disorder for which impaired EBV-latent $CD8^+$ T-cell immunity is a risk-factor.[7] A comparison of herpesvirus-specific cellular immunity in PBSC versus PB has yet to be performed.

We assayed the PBSC of 16 patients and the PB of 26 age-matched healthy volunteers. Although PBSC was obtained in patients and compared with PB of healthy subjects, our previous data indicate that CMV/EBV effector T-cell immunity is not impaired in these patients.[8] The study had ethics approval and was conducted in accordance with the Declaration of Helsinki. In line with Moss in BM versus PB,[6] $CD8^+$ T cells were significantly increased and naive $CD8^+$ T cells were reduced in PBSC relative to PB. Otherwise, $CD8^+$ T-cell subsets in PBSC relative to PB were strikingly different compared with BM (Table 1). Undifferentiated $CD8^+$ T cells (coexpressing the costimulatory molecules CD27 and CD28) were reduced. In addition, $CD8^+$ T cells expressing the lymphoid tissue homing molecule CD62L were lower which is consistent with recent mobilization of T cells from BM into the circulation. In keeping with this, we observed elevation of the chemokine receptors CXCR3 and CCR5 (markers of migratory effector T cells), but not CXCR6 (which facilitates egress into the lung, liver, and joints[9]), whereas in BM there is enrichment for $CXCR3^-CCR5^+CXCR6^+CD8^+$ T cells. As expected, the normal hierarchy of EBV lytic greater than latent T-cell responses seen in PB (P = .01) was preserved in PBSC (P = .03). Critically and in contrast to BM,[6] in PBSC EBV-latent peptide–specific interferon-γ (IFN-γ) secreting $CD3^+CD8^+$ T cells were 20-fold lower than in PB (perhaps reflecting the lower EBV viral load in PBSC), whereas EBV-lytic and CMV peptide–specific IFN-γ $CD8^+$ T cells were equivalent to PB. These results imply that within PBSC there is selective recruitment of $CD8^+$ T-cell populations with a distinct functional and homing phenotype. In contrast to BM, EBV-latent but not CMV peptide–specific $CD8^+$ T-cell immunity is impaired

in PBSC relative to PB. The data have implications for HSCT and adoptive immunotherapy.

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To the editor:

Antinuclear antibody (ANA)–positive thrombocytopenia: primary, but with a difference

In the recent Vicenza Consensus Conference,[1] 2 clinical-immunologic entities have been considered when defining the criteria for differentiating "primary" from "secondary" forms of immune thrombocytopenias. However, although the thrombocytopenia associated with the presence of antiphospholipid antibodies is discussed at some length (obviously within the limits of a standardization conference), this is not so for ITP with antinuclear antibodies (ANA), which is even more complex and challenging.

There are 2 eras in the study and in the gradual elucidation of this intriguing clinical and immunologic entity. The first clinical era included the description of distinct histologic patterns in spleens resected from apparently idiopathic ITP patients who then went on to develop systemic lupus erythematosus (SLE).[2,3] At the same time there was a hot debate as to whether splenectomy for ITP could precipitate SLE,[4] a hypothesis that was ultimately disproved.[5] The second era is founded mainly on longitudinal studies of patients with ITP in which low-titered ANAs did not predict for the late development of SLE,[6] but high-titer ANA, irrespective of subtype, did.[7,8] In a recent study Abbadi et al[9] have found that a positive ANA test (no pattern specified) predicted for a poor response to initial steroid therapy in adults with ITP.[9]

There is no doubt that an isolated positive ANA test in low titers does not contradict the diagnosis of primary chronic ITP, even it there already appears to be a different response to corticotherapy. However, the condition may progress, step by step, along with the increasing amount of ANA and, of course, of other antibodies such as anti-ds DNA, anti-Sm and antinuclear ribonucleoprotein antibodies. In a landmark study, Arbuckle et al[10] have found that in 115 of 130 patients with SLE (88%), at least one SLE autoantibody tested was present before the diagnosis ($\leq$ 9.4 years earlier; mean, 3.3 years). In this clinical material ANAs appeared significantly earlier than the other, more "ominous" antibodies. Similarly, in an imprecise number of ANA-positive ITP patients, a progressive spreading of autoimmunity ("a crescendo of autoimmunity"[10]) may take place, from organ-specific to non–organ-specific antibodies.

In conclusion, the potential evolution from ITP to SLE depends on a galaxy of genetic and epigenetic factors that dictate the fate of any single case. However, the demonstration of varying degrees of steroid-refractoriness in the ANA-positive subgroup, together with long clinical and immunologic histories such as those that have been discussed warrant, in my opinion, a special consideration for this entity, which even at the stage of conventional "primariness" carries some degree of difference.

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