cytes has been widely investigated. However, to our knowledge, the results available[9-13] refer to numerically limited series and, to a certain extent, are discordant depending on the method used.

The method we used was able to detect maternal contamination from as few as 2×10^4 nucleated cells with a sensitivity of 0.04%, comparable to that reported by Sociè et al,[12] without resorting to radioactivity.

Moreover, we were able to demonstrate an exchange of cells from child to mother through the placenta/uterus interface, supporting previously published studies that have shown the passage of fetal cells into the maternal circulation during pregnancy.[10,14]

However, we are aware that our series is limited, too; the combination of minisatellite amplification and chemiluminescence has never been used to this purpose and it proved to be highly sensitive.

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Mycosis Fungoides and Total Skin Electron Beam Radiation

To the Editor:

We are writing to clarify comments concerning total skin electron beam radiation (TSE) made by Diamandidou et al[1] in their comprehensive review of mycosis fungoides and the Sezary syndrome.

The technical description of TSE in the review did not distinguish between premodern and modern methods of TSE. Modern TSE is defined by a skin surface dose of 35 to 36 Gy delivered with electrons of at least 4 MeV energy.[2-4] This TSE optimizes the distribution of dose within the main target volume (epidermis and dermis, to a depth of 5 mm; including blood present in the skin during radiation). It also increases the penetration of electrons to between 2 to 3 cm to encompass many superficial lymph nodes.[2] These attributes are clinically significant. A meta-analysis of the main technical parameters of TSE showed that modern TSE is associated with very high rates of complete remission, with even advanced disease having a rate in excess of 70%.[2,3] Of course, a key question is whether modern TSE improves survival as compared with premodern TSE or no TSE.

The survival experiences of patients receiving less optimal versions of TSE were compared with the experiences of patients managed with other topical therapies in 4 studies. These included contemporaneous,[5] concurrent,[4,6] and randomized[7] controls. All 4 studies showed that premodern TSE achieved only moderate rates of complete remission and was not associated with improved survival. For example, in the randomized trial,[7] combined premodern TSE and systemic chemotherapy was no better than conservative management in 103 randomized patients, although it should be noted that a majority of the patients in this trial had nodal and visceral disease (and were stage IV). In contrast, both Hoppe et al[8,9] and Jones and Thorson[4] have separately shown that more optimal versions of TSE are associated with improved progression-free and overall survivals.[3,8] Kim et al[10] have just reported a comparison of mechlorethamine versus a predominantly historical and essentially premodern TSE control group for only stage IA disease. None of 34 TSE patients and 3 of 73 mechlorethamine patients died of MF (5% difference at 10 years; $P = .18$). Recently, Jones and Thorson[4] were able to

demonstrate that modern TSE (when delivered early on in the course of disease) is highly associated with improved survival as compared with a concurrent control group that did not receive TSE in accordance with patient preferences. The survival improvement with TSE is estimated at approximately 10% for all T and N combinations. Clearly, all of the data just cited, now totaling more than a 1,000 patients, form an internally consistent pattern. This indicates that modern optimized TSE changes the natural history of MF and improves survival.

Modern TSE has little chronic toxicity,[2] and treatment with TSE as first or second line therapy does not preclude another application of TSE later in the course of disease, if it is required.[11] The role for TSE in the management of patients with mycosis fungoides should be predicated on modern data that support both palliative and survival benefits with acceptable toxicity.

Adjuvant therapies such as psoralen plus UV A (PUVA), interferon, or photophoresis might improve on the results of modern TSE. Data suggest that adjuvant PUVA significantly improves the duration of remissions when treating advanced patch/plaque disease, as compared with concurrent controls, and a trend toward improved survival is apparent.[12] Such retrospective findings will now be prospectively evaluated by randomizing patients with patch/plaque disease to observation or adjuvant PUVA after TSE at both Yale University and Hamilton.

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Response

We thank Drs Jones and Wilson for their interest in our recently published review on mycosis fungoides/Sezary syndrome (MF/SS).[1] They raise several important issues. First, they suggest that modern total skin electron beam (TSEB) technique using 35 to 36 Gy delivered with electrons of at least 4 MeV energy (the MeV determines the depth of penetration) allows deeper penetration than older techniques, ie, to 2 to 3 cm, a difference that is important because it encompasses superficial lymph nodes. At our institute, we use a skin surface dose of 32 Gy delivered with electrons of 6 MeV. We agree that the optimal dose of penetration is up to 5 mm. However, despite the fact that the energy used here is higher than the 4 MeV quoted by Jones and Wilson, it does not significantly penetrate to 2 to 3 cm as they claim for 4 MeV. Indeed, at 2 cm, there is only 20% of the surface dose and, at 3 cm, it is negligible (Clinac 2100C-II HDTSe–Internal Release report, M.D. Anderson Cancer Center, 1994). These results are similar to those previously published by Fraass et al[2] and indeed are consistent with the data reported by Jones et al.[3]

In their letter, Jones and Wilson claim that overall survival is improved in patients who are treated with TSEB. The current literature does not adequately support such a claim. In the retrospective cohort analysis of the Stanford experience published in 1996,[4] there was no improvement in survival in stage IA patients treated with TSEB as compared with those treated with mechlorethamine, despite the superior response rate to TSEB. Furthermore, a randomized trial conducted by the National Cancer Institute[5] showed no difference in survival between patients treated with TSEB combined with chemotherapy versus those treated conservatively with topical agents. Finally, the increase in survival referred to by Jones and Wilson was recently published in a letter concerning a nonrandomized trial comparing patients who chose radiotherapy versus those who were managed with alternative therapies.[6] Limited details of the study are available, but patients who chose TSEB were reported to have a superior overall survival, with this difference being most significant in the patients treated since 1980.

In conclusion, we agree that TSEB produces high response rates without severe toxicity. In our opinion, the outcome cited in our review[1] for patients treated with this modality is not overly pessimistic. However, despite the high response rates, a well-controlled trial that supports a superior survival for patients treated with this modality has not yet been reported.

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BCR-ABL Transcript With an e19a2 (c3a2) Junction in Classical Chronic Myeloid Leukemia

To the Editor:

In a recent issue of *Blood*, Pane et al[1] reported three cases of neutrophilic-chronic myeloid leukemia (CML-N) that exhibited a t(9;22) chromosomal translocation. In all cases, a rare type of BCR-ABL rearrangement with a breakpoint between exons e19 (c3) and e20 (c4) of the BCR gene (designated the μ-bcr region) was documented. The same group first described such a breakpoint in 1990[2] and, interestingly, now believe that their initial two cases would be better reclassified as CML-N, rather than as typical or classical CML.[1] They speculate that the inclusion of additional BCR sequences in the BCR-ABL fusion gene, coding for a large $p230^{BCR-ABL}$ product, enables more of the leukemic granulocytes to proceed to complete maturity. A further patient reported by Wada et al[3] was similarly described as atypical Ph^+ CML. In contrast to the above-mentioned reports, we present a case with the e19a2 BCR-ABL transcript that exhibits all the features of typical or classical CML.

A 70-year-old man presented with a history of malaise and weight loss. His hemoglobin level was 9.5 g/dL, white blood cell count 68.3×10^9/L, neutrophils 44%, lymphocytes 5%, monocytes 2%, eosinophils 5%, basophils 5%, metamyelocytes 24%, myelocytes 7%, promyeloblasts 2%, myeloblasts 6%, and platelet count 373×10^9/L and he had a leukocyte alkaline phosphatase (LAP) score of 11 (normal range, 20 to 110). The spleen was palpable 15 cm from the costal border and there was 2 cm hepatomegaly. Trephine biopsy showed a marked increase in bone marrow cellularity, eosinophilia, megakaryocytes with some mononuclear forms, and an increased reticulin (grade 3). Cytogenetic analysis of 20 bone marrow metaphases, using G-banding, showed 45,X-Y, t(9;22)(q34;q11) in all cells. BCR-ABL mRNA was analyzed by multiplex polymerase chain reaction (PCR),[4] using four primers to generate PCR products from BCR-ABL and normal BCR gene transcripts. This resulted in a band of approximately 900 bp, in addition to the 808-bp band representing the BCR transcript. Using two of the multiplex primers (B2B, 5′ ACAGAATTCCGCTGACCATCAATAAG 3′; and CA3, 5′ TGTTGACTGGCGTGATGTAGTTGCTTGG 3′), the 900-bp product was still generated, indicating that the additional sequence was due to exons downstream of e14(b3). The product was sequenced on a PE Applied Biosystems 373 automated sequencer (Applied Biosystems, Foster City, CA) and shown to represent an in-frame BCR-ABL e19a2 transcript.[2,3]

CML-N, also known in the literature as chronic neutrophilic leukemia, is characterized by a more benign course when compared with classical CML,[1,5] with a lower white blood cell count with minimal basophilia, a milder anemia, less prominent splenomegaly, and a normal LAP score. In contrast, our case was typical of CML, with a significant basophilia, a relatively high proportion of circulating immature granulocytes, a low LAP score, and a marked splenomegaly. BCR-ABL transcripts with the e19a2 junction, therefore, are not restricted to atypical cases but may occur in classical CML.

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