Significance of Detection of Occult Non-Hodgkin’s Lymphoma in Histologically Uninvolved Bone Marrow by a Culture Technique


Prolonged disease-free survival of patients with recurrent or resistant non-Hodgkin’s lymphoma (NHL) has been achieved with high-dose therapy followed by autologous bone marrow transplantation (ABMT). A concern with the use of ABMT is that the marrow that is reinfused may contain undetected NHL cells with the potential to reestablish metastatic disease in the recipient. Using a culture technique that is sensitive for detecting occult lymphoma cells in BM, we analyzed histologically normal marrow harvests from 59 consecutive patients with intermediate- or high-grade NHL who were candidates for high-dose therapy and ABMT. The culture results indicated that 22 of the patients had occult lymphoma in their marrow. Forty-three patients underwent high-dose therapy followed by ABMT. Twenty-four achieved a complete clinical remission. Those with occult lymphoma in their harvests (11 patients) continued to relapse for up to 3 years, whereas no relapses were observed beyond 8 months in 13 patients receiving marrow that did not contain detectable lymphoma cells using the culture technique. The relapses in the patients who achieved a complete remission occurred at sites of prior bulky disease rather than at new sites, suggesting that the ability to detect occult lymphoma cells in marrow is a marker of biologic aggressiveness and/or resistance to therapy, or that the reinfused cells could only grow in previously involved sites. The detection of lymphoma cells in marrow used for ABMT is an important adverse prognostic factor, and appears to be independent of other clinical predictors of outcome such as sensitivity or resistance of disease to prior chemotherapy.

MATERIALS AND METHODS

Patients. In this study, BM was cultured from 61 consecutive patients with intermediate- or high-grade NHL who were evaluated at the University of Nebraska Medical Center (UNMC) from November 1985 to December 1988 as potential candidates for treatment with high-dose therapy and ABMT. Complete follow-up data was obtained for the 59 patients described in this report. Cultures were initiated using either the cells recovered from stainless steel screens used to filter the entire marrow harvest or from 5 mL aliquots of marrow removed at the 200 mL collection point of the harvest. These procedures gave equivalent results. The same marrows that were cultured were examined histologically for evidence of lymphoma, as were bilateral posterior iliac crest aspirate smears, clot sections, and core biopsies from all of these patients. Immunophenotyping of the primary tumors was performed using either frozen or paraffin section immunoperoxidase techniques. After the harvest procedure, 14 patients did not receive ABMT, and 45 received high-dose therapy that varied according to the histologic subtype of lymphoma treated, and consisted of Carmustine, etoposide, cytarabine, and cyclophosphamide, or Carmustine, etoposide, cyclophosphamide, and hydroxyurea, or cyclophosphamide and six fractions of total body irradiation (total 12 Gy). This therapy was followed by hematopoietic rescue with either 1 to 2 x 10^8 marrow cells/kg body weight (43 patients) or approximately 7 x 10^8 autologous peripheral mononuclear stem cells/kg body weight harvested by apheresis (two patients). After discharge, the patients were followed-up by their personal physicians, who were contacted regularly for follow-up information. The patients were fully restaged on day 100 and at 6 months and 1 year posttransplant, and followed-up by clinical and laboratory examinations every 2 to 3 months. These studies included a repeat BM if a previous marrow had ever been positive or suspicious. However, repeat BM examinations were not routinely performed on patients who had clear evidence of relapse at other sites.

Culture technique. Cells, fat, and particulate material collected during the filtering process were scraped from the screens and
placed into Hank's Balanced Salt Solution. Particles were allowed to settle from this suspension for 5 minutes at room temperature. Material in this suspension or a 5 mL aspirate was layered onto lymphocyte separation medium (LSM; Organon Teknika, Durham, NC) and centrifuged at 400g for 20 minutes. The cells collected by LSM separation were washed once by centrifugation (400g for 7 minutes) and then resuspended in tris-buffered ammonium chloride (pH 7.2) for 5 minutes to lyse mature red cells. Complete culture medium was added to each tube and the suspensions were washed again. Cultures were established in 25 cm² T-flasks using a modification of a technique described by Philip et al.² Using RPMI 1640 medium supplemented with 20% fetal calf serum, 1% lymphocyte-conditioned medium, penicillin (100 U/mL), and streptomycin (100 µg/mL). Flasks containing 5 x 10⁵ cells in 10 mL of medium were cultured at 37°C in 5% CO₂ in air. Just before the weekly change of half the medium, the supernatant cellularity of each culture was determined using an electronic cell counter (Coulter Model ZBI, Hialeah, FL). The cultured cells were then used for further analyses.

Molecular probing techniques. A portion of the patient’s tumor, BM, or BM cells harvested from the culture flasks were studied by molecular probing for Ig heavy chain (J₅₅) and T-cell β receptor (CT₅) gene rearrangements. DNA was extracted using guanidinium isothiocyanate, followed by extraction with phenol:chloroform and then chloroform alone. Extracted DNA was precipitated with 80% cold ethanol, and dissolved in tris buffer and quantitated. The restriction enzymes EcoRI, BamHI, and HindIII were used to digest 10 µg DNA. Enzyme-digested DNA was electrophoresed in 0.75% agarose with tris-borate buffer, pH 8.0, at 40 V for 16 to 18 hours. The DNA was transferred to nylon membranes and hybridized with appropriate radiolabeled probes. The J₅₅ probe was obtained from Dr Philip Leder (Harvard University) and the CT₅ probes were obtained from Drs T.W. Mak (Ontario Cancer Institute) and Jefferey Sklar (Harvard University). The blots were hybridized to the respective nick-translated, cloned DNA probes at 42°C in 50% formamide, 5X SSC (0.75 mol/L sodium chloride and 75 mmol/L sodium citrate), 3X Denhardt’s solution, 1% sodium dodecyl sulfate (SDS), and 100 µg/mL denatured salmon sperm DNA. The hybridized blots were washed at 52°C in 0.2X SSC and 0.1% SDS. Autoradiography was performed using Kodak X-O-Mat AR-5 X-ray film at −70°C. Raji cell DNA was used as the positive control for the Ig gene rearrangement studies, and CEM cell DNA was used as the positive control for the T-cell receptor gene rearrangement analysis. The BamHI W probe was used for the detection of Epstein-Barr virus (EBV) genome as described previously.²⁶

Data analysis. This study was approved by the Institutional Review Board at UNMC. The patients signed a consent form that cautioned them that undetected tumor cells might be present in their marrow harvest and that their marrow would be studied by various means in an attempt to detect tumor cells. However, they were told that standard histopathologic analysis would be used as the basis for the decision to reinfuse the marrow. The Institutional Review Board permitted the maintenance of identifiers on these data until the final analysis was completed. Two separate databases were established. One database included the clinical and standard histopathologic information for each patient. The second database contained the laboratory information including, for example, the results of the culture studies and molecular analysis of the cultured cells. These databases were merged to perform the present analyses.

Quantitative measurements such as cellullarities are presented as mean values and were tested for statistically significant differences with the two-tailed Student’s t-test. The distributions of histologic subtypes, immunophenotypes, and disease sensitivity to prior chemotherapy between culture positive and negative groups were tested using Fisher’s exact test. Multivariate analysis was performed and survival curves over the 3-year period of the study were compared using the log-rank test using the NCSS statistical package.²⁷ In all cases, values of P ≤ .05 were considered significant.

RESULTS

The majority of the cultures established from histologically uninvolved BM obtained from NHL patients exhibited the characteristics of long-term cultures established from the BM of normal donors. Such cultures showed a high supernatant cellularity during the first week. However, the supernatant cellularity decreased progressively with time as an adherent layer was established. After about 4 weeks of culture, the supernatant cellularity had decreased to low levels and a subconfluent adherent layer was the primary feature of the cultures (Fig 1A). However, the cultures from approximately one-third of the NHL patients exhibited a different pattern of growth. The initial high supernatant cellularity was maintained or, after an initial decrease, the supernatant cellularity began to increase so that, after 4 weeks of culture, supernatant and lightly adherent cells were plentiful (Fig 1B). The supernatant cellularities for cultures that were subsequently judged to be positive or

![Fig 1. Phase micrographs of cultured BM from patients with NHL. (A) Culture with no evidence of lymphoma cells; (B) culture with high supernatant cellularity suspected to contain lymphoma cells.]
negative with respect to the presence of occult lymphoma are shown in Fig 2.

Morphologically, the cultures exhibiting a high supernatant cellularity after 4 weeks of growth contained large abnormal lymphoid cells (Fig 3). These cells, suspected to be tumor cells, were observed in cultures of 22 of the 59 patients. An attempt was made to confirm that the suspect cells were clonal and to match their genotype to that of the original tumor cells by the use of molecular techniques. Of the 22 patient samples suspected to contain occult tumor cells, it was possible to obtain sufficient DNA for molecular studies and the corresponding information on the original tumor for comparative purposes in 13 cases. Clonal gene rearrangements matching those of the original tumor were found in the cultured cells in 11 of the 13 cases, one of which is illustrated in Fig 4. In this case, the suspected tumor cells detected in culture were B cells with a clonal rearrangement matching the patient’s lymph node tumor. This rearrangement was not evident in the uncultured fresh BM sample. The remaining two cases showed no evidence of clonal rearrangements. Additionally, five cases that were judged to be negative for tumor cells on morphologic grounds also proved to be negative by molecular probing.

These observations suggest that 19 of the 59 NHL patients (32%) had occult lymphoma cells in their histologically uninvolved marrow harvest. Up to 4 of the 22 cases considered to be positive on a morphologic basis may have represented virus-expanded lymphoblastoid cells based on the strong hybridization signal of their DNA with the probe for EBV, or cytokine-expanded normal lymphoid populations. One patient with a confirmed B-cell lymphoma had a clonal T-cell population evident in his marrow. This patient subsequently relapsed with an abdominal T-cell malignancy that was suspected to be a second malignancy.

The clinical characteristics of the patients are summarized in Table 1. The median age of these patients was 33 years (range, 10 to 68 years). The male to female ratio was 35:24, and sex and age were not related to the culture results. Patients older than the median age were significantly overrepresented in the early death category (9 of 12) regardless of the culture results ($P < .02$). There were no apparent differences in the causes of early death in patients with positive or negative marrow cultures. The proportion of patients who were culture positive but did not undergo high-dose therapy (5 positive of 14 total), the proportion for whom the clinical outcome was not evaluable due to early death after high-dose therapy (4 positive of 12 total), and the proportion who failed to achieve a complete remission.

Fig 2. Supernatant cellularity of cultures that were subsequently shown to contain lymphoma cells (□) or be free of lymphoma cells (O). Asterisks indicate values significantly different from negative cultures ($P < .05$).

Fig 3. Cytologic preparation showing morphologic evidence of lymphoma (indicated by arrow) from a culture suspected to contain tumor cells based on a high supernatant cellularity.

Fig 4. Southern blots of DNA restriction cut with EcoRI showed a clonal band (indicated by an arrowhead) in the lymph node and the cultured cells from the BM (LN and CC, respectively). HindIII and BamHI showed similar identical clonal bands (not shown). Direct analysis of BM failed to yield clonal bands. The T-cell genes were germline in all specimens. PL, placenta (germline); LN, lymph node; BM, bone marrow; CC, cultured cells from bone marrow.
Table 1. Clinical Characteristics of 59 Patients With Intermediate- and High-Grade NHL Whose BM Harvest Was Evaluated by a Culture Technique for the Presence of Tumor Cells

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. Studied</th>
<th>Culture Results</th>
<th>Lymphoma Grade</th>
<th>Immuno-</th>
<th>Prior</th>
<th>Disease</th>
<th>Alive at Last Follow-Up</th>
<th>Causes of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age (yr/sex)</td>
<td></td>
<td>phenotype</td>
<td>Positivity</td>
<td>Sensitive/Resistant</td>
<td>in CR</td>
<td></td>
</tr>
<tr>
<td>Not transplanted</td>
<td>14</td>
<td>5 pos 22/3,2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3S,2R,0NE</td>
<td>NA</td>
<td>3:3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 neg 33/4,5</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>5,3,1NE</td>
<td>NA</td>
<td>7:3</td>
</tr>
<tr>
<td>Early death after transplantation</td>
<td>12</td>
<td>4 pos 38/2,2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>15,1R,2NE</td>
<td>NA</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>8 neg 45/5,3</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>45,4R,0NE</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 neg 30/2,0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>05,2R,0NE</td>
<td>0</td>
<td>0:0</td>
</tr>
<tr>
<td>No response to high-dose therapy: transplanted</td>
<td>9</td>
<td>2 pos 30/2,0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>25,0R,2NE</td>
<td>0</td>
<td>0:0</td>
</tr>
<tr>
<td>Achieved CR with high-dose therapy: transplanted</td>
<td>24</td>
<td>11 pos 34/7,4</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>6S,1R,4NE</td>
<td>6</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 neg 33/8,4</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>95,2R,2NE</td>
<td>3</td>
<td>10:10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 pos 34/14,8</td>
<td>13</td>
<td>9</td>
<td>13</td>
<td>10S,6R,6NE</td>
<td>4:4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 pos 32/21,6</td>
<td>13</td>
<td>24</td>
<td>9</td>
<td>20S,12R,5NE</td>
<td>17:13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; DAH: diffuse alveolar hemorrhage.
*For all patients the median age was 33 (35 males, 24 females).
†Among those patients who achieved a CR the distribution was 15S,3R,6NE, whereas among those patients who did not achieve a CR the distribution was 2S,5R,2NE.

after high-dose therapy (2 positive of 9 total) were similar to that of the entire group of patients.

Thirteen of 22 culture-positive patients (59%) had high-grade histology and nine had intermediate-grade histology using the Working Formulation criteria. In contrast, 13 of 37 culture-negative patients (35%) had high-grade histology, and the remaining 23 had intermediate-grade histology. This finding is borderline significant (P = .05), indicating that a greater proportion of high-grade lymphomas were culture positive. Regarding the immunologic phenotype, 18 (31%) of the patients had tumors of T-cell type and 41 (69%) had tumors of B-cell type. There were no significant differences in culture results attributable to the immunologic phenotype of the tumor. In the group of patients who achieved a complete response with high-dose therapy and ABMT, there were no significant differences between the culture-positive and -negative patients with regard to histologic type or immunophenotype. Nine of 22 (41%) culture-positive patients had prior histologic evidence of marrow involvement compared with 5 of 37 (14%) culture-negative patients, although all of the patients had histologically negative marrows at the time of harvest. This difference is significant (P < .02).

These patients had undergone multiple conventional chemotherapy treatments without response or with relapse so that information on their original disease stage was not analyzed. However, because the outcome of ABMT in NHL can be predicted on the basis of patient response (sensitive or resistant disease) to prior chemotherapy, the response to chemotherapy was evaluated (Table 1). Sixteen of 22 (73%) culture-positive patients had disease and recent prior chemotherapy that permitted this evaluation, as compared with 32 of 37 (86%) culture-negative patients. These proportions are similar. Ten of the 16 (63%) culture-positive patients and 20 of 32 (63%) culture-negative patients had sensitive disease. However, a greater proportion of patients who had sensitive disease (83%) achieved a complete remission as compared with those who did not (29%; Table 1). Six of 11 (55%) culture-positive patients and three of 13 (23%) culture-negative patients were in clinical remission or a state of minimal disease at the time of transplantation (Table 1). This difference is not significant.

Fourteen of the 59 patients were harvested prophylactically and did not undergo transplantation. Four progressed or had deterioration of their performance status such that the procedure was precluded. Two patients decided against having a transplant. One patient who has recently relapsed will be transplanted with his culture-negative marrow, and seven patients are alive in clinical remission.

The clinical outcome of the culture-positive and -nega-
tive patients who achieved a complete remission with high-dose therapy and ABMT differed significantly (Fig 5). Only 3 of 13 culture-negative patients have died (two relapses, one cerebrovascular accident with no tumor evident at autopsy) with follow-up of up to 3 years (median, 14 months; range, 8 to 39 months). These relapses all occurred within 8 months of high-dose therapy and ABMT. In contrast, 10 of 13 culture-positive patients have relapsed. Although half of the latter relapses occurred before 1 year, other relapses have occurred up to 3 years after treatment. This difference is statistically significant ($P < .04$). The survival at 3 years for all culture-positive patients was 55.5% (1 of 18), whereas that of the culture-negative patients was 35.7% (10 of 28). This difference is significant ($P < .02$). These data suggest that the culture technique has prognostic significance for patients who are candidates for ABMT. The pattern of relapse in these patients was analyzed with respect to the site(s) of original bulky disease to evaluate the consequences of potential tumor cell infusion. The sites of relapse were determined for the 10 culture-positive patients who relapsed, all of whom relapsed at sites of prior disease (Table 2).

**DISCUSSION**

The results of this investigation indicate that occult lymphoma cells are present in harvested BM in approximately one-third of patients with intermediate- or high-grade NHL. The culture system had a technical failure in two instances (3%), in one case due to an inadequate sample and in the other due to equipment failure. Bacterial or fungal contamination of the cultures was not encountered. The initial difficulty of ensuring that enough DNA was obtained from the cultures for molecular analysis was overcome by collecting and pooling cellular DNA from the cultures with morphologically abnormal supernatant cells at each feeding. The nature of the abnormal cells, which were initially detected based on their growth and morphologic appearance in the culture supernatants, was confirmed by molecular studies to consist of clonal populations matching the phenotypes and genotypes of the original tumors in 80% of the cases. Of the remainder, one was a clonal T-cell population cultured from the marrow of a patient with a B-cell lymphoma, and three cases with morphologically abnormal cells showed no evidence of clonal rearrangements. Conceivably, the former may have represented a second tumor population. Alternatively, an activated normal T cell present in the harvest may have expanded clonally in the culture system. In three non-clonal cases, we strongly suspect that the cells were EBV-infected lymphoblastoid cells. Clearly, studies for herpes virus infection, and subsequent confirmation that the cells grown out in culture are clonal and have rearrangements identical to those of the primary tumor, are important. Nonclonal amplification of EBV-infected cells and cells derived from second malignancies unrelated to the original primary appear to have been detected.

The sensitivity of the culture technique applied to patient samples cannot be assessed. However, calibration studies performed using cell lines suggest that, when compared with light microscopy, the culture technique has the potential of a 100-fold increase in the sensitivity of tumor cell detection. Therefore, this technique may be capable of detecting one tumor cell in 10⁴ nucleated marrow cells. Similar sensitivities have been reported with other culture approaches for the detection of minimal residual disease. Even so, minimal residual disease in the marrow at this sensitive level of detection may be insignificant when compared with the total body burden of tumor cells, unless the growth fraction of tumor in the marrow is much higher than that of tumor at other sites. Despite these considerations, there was a significant correlation between the culture detection of tumor cells in the marrow of these patients and their clinical outcome.

The prognostic significance of the detection of tumor cells in histologically uninvolved BM appears to be independent of the categorization of the disease as “sensitive” or

**Table 2. Patterns of Relapse in Marrow Culture-Positive Patients Who Achieved a Complete Remission**

<table>
<thead>
<tr>
<th>Primary Sites of Original Disease (no. of patients)</th>
<th>Primary Sites of Relapse (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous and nodal (2)</td>
<td>Nodal (2)</td>
</tr>
<tr>
<td>Nodal + extranodal thoracic (2)</td>
<td>Nodal (1), extranodal thoracic (1)</td>
</tr>
<tr>
<td>Extranodal abdominal disease only (1)</td>
<td>Extranodal abdominal (1)</td>
</tr>
<tr>
<td>Cutaneous and extranodal abdominal (1)</td>
<td>Cutaneous (1)</td>
</tr>
<tr>
<td>Nodal + extranodal abdominal (2)</td>
<td>Nodal (1), extranodal thoracic and abdominal (1)</td>
</tr>
<tr>
<td>Nodal + extranodal thoracic/abdominal (2)</td>
<td>Nodal (1), extranodal thoracic (1)</td>
</tr>
</tbody>
</table>

Extranodal thoracic and extranodal abdominal sites include, respectively, disease in any thoracic or abdominal organ. During the course of multiple chemotherapy treatments and subsequent relapses, these patients developed evidence of disease at both original sites and/or new sites of disease within these organs.
"resistant," which is thought to be the most important factor for predicting transplantation response. Another factor previously associated with a favorable outcome is intermediate- versus high-grade histology. In this study, there was a similar correlation in that intermediate-grade lymphomas were overrepresented in the culture-negative patient group, whereas the culture-positive group had more high-grade lymphomas. Although T-cell lymphomas were more frequent than B-cell lymphomas in the culture-positive group, this difference was not significant. Three of five culture-positive patients who were harvested remain in complete remission, even though they have not been transplanted. Because of the small sample size, the significance of this observation must be treated with caution. However, it would support the hypothesis that reinfused cells are not the cause of relapse. Apparently, it is not essential to achieve a complete remission by conventional therapy to achieve a good outcome with transplantation (Table 1). The analysis of sites of relapse compared with sites of disease at initial presentation suggests that the majority of relapses occurred at sites of primary bulky disease rather than as a result of the reinfused tumor cells. In the latter situation, one would predict the occurrence of systemic relapse or relapse at sites that were previously free of disease. Although it is possible that tumor cells in the reinfused BM migrated to physiologically relevant sites of lymphocyte differentiation, thus accounting for the patterns of relapse, we suspect that the simpler explanation that relapse occurred at sites of original bulky disease because of the failure of high-dose therapy to completely eradicate tumor at these sites is correct. If one accepts this explanation, then the correlation of the detection of tumor cells in the marrow with the likelihood of relapse must be indirect, and one could postulate that the detection of tumor cells in the marrow serves as a marker of the degree of "malignancy" or resistance to therapy.

The amplification of minimal residual lymphoma cells in BM harvests by the culture technique described in this report may have advantages when compared with increasingly sophisticated monoclonal antibody and molecular techniques for detecting such tumor cells. Although such techniques may be more sensitive in their ability to detect tumor cells than the culture technique, these assays do not require the expression of any functional attributes of the detected tumor cells. Such cells may be no longer clonogenic, or the host immune system or other factors may be preventing their clonal expansion. In the former situation, although tumor cells are present, they may not be clinically significant. When culture techniques are used to detect occult tumor cells, cellular expression of their proliferative potential to expand clonally is required. It would be of interest to compare other tumor detection techniques to our culture technique in an attempt to evaluate this hypothesis further.

In conclusion, although we do not have a good biologic understanding of the correlation between the presence of occult tumor cells in the BM of patients with NHL and their clinical outcome, the results of our study indicate that such a correlation exists and is prognostically significant. Consequently, patients with evidence of marrow metastases based on culture results should be considered candidates for alternative therapies, including the use of peripheral blood stem cell transplantation. Preliminary data from our laboratory suggests that peripheral stem cell harvests are less likely to be contaminated with tumor cells in patients whose BM is positive by either histologic or molecular criteria. Clearly, further studies designed to confirm or refute these findings are needed.

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