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Blood 1996 Oct 1;**88(7)**:2780-2786

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Freedman AS, Gribben JG, Neuberg D, Mauch P, Soiffer RJ, Anderson KC, Pandite L, Robertson MJ, Kroon M, Ritz J, Nadler LM

Division of Hematologic Malignancies and Biostatistics, Dana-Farber Cancer Institute, Boston, MA.

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MeSH Terms:

- Adult
- Antineoplastic Agents, Combined/therapeutic use*
- Antineoplastic Agents, Combined/administration & dosage
- Bone Marrow Transplantation*
- Combined Modality Therapy
- Cyclophosphamide/administration & dosage
- Disease-Free Survival
- Doxorubicin/administration & dosage
- Female
- Follow-Up Studies
- Human
- Immunoglobulins, Heavy-Chain/genetics
- Life Tables
- Lymphoma, Follicular/therapy
- Lymphoma, Follicular/radiotherapy
- Lymphoma, Follicular/mortality
- Lymphoma, Follicular/drug therapy*

High-Dose Therapy and Autologous Bone Marrow Transplantation in Patients With Follicular Lymphoma During First Remission

By Arnold S. Freedman, John G. Gribben, Donna Neuberg, Peter Mauch, Robert J. Soiffer, Kenneth C. Anderson, Lini Pandite, Michael J. Robertson, Mary Kroon, Jerome Ritz, and Lee M. Nadler

We report the results of a study in previously untreated advanced stage patients with follicular lymphoma (FL) who underwent uniform induction chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) followed by myeloablative therapy and anti-B-cell monoclonal antibody purged autologous bone marrow transplantation (ABMT). Eighty-three patients with previously untreated, low-grade FL were enrolled. After CHOP induction, only 36% achieved complete remission (CR) and 77 patients underwent ABMT. Before BM harvest, 70 patients had a known t(14;18), as determined by polymerase chain reaction (PCR), and all remained PCR positive in the BM at harvest. After ABMT, the disease-free survival (DFS) and overall survival are estimated to be 63% and 89% at 3 years, respectively, with a median follow-up of 45 months. Patients whose BM was PCR negative after purging experienced significantly longer freedom from recurrence (FFR) than those whose BM remained PCR positive ($P = .0006$). Continued PCR negativity in follow-up BM samples was also strongly predictive of continued CR. This study suggests that a subset of patients with advanced FL may experience prolonged clinical and molecular remissions following high-dose ablative therapy, although longer follow-up will be necessary to determine potential impact on overall survival.

ADVANCED STAGE follicular non-Hodgkin's lymphoma (FL) is an incurable disease with current conventional therapy. Although many of these patients achieve a complete remission (CR) with standard treatment, the median duration of first CR is generally short, ranging from 12 to 36 months.[1] However, virtually all patients in clinical CR harbor evidence of residual lymphoma cells when assessed by sensitive molecular techniques.[2-7] More importantly, virtually all patients relapse, with a disease-free survival (DFS) of only 25% at 5 years and less than 10% at 10 years.[8] Although patients with low-grade lymphomas will often respond to reinstitution of conventional treatment following relapse, the quality and duration of subsequent responses progressively decreases.

High-dose therapy with autologous hematopoietic stem cell support can salvage a subset of patients with relapsed intermediate and high-grade non-Hodgkin's lymphoma (NHL). A similar approach has been investigated in patients with relapsed low-grade lymphoma.[9-13] Through careful patient selection and advances in supportive care, the treatment related mortality is under 5%. However, the use of high-dose therapy with intent to cure patients with previously relapsed FL has had limited impact to date. In several series, at best 40% of highly selected patients with good performance status and sensitive disease are alive and in unmaintained remission at 4 years. In addition, there is considerable patient selection before autologous bone marrow transplantation (ABMT) in these patients, and only approximately 50% of patients with relapsed FL who are initially considered as candidates for ABMT actually undergo the treatment. If the results from these studies were plotted on an "intent to treat basis," the results would appear considerably worse. Therefore, at best 20% of patients with relapsed disease may actually benefit from high-dose therapy.

One strategy, which has been taken to improve the treatment of patients with leukemia and lymphomas with poor prognosis, is the use of high-dose consolidative therapy earlier in the course of disease. For example, in acute leukemias and chronic myelogenous leukemia (CML), earlier use of allogeneic BMT yields improved results over that seen in advanced disease.[14] Similarly, the use of high-dose therapy and ABMT in patients with intermediate and high-grade lymphoma with poor prognosis following conventional therapy, may lead to an improvement in DFS as consolidation. High-dose therapy and autologous hematopoietic stem cell support for patients with FL in first remission may permit successful treatment for patients before the development of resistant disease following extensive conventional therapy.

In the present study, we report the results in patients with previously untreated advanced stage FL who, on an intent to treat basis, underwent uniform induction chemotherapy followed by high-dose chemoradiotherapy and anti-B-cell monoclonal antibody purged ABMT. The goal of this study was to assess whether this approach was associated with any evidence of improvement in the DFS at 24 and 36 months post-ABMT as compared with that seen historically with conventional therapy alone. In the results to be reported below, we demonstrate that 63% of patients are disease-free at 36 months post ABMT and that 35 of 66 patients (53%) with a polymerase chain reaction (PCR) amplifiable bcl-2/IgH rearrangement are in molecular remission at their last follow-up. Although still preliminary, these results suggest that a percentage of patients with advanced stage FL may experience prolonged remissions.

MATERIALS AND METHODS

Selection of patients and treatment protocol. Patients were eligible for this study if they were physiologic age 55 years or less; had

From the Division of Hematologic Malignancies and Biostatistics, Dana-Farber Cancer Institute, Boston; the Department of Radiation Therapy, Brigham and Women's Hospital, Boston; and the Departments of Medicine and Radiation Oncology, Harvard Medical School, Boston, MA.

Submitted April 9, 1996; accepted May 22, 1996.

Supported by National Institutes of Health Grants No. CA34183 and CA66996.

Address reprint requests to Arnold S. Freedman, MD, Division of Hematologic Malignancies, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115.

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0006-4971/96/8807-0038$3.00/0

previously untreated FL as defined by the Working Formulation (WF) including: follicular small cleaved cell (WF-B), and follicular mixed small cleaved and large cell (WF-C); and had lymphoma cells that expressed the CD20 (B1) antigen as previously described. Patients had to have stage IIIB, IIIE, or III with masses greater than 10 cm, or stage IV disease. Patients with stage IV disease by virtue of minimal adenopathy (<1 cm) and less than 5% marrow involvement were excluded. Additional criteria for entry included the absence of comorbid disease of the heart, kidney, lung, and liver and a Karnofsky score above 80%. All patients were treated with 6 to 8 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP). At the completion of CHOP, patients in CR or minimal disease state went on to BM harvest. Minimal disease status was defined as lymph nodal mass less than 2 cm in its greatest diameter and histologic evidence of BM involvement of 20% or less of the intratrabecular space as determined by iliac crest biopsy. Patients with 1 to 3 masses greater than 2 cm after completion of CHOP could receive involved field radiotherapy of 2200 to 2500 cGy. Informed consent was obtained from all patients.

Preparative therapy consisted of cyclophosphamide, 60 mg/kg of body weight, infused on each of 2 consecutive days before radiotherapy. Total body irradiation (TBI) was administered in fractionated doses (200 cGy) twice daily on 3 consecutive days (total of 1,200 cGy) in all patients. Supportive care was provided as previously described.[15]

Collection, processing, and infusion of marrow. BM was obtained, treated in vitro as previously described, and stored within 4 weeks of its use.[15] No patients were excluded from the protocol after BM harvest. BM cells were treated with anti-B1 (CD20), -B5, and J5 (anti-CD10) and rabbit complement. After treatment, the cells were cryopreserved as previously described.[15] Within 18 hours of the completion of radiotherapy the cryopreserved marrow cells were rapidly thawed and diluted in medium containing DNAase as previously described.[15]

Evaluation. Before treatment, all patients were evaluated by physical examination, blood-chemistry profile, complete blood count, chest x-ray, abdominal-pelvic computed tomography (CT) scanning (chest CT if indicated), BM aspirate and biopsy, as well as cell surface phenotypic studies of peripheral blood (PB) and BM mononuclear cells. Other studies such as gallium scanning were done as needed to determine the extent of disease. Follow-up restaging was performed every 6 months after transplantation or as clinically indicated for the first 2 years post-ABMT and yearly thereafter. CR was defined as the disappearance of all measurable and evaluable disease.

PCR analysis. Nested PCR amplification at the major breakpoint region (MBR) and minor cluster region (mcr) of the bcl-2/IgH rearrangement of t(14;18) were performed as previously described.[16] Analysis was performed initially on diagnostic material (lymph node biopsy, BM aspirate if histologically involved). Samples were analyzed at the completion of induction therapy and at the time of BM harvest. Assessment was also performed after ex vivo marrow purging. Serial BM and PB samples at the time of restaging after ABMT were also analyzed.

Statistical methods. Failure was defined as relapse of disease or death in remission. DFS was calculated from the day of marrow transplantation (day 0) to date of failure, or to date last known alive and disease-free. Time to relapse (freedom from recurrence [FFR]) was calculated from the day of marrow transplantation to the date of relapse; deaths in remission were considered censored for this analysis. DFS curves and FFR curves were estimated by the method of Kaplan and Meier,[17] with confidence intervals calculated using Greenwood's formula, and compared by the log rank test.[18] The Cox proportional hazards model was used to assess prognostic factors for FFR and DFS and to build multiple regression models. Models investigating post-ABMT PCR assessments of minimal residual disease incorporated this factor as a time-varying covariate. Exact binomial confidence intervals were calculated for binomial proportions.

Table 1. Patient Characteristics

Total	77
Sex	
Female	33
Male	44
Age at ABMT (yr)	
<35	12
35-50	60
>50	5
Histology	
Follicular small cleaved	65
Follicular mixed	12
Stage	
III	13
IV	64
Mass > 10 cm	9
Mass > 5 cm	48
B symptoms	19
Sites of involvement	
Lymph node	77
Mediastinal mass	14
Spleen	11
Liver	3
Extranodal (exclusive of BM)	19
BM involvement	62
1% to 5%	24
6% to 10%	6
11% to 20%	6
>20%	23
Not quantified	3

RESULTS

Patient characteristics. Eighty-three patients (median age, 43 years) with previously untreated, advanced stage FL were eligible and registered on this study. Patients had to have stage IIIB, IIIE, or III with masses greater than 10 cm, or stage IV disease. These patients had progressive disease at the time of consideration and patients with minimal stage III/IV disease were excluded. At diagnosis, 71 of the 83 patients had follicular small cleaved cell (FSC) histology, 12 had follicular mixed small cleaved and large cell lymphoma. Between April 1988 and June 1993, 77 patients (93%) achieved a protocol eligible minimal disease state at the completion of induction and went on to ABMT. Three patients (4%) failed to attain a protocol eligible PR, two further patients were diagnosed with second tumors (melanoma and seminoma) and one patient declined further therapy. The characteristics of the 77 patients who underwent ABMT are detailed in Table 1. Sixty-four patients (83%) had stage IV disease, largely by virtue of BM involvement and 30% of patients had greater than 20% infiltration of their BM by lymphoma. The majority of patients had bulky disease with 62% having masses greater than 5 cm and 12% had masses greater than 10 cm. Serum lactate dehydrogenase (LDH) was seldom elevated in these patients at the time of commencing induction therapy (4 of 45 patients in whom pretreatment

Table 2. Clinical Outcome

Total	77
Treatment-associated deaths	6 (DAH-2, MDS-3, suicide-1)
CCR	43 (median F/U, 45 months)
Relapse (alive)	28 (23)
Sites of relapse	
Previous sites	22
Previous and new sites	2
New sites	4
BM relapse	
Histologic BM involvement at diagnosis	11
BM+ at harvest	10
BM− at harvest	1

values were available). Extranodal sites of involvement, exclusive of the marrow, including skin, peripheral blood, as well as pleural and peritoneal fluid were present in 25% of patients and 25% of patients had B symptoms.

Response to induction therapy. All patients were treated with 6 to 8 cycles of CHOP, and 10 patients received involved field radiation therapy to residual sites that were greater than 2 cm at the completion of chemotherapy. In contrast to the reported CR rate with CHOP of 60% to 70% in patients with advanced follicular NHL, only 28 patients (36%, 90% confidence interval, 27% to 46%) achieved clinical CR following induction therapy. Histologic marrow involvement was seen in 36 of the patients at harvest (47%, 90% confidence interval, 37% to 57%). These results suggest that patients who elected to proceed to ABMT did not have exquisitely sensitive and/or minimal amounts of disease.

PCR analysis following induction. Of the 77 patients who underwent BM harvest, 70 (91%) had a PCR-amplifiable bcl-2 translocation. Six patients had no evidence of a PCR amplifiable bcl-2/IgH rearrangement at either the mbr and mcr breakpoints in diagnostic tissue and in one further patient no premarrow purging sample was available for analysis. In keeping with our findings in previously relapsed patients who were treated with ABMT,[19] all 70 patients continued to have PCR detectable disease at the time of BM harvest, irrespective of the presence or absence of histologic appearance of the marrow biopsy. After ex vivo marrow treatment, 30 patients (43%) had no PCR detectable disease whereas 40 patients (57%) were reinfused with marrow that contained residual PCR detectable lymphoma cells. There was no significant association between the outcome of purging and the presence of histologic evidence of disease. However, only one of six patients with greater than 5% marrow involvement histologically purged negative.

Treatment outcome. There were two acute in-hospital treatment-related deaths both from diffuse alveolar hemorrhage syndrome (Table 2). Four late deaths from nonlymphomatous causes were observed. Five patients have developed myelodysplasia (MDS) post-ABMT. Three patients have died without evidence of lymphoma following HLA-matched sibling and matched unrelated donor allogeneic bone marrow transplants at 24, 32, and 40 months, respectively. Two additional patients remain alive: one patient relapsed at 13 months and developed MDS at 65 months; the other patient developed MDS at 18 months and remains without relapse of lymphoma at 35+ months post-ABMT. An additional patient committed suicide at 28 months.

Of the remaining 71 patients, as of November 1, 1995, there have been 28 relapses. Forty-three patients remain in CCR with a median followup of 45 months (range, 14 to 82 months). The Kaplan-Meier estimate of the percentage of patients alive and disease-free at 3 years is 63% (90% confidence interval, 55% to 74%) (Fig 1A). The estimate of the overall survival at 3 years is 89% (90% confidence interval, 82% to 96%) (Fig 1B).

Of the 28 patients who relapsed, the overwhelming majority of patients relapsed in sites of prior disease (Table 2). Entirely new sites of disease were observed in only six patients, and in four of these patients were new sites the only sites of relapse. Eleven of the 28 relapses involved the marrow, all of whom had a history of bone marrow infiltration, 10 at the time of harvest. Following relapse, 23 of 28 patients are alive at a median follow-up of 49 months post-ABMT.

PCR analysis following ABMT. The effect of marrow purging was examined in the 70 informative patients who had a previously known bcl-2 rearrangement, all of whom

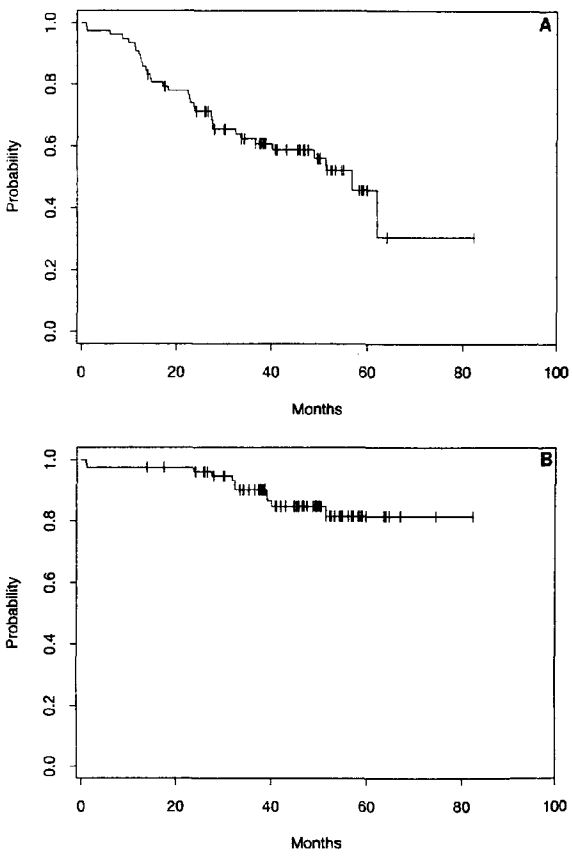

Fig 1. Kaplan-Meier estimate of probability of DFS (A) and overall survival (B) for 77 patients following ABMT.

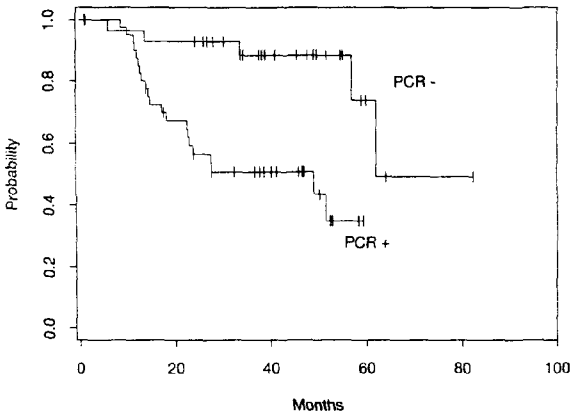

Fig 2. Kaplan-Meier estimate of FFR following ABMT, for 70 informative patients who were either PCR negative (PCR−) or PCR positive (PCR+) after ex vivo purging.

had postlysis marrow samples. Among the 30 patients who were PCR negative after purging, there have been five relapses, while there have been 21 relapses among the 40 patients who were PCR positive after purging. The 3-year FFR for the PCR negative patients is 88%, while the FFR for the patients who were PCR positive postlysis is 51% (P = .0006) (Fig 2).

BM samples were analyzed for assessment of minimal residual disease following ABMT. Analysis was restricted to samples obtained at least 3 months after ABMT, but more than 1 month before clinical evidence of relapse. A total of 476 samples were analyzed from 66 patients. No samples were available for analysis from four patients who had a documented PCR amplifiable bcl-2/IgH rearrangement. Two of these patients died during ABMT and two patients had no follow-up BM samples sent for PCR analysis. The results obtained at the time of and following ABMT in these patients are shown in Fig 3. In 28 patients, no BM samples analyzed had evidence of PCR detectable lymphoma at any time point after ABMT (Fig 3A). Of note, in only four of these 28 patients (14%) were PCR detectable lymphoma cells detected after immunologic purging. Only three of these 28 patients (11%) have relapsed to date, one patient with lymphoma lacking a bcl-2 rearrangement. PCR detectable minimal residual disease was detected in every BM sample obtained after ABMT in 21 patients, 20 of whom (95%) were infused with autologous BM that contained residual PCR detectable lymphoma (Fig 3B). Sixteen of these 21 patients (76%) have relapsed to date. The remaining 17 patients had different results obtained at different time points after ABMT (Fig 3C). In nine of these patients, PCR detectable lymphoma cells were detected early after ABMT, but no PCR detectable lymphoma cells could be detected in later samples. The time taken to convert from PCR positivity to PCR negativity varied from 1 year to almost 3 years after ABMT. Only one of these patients has relapsed to date. In four patients (UPN #1312, 1370, 1415, and 1487), no discernible pattern could be observed. In four patients (UPN #1348, 1369, 1476, and 1496), no PCR detectable lymphoma cells were observed early after ABMT, but lymphoma cells were detected by PCR at later time points and persisted on subsequent sampling. The time to appearance of first detectable minimal residual disease in these patients varied from 1 year to 4 years after ABMT.

Prognostic models. In an attempt to identify prognostic variables for these patients, a number of factors were examined in a univariate comparison of DFS using the log rank test. These included: age, sex; stage (III v IV); follicular small cleaved versus follicular mixed histologies; B symptoms; extranodal (extramedullary) disease; elevated LDH; mass >5 cm; BM involvement at diagnosis; BM involvement at harvest; interval from diagnosis to ABMT; and remission status at harvest (CR v PR). The clinical parameters that were associated with unfavorable DFS ($P < .05$) in univariate analysis were: PR at ABMT; BM involvement at diagnosis; BM involvement at harvest; stage IV disease; interval of 2 or more years from diagnosis to ABMT; and age 40 and above. The presence of PCR-detectable lymphoma cells in the postpurging BM and in follow-up BM samples posttransplant were also associated with an unfavorable DFS.

A stepwise proportional hazards regression was performed to identify factors which affected DFS. To extend analyses involving PCR results to all 77 patients, candidate variables were expanded to include an indicator of the presence of the bcl-2 translocation in diagnostic tissue, as well an indicator of PCR positivity postlysis. Posttransplant PCR positivity in follow-up BM samples was also included as a candidate variable. The PCR positivity postpurging was the strongest factor in the multiple regression model, increasing the risk of failure for these patients to 5.1 times that of patients who were either PCR negative postlysis or who lacked the translocation. The absence of the translocation was not significantly associated with DFS. Other clinical factors associated with a poor prognosis include an interval from diagnosis to ABMT of greater than 2 years (4.0 times); histologic involvement of the marrow at harvest (3.7 times); and a history of B symptoms (2.6 times).

DISCUSSION

In this report, we present the results of a study of previously untreated patients with advanced stage FL who were uniformly treated with CHOP induction followed by high-dose chemoradiotherapy and ABMT in first remission. Within the context of studies of conventional therapy in this disease, the follow-up is relatively short, however considering that the median progression-free survival in patients treated conventionally is approximately 2 years,[20] we have observed over a twofold increase in DFS in patients undergoing ABMT in first remission. These results are comparable to those of a retrospective analysis of patients with FL undergoing ABMT in second remission, where it has been suggested that there is a prolongation of DFS when compared with conventional therapy.[12] Considering that only 36% of the patients in the present study who underwent ABMT were in clinical CR at the time of ABMT, the current results are encouraging.

In FL, the evaluation of any impact on remission duration

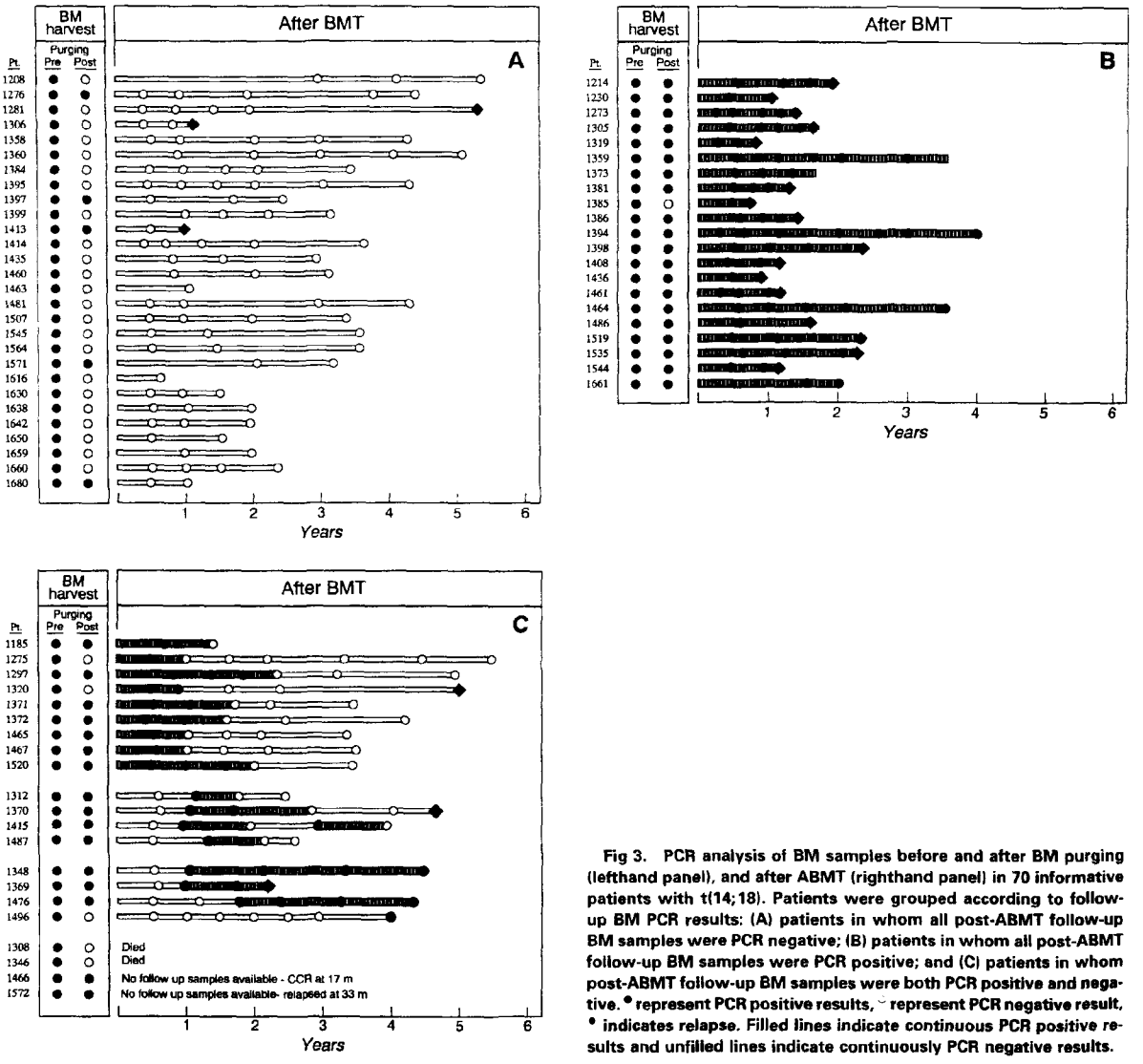

Fig 3. PCR analysis of BM samples before and after BM purging (lefthand panel), and after ABMT (righthand panel) in 70 informative patients with t(14;18). Patients were grouped according to follow-up BM PCR results: (A) patients in whom all post-ABMT follow-up BM samples were PCR negative; (B) patients in whom all post-ABMT follow-up BM samples were PCR positive; and (C) patients in whom post-ABMT follow-up BM samples were both PCR positive and negative. ● represent PCR positive results, ○ represent PCR negative result, • indicates relapse. Filled lines indicate continuous PCR positive results and unfilled lines indicate continuously PCR negative results.

and survival will require exceedingly long follow-up. At the time of this analysis, it is not clear whether there will be a plateau in the DFS curve for patients treated on this study. Therefore, an endpoint other than remission duration and survival would be useful for examining the effect of ABMT. We have previously reported that detection of minimal residual disease by PCR following ABMT is a very useful predictor of relapse.[16,21] Analogous to our studies of patients transplanted in second or greater remission, we demonstrate here that the continued absence of PCR detectable lymphoma cells in follow-up BM samples is a sensitive predictor of continuous remission following ABMT in first remission. Furthermore, those patients in whom PCR detectable disease is present early after ABMT and becomes negative over time, appear to remain in clinical and molecular remissions. Conversely, patients who were continuously PCR positive in follow-up BM specimens or who converted from negative to positive, will almost invariably relapse. These studies are in contrast to reports of persistent PCR-detectable lymphoma cells in a select subset of patients, with both early and advanced staged disease, who remain in continuous clinical remission following conventional treatment.[2,5,22-24] In those patients, it is unclear whether those PCR-detectable cells are capable of contributing to relapse or more likely whether with longer follow-up those patients will have clinical relapse. It appears from our studies of high-dose therapy in this specific patient population that the persistence or development of PCR-detectable lymphoma cells is highly predictive of relapse and may be a suitable surrogate endpoint for assessing the efficacy of ABMT in a disease with a very long natural history.

At the inception of this study, we did not anticipate that

approximately 10% of patients might die of nondisease specific causes and that nearly 40% of the remaining patients would relapse at the time of this analysis. Perhaps the most unanticipated event observed thus far in five patients (6%) has been myelodysplasia, seen at a median of 32 months post-ABMT. Three of these patients have died and the prognosis of the remaining patients and other patients who might develop MDS is likely to be poor.[25-29] It is unknown whether this level of toxicity may outweigh the benefits of ABMT. Presently, 32 patients are in both clinical and molecular remission. As to whether these patients are truly cured without incurring additional long-term unacceptable toxicity will require much longer follow-up.

A major question is whether the patients treated on this study were in fact a subgroup of patients with a poor prognosis. The International Prognostic Index for Aggressive Lymphomas has been applied to patients with FL, and risk groups of patients have been been identified.[30,31] Using these criteria, the vast majority of patients with FL present with low or low-intermediate risk disease, with less than 5% of patients having high-risk with a median survival of approximately 2 years. Virtually all patients in the present study were of low-intermediate risk by virtue of stage III/IV disease and the presence of extranodal disease. With conventional therapy, these patients have a median survival of about 10 years.[31] By these criteria, our patients do not appear to have a very poor prognosis. One factor that suggests an unfavorable prognosis in the patients selected for this study was the CR rate of 36% following CHOP induction. This is markedly lower than the 70% CR rate to CHOP reported for advanced stage FL patients.[32,33] Although one interpretation is that 6 to 8 cycles of CHOP was inadequate therapy, we believe we did not select patients with exquisitely sensitive disease with a favorable prognosis. Patients who do not achieve a CR after treatment with conventional therapy have a median survival of 4 years and a DFS of 1 year.[32] Therefore, we believe that few, if any, of our patients would experience long-term DFS with additional treatment short of myeloablative.

If the 30 patients who are presently in a clinical and molecular CR remain so, these results would be superior to conventional and ABMT in second remission. Since following relapse, only 50% of patients are candidates for ABMT, then only 20% of relapsed patients experience long-term DFS. Therefore, the results in the present study appear to be encouraging and merit further exploration. The results of this study show that patients whose marrow can be purged of PCR-detectable lymphoma cells remain in clinical and molecular CR. Whether purging contributes to relapse or is a prognostic marker is presently unknown. However, for the subset (40%) of patients who purge PCR negative, ABMT may be sufficient therapy, and no additional therapy appears warranted. In contrast, those patients who are PCR positive either after purging and/or in follow-up BM samples, have an overwhelming likelihood of relapse and merit novel approaches. Specifically, future studies using stem cell support in FL should be directed at attaining a PCR negative state through the development of more efficient purging techniques.[34] Moreover, for the patients who remain PCR positive after purging and who persist or develop PCR-detectable lymphoma in follow-up BM samples, additional treatment with either antibodies, cytokines, and/or vaccines are merited.[35-38] We believe that high-dose myeloablative therapy will potentially become an important treatment approach for advanced stage poor prognosis patients with FL. To improve the therapeutic index, future studies must be directed at decreasing toxicity and improving eradication of minimal residual disease.

ACKNOWLEDGMENT

We are indebted to the nurses of the Dana-Farber Cancer Institute, the housestaff of the Brigham and Women's Hospital and Beth Israel Hospital, the fellows of the Dana-Farber Cancer Institute, the social workers of the Dana-Farber Cancer Institute for their excellent care of these patients. We also thank the technicians of the Clinical Immunology laboratory and the Blood Component Lab for processing of the bone marrows; the oncologic surgeons of the Brigham and Women's Hospital and New England Deaconess Hospital for their surgical assistance; and the staffs of the Departments of Radiology and Infectious Disease for their assistance in patient care.

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