High-Dose Therapy and Autologous Stem-Cell Transplantation Versus Conventional-Dose Consolidation/Maintenance Therapy as Postremission Therapy for Adult Patients With Lymphoblastic Lymphoma: Results of a Randomized Trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group

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Purpose: To determine whether a combination of high-dose therapy and autologous stem-cell transplantation (ASCT) is superior to conventional-dose consolidation and maintenance chemotherapy as postremission therapy in adults with lymphoblastic lymphoma.

Patients and Methods: One hundred nineteen patients were entered onto this prospective randomized trial from 37 centers. Patients received standard remission induction therapy, and responding patients were randomized either to continue with a conventional consolidation/maintenance protocol (CC) or to receive high-dose therapy and ASCT. In some centers, patients with HLA-identical sibling donors were registered on the trial but proceeded to allogeneic bone marrow transplantation (BMT) without randomization.

Results: Of the 119 patients entered, 111 were assessable for response to induction therapy. The overall response rate was 82% (56% complete response, 26% partial response). Of the 98 patients eligible for randomization, 65 were randomized, 31 to ASCT and 34 to CC. Reasons for failure to randomize included patient refusal (12 patients), early progression or death on induction therapy (eight patients), excessive toxicity of induction regimen (six patients), and elective allogeneic BMT (12 patients). With a median follow-up of 37 months, the actuarial 3-year relapse-free survival rate is 24% for the CC arm and 55% for the ASCT arm (hazard ratio = 0.55 in favor of the ASCT arm; 95% confidence interval [CI], 0.29 to 1.04; P = .065). The corresponding figures for overall survival are 45% and 56%, respectively (hazard ratio = 0.87 in favor of the ASCT arm; 95% CI, 0.42 to 1.81; P = .71).

Conclusion: The use of ASCT in adults with lymphoblastic lymphoma in first remission produced a trend for improved relapse-free survival but did not improve overall survival compared with conventional-dose therapy in this small randomized trial.


LYMPHOBLASTIC lymphoma (LBL) is a rare disease, accounting for approximately 2% of all cases of non-Hodgkin's lymphoma (NHL). It is a neoplasm of precursor B or T lymphocytes, classified as precursor B- or T-lymphoblastic leukemia/lymphoma in the Revised European-American Lymphoma classification, and is identical to acute lymphoblastic leukemia (ALL) in terms of cellular morphology, immunophenotype, and genotype. The clinical distinction between LBL and ALL has been variable and arbitrary and is usually based on the extent of nodal disease, the degree of bone marrow infiltration, and the presence of circulating blast cells in the peripheral blood, although it is now widely accepted that LBL and ALL represent different manifestations of the same underlying disease.

Approximately 80% of adult cases of LBL have a T-cell phenotype. It is a clinically aggressive disease, characterized by an increased incidence in adolescents and young adults, male predominance, and frequent involvement of the mediastinum, pleura, and pericardium. Meningeal and bone marrow involvement are also common.

The optimal treatment for adult LBL remains uncertain. In view of its rarity, few clinical trials have been conducted, and most data are derived from single-institution or registry-based studies in selected patients. Initial studies of patients
treated with first- and second-generation regimens developed for the treatment of intermediate grade NHL reported long-term disease-free survival rates of only 15% to 30%.4,5 The subsequent use of intensive chemotherapy/radiotherapy regimens similar to those used in ALL produced complete response rates of 70% to 80%, with 40% to 60% of patients achieving long-term disease-free survival.6-8

The high complete remission (CR) rate with high subsequent relapse rate provides the rationale for the use of high-dose therapy and stem-cell transplantation to consolidate first remission in these patients. Both autologous and allogeneic stem-cell transplantation have been used, and studies from single centers and registries have resulted in 60% to 80% long-term disease-free survival rates in patients receiving this treatment in first remission.9-14 However, these data must be interpreted cautiously in view of the potential selection bias inherent in single-institution and registry-based studies. Several of these studies have restricted the use of high-dose therapy to patients thought to have poor-risk disease, although the definition of poor risk has been inconsistent. In view of this, we have undertaken a prospective, randomized trial to compare high-dose therapy and autologous stem-cell transplantation (ASCT) with conventional-dose consolidation and maintenance chemotherapy as postremission therapy for adult patients with LBL. The primary aim of this study was to determine whether consolidation with high-dose therapy was superior to conventional-dose therapy. Secondary aims of the study were to assess the predictive value of the International Prognostic Index15 (IPI) for NHL in adult patients with LBL using prospectively collected data and to collect data prospectively on patients undergoing allogeneic bone marrow transplantation (BMT) in first remission who were registered but not randomized in this study.

PATIENTS AND METHODS

Eligibility

Patients with newly diagnosed lymphoblastic lymphoma, histologically confirmed after pathology review, were eligible for this study. Prior chemotherapy or radiotherapy was not permitted, except for emergency treatment given at presentation for the immediate relief of a life-threatening disease, such as airway obstruction. Other eligibility criteria included age ≥15 years, any stage according to the Ann Arbor system,16 absence of circulating blast cells in the peripheral blood, and normal renal, hepatic and cardiac function, unless directly attributable to lymphomatous infiltration. Written, informed consent was mandatory. Patients infected with the human immunodeficiency virus were excluded from this study. Individual centers were required to adopt a consistent policy with respect to patients who had HLA-identical siblings. Some centers elected to offer these patients allogeneic BMT if they achieved CR after induction therapy. These patients were registered with the trials centers but were not eligible for randomization.

Investigations at Study Entry

All patients were staged according to the Ann Arbor system and were also allocated into risk groups as described by the International Prognostic Factors Project for NHL.15 Staging investigations comprised full clinical history and physical examination, including determination of World Health Organization performance status; full blood count and differential WBC count; peripheral-blood lymphocyte immunophenotype; erythrocyte sedimentation rate; serum biochemistry profile, urate, and lactate dehydrogenase (LDH); chest x-ray; computed tomography of the chest, abdomen, and pelvis; bone marrow aspirate and trephine biopsy for morphology and lymphocyte immunophenotype; and CSF sampling for glucose, protein, cytology, and immunophenotype. Additional imaging investigations including magnetic resonance imaging, and radionuclide bone scans were used as clinically indicated.

Study Design

An outline for the overall design of the trial is given in Fig 1. To promote accrual onto this study, a permissive trial design was adopted. Individual centers could elect to use any dose-intensive induction regimen with proven activity in LBL, although specific regimens were recommended. Similarly, the choice of high-dose regimen and conventional-dose consolidation/maintenance regimen was permissive, although recommended protocols were specified. The source of stem cells and protocols for ex vivo manipulation of progenitor cells was also flexible. Each center was required to use the same regimen for all patients entered onto the trial.

Induction Therapy

The recommended induction regimens were either a modified LSA1 regimen,6 or the induction regimen reported by Coleman et al from Stanford University.7 Details of these regimens are given in Figs 2 and 3 respectively. Centers wishing to use other induction regimens were required to seek approval from the principle investigators before study entry. All patients were assessed for response to induction therapy during days 70 to 77 after commencement of treatment. Response assessment included a complete history and physical examination, full blood count and peripheral blood lymphocyte immunophenotype, serum biochemistry profile including LDH, chest x-ray, CT scan of chest, abdomen and pelvis (if
abnormal at study entry), bone marrow aspirate and trephine biopsy (including lymphocyte immunophenotype), and repeat CSF if abnormal at presentation.

Response Criteria

CR was defined as complete disappearance of all previously detectable clinical, radiologic, and histologic/immunophenotypic evidence of disease. Partial remission (PR) was defined as more than 50% reduction in the sums of the products of the biperpendicular diameters of all measurable disease. No response was defined as less than 50% reduction in the sums of the products of the biperpendicular diameters of all measurable disease. Progressive disease was defined as any increase in the size of previously documented disease or the appearance of disease at new sites.

Randomization

Patients who achieved a complete or partial response to induction therapy were eligible for randomization, with the exception of those patients for whom allogeneic BMT was planned. Patients who failed to achieve at least a partial remission, or those with progressive disease on induction therapy, were taken off trial therapy and treated at the discretion of the responsible physician. They remained on study for follow-up and were included in analyses of response and survival.

Randomization was performed at the Medical Research Council Clinical Trials Unit, Cambridge, United Kingdom, and Unit of Clinical Epidemiology and Trials, National Cancer Institute, Genova, Italy. Telephone randomization was provided by both trials offices. Treatment was allocated using predefined random permuted blocks of variable size.

Conventional-Dose Consolidation/Maintenance Therapy

Patients receiving the modified LSA₂L₂ regimen as induction therapy continued on the maintenance arm of this protocol as described in Fig 2. Similarly, for patients receiving the Stanford University protocol as induction therapy, maintenance was given according to the schedule in Fig 3. For patients receiving other regimens, most received oral maintenance therapy with 6-mercaptopurine and methotrexate, according to various schedules, usually continued until a total of 1 year or until all therapy was completed.

High-Dose Therapy

The two recommended high-dose regimens were (1) carmustine 300 mg/m² administered intravenously (IV) days −6, etoposide 100 mg/m² IV on days −5 to −2, cytarabine 200 mg/m² IV on days −5 to −2, and melphalan 140 mg/m² IV on day −1, with reinfusion of autologous hematopoietic progenitor cells on day 0, and (2) high-dose cyclophosphamide plus total-body irradiation (TBI) (cyclophosphamide 60 mg/kg IV on days −5 and −4, TBI 2 Gy twice daily on days −3 to −1, with reinfusion of autologous hematopoietic progenitor cells on day 0). Some variations of the cyclophosphamide/TBI schedule were used. Other high-dose regimens included carmustine, etoposide, cytarabine, and cyclophosphamide.

Source of Autologous Hematopoietic Stem-Cell Rescue

During the period of this study, practice in most participating centers changed from the use of autologous bone marrow to peripheral-blood progenitor cells. Either source of cells was allowed in the study. Autologous bone marrow was collected from the posterior iliac crests of patients under general anesthesia. Target cell doses were determined by individual participating centers. Peripheral-blood progenitor-cell mobilization and collection was undertaken according to active protocols at individual centers using standard target cell doses. The use of ex vivo purging or positive stem-cell selection was allowed but was not mandatory.
Supportive Care

Supportive care measures, including prophylaxis, management of acute tumor lysis, antimicrobial use, and blood product support, were all carried out according to the active protocols of the participating centers. For those patients undergoing stem-cell transplantation, all procedures were carried out in registered transplantation centers, and nursing procedures, antimicrobial, hematopoietic growth factor, and blood product support were given according to standard management policies and active protocols within each center.

Follow-Up

Formal assessment of response took place between 30 and 60 days after the completion of all trial therapy. This included a complete history and physical examination, full blood count, differential WBC count, peripheral-blood lymphocyte immunophenotype, serum biochemistry profile including LDH, chest x-ray, and repeat of any other investigations that were abnormal at the first restaging. Centers were required to submit follow-up data at 3, 6, 9, and 12 months from randomization and at 6-month intervals thereafter.

Treatment of Relapsed/Progressive Disease

For patients randomized to the high-dose arm, patients with relapsed or progressive disease were treated at the discretion of the individual treating physicians. Patients randomized to conventional-dose therapy were treated, where possible, with a second-line regimen to induce a second remission. The choice of second-line regimen was permissive. Patients achieving a second CR then proceeded to high-dose therapy and ASCT.

Statistical Considerations

The primary end point for the determination of the sample size was overall survival. An initial sample size of 200 randomized patients was estimated, based on the ability to detect an improvement in 5-year overall survival from an anticipated 30% in the control arm to 60% on the high-dose arm with a significance level of 5% and 95% power. An interim analysis was planned after the entry of the first 100 patients and thereafter on an annual basis, depending on the accrual rate.

Survival curves were constructed according to the Kaplan-Meier method. All survival analyses were performed on an intent-to-treat basis. Overall survival was calculated from the date of presentation to the date of death. Relapse-free survival was calculated from the date of presentation to the date of relapse/progression or death. Surviving patients were censored at the last date on which they were known to be alive for overall survival and alive without relapse or progression for relapse-free survival. Survival analyses relating to the whole population were dated from the start of induction therapy. Those analyses involving only randomized patients were dated from the date of randomization.

Treatment comparisons were made using the log-rank test.

RESULTS

Between November 1992 and April 1997, a total of 119 patients from 33 centers in Europe were registered on this trial. Recruitment to the trial was discontinued at this point because of the low accrual rate.

The median age at presentation was 26.0 years (range, 14.6 to 65.2 years). The presenting features of all registered patients are summarized in Table 1. The study population showed the expected male predominance, with 68% of patients having a T-cell immunophenotype and more than 60% having Ann Arbor stage III or IV disease. According to IPI risk groups, 15 patients (13%) had low-risk disease, 43 (36%) had low/intermediate, 33 (28%) had high/intermedi-
ate, and 20 (11%) had high-risk disease. It was not possible to allocate eight patients to IPI risk groups, because values for serum LDH at presentation were not available. Details of induction therapy are given in Table 2. Seventy percent of patients received the modified LSA2 L2 regimen, and a further 14% received the Stanford University regimen. The remaining patients received a variety of other regimens, including doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisolone, and various regimens developed for the treatment of ALL, including the Medical Research Council UKALL 12 protocol.

Response to Induction Therapy

Of the 119 patients entered onto the study, 111 were assessable for response to induction therapy. Seven patients suffered early deaths, six as a result of disease progression and one as a result of acute tumor lysis syndrome. A further patient was subsequently found to be ineligible. Responses to induction therapy are listed in Table 3. Ninety-eight patients responded to induction therapy for an overall response rate of 82% (CR, 56%; PR, 26%). Complete response rates were higher in patients receiving the Stanford regimen, compared with LSA2 L2 (73% vs 57%), although this difference was not statistically significant ($P = .24$).

Of the 98 patients eligible for randomization, 65 were randomized, 31 to high-dose therapy and ASCT and 34 to conventional salvage therapy. The reasons for failure to be randomized are listed in Table 4. Twelve responding patients received allogeneic BMT, and 12 responding patients refused randomization.

The characteristics of the randomized patients are listed in Table 5. A significantly higher proportion of patients randomized to the conventional arm had bone marrow involvement at presentation ($P = .036$). Of the randomized patients, eight (12%) were in the low-risk group according to the IPI, 22 (34%) were low/intermediate risk, 20 (31%) were high/intermediate risk, and 10 (15%) were high risk. Incomplete data were available for five patients. Therefore, the distribution of patients in the IPI risk groups was the same for the randomized and conventional arms.
patients as for the entire population at presentation. No apparent selection of patients according to risk group therefore occurred in the induction phase of therapy.

**Survival**

The actuarial overall survival from the date of registration/start of induction chemotherapy for all registered patients is shown in Fig 4. With a median follow-up of 37 months for surviving patients, the 3-year actuarial overall survival rate is 46%.

The relapse-free and overall survival rates according to randomized arm are shown in Figs 5 and 6, respectively. These survival curves were calculated from the date of randomization. The 2-year relapse-free survival rates were 29% and 50% in the conventional arm and the ASCT arm, respectively, with a hazards ratio of 0.55 (95% confidence interval, 0.29 to 1.04; \( P = .065 \)). The corresponding figures for overall survival were 53% and 57%, respectively, with a hazards ratio of 0.87 (95% confidence interval, 0.42 to 1.81; \( P = .71 \)).

Of the 20 patients who experienced relapse after randomization to the conventional-dose arm, 17 were treated with further combination chemotherapy, using various regimens. Of these, nine patients achieved a second complete or partial response and proceeded to high-dose therapy and ASCT in second remission. Five of these patients are in continuing CR after ASCT.

A total of 12 deaths have occurred on the ASCT arm. Eleven patients died with relapsed/progressive disease and the remaining patient died from toxicity, 4 months after ASCT. Seventeen deaths have occurred on the conventional arm, 16 owing to relapse or progression, and one as a result of an unknown cause.

We found no evidence of a difference in outcome according to age, sex, World Health Organization perfor-
mance status at registration, Ann Arbor stage at registration, bone marrow involvement at registration, immunophenotype, elevated LDH at registration or randomization, or status after induction. There was a trend for improved overall survival in the ASCT arm for patients who had “B” symptoms at presentation, although this did not achieve statistical significance.

Survival After Allogeneic BMT

The actuarial overall survival of the 12 patients who underwent allogeneic BMT in first remission is shown in Fig 7. The 3-year actuarial overall survival rate for this group was 59%. Five patients have died, two from progressive disease and three from early regimen-related toxicity.

Survival According to IPI

Actuarial overall survival for randomized patients according to number of risk factors in age-adjusted IPI is shown in Fig 8. A significantly lower overall survival with increasing number of risk factors was observed (P = .016, log-rank test).

DISCUSSION

Several single-institution series have reported response rates of 60% to 100% and long-term disease-free survival rates of 40% to 60% for adult patients with LBL treated with dose-intensive combination chemo-/radiotherapy regimens similar or identical to those used in the treatment of ALL. In a report from Stanford University, Coleman et al described 44 adult patients treated with one of two novel regimens using initial multiagent chemotherapy for remission induction, a CNS prophylaxis block (including high-dose systemic methotrexate in the first regimen and CNS irradiation in the second), and subsequent consolidation and maintenance therapy until a total of 1 year on therapy had been completed. They reported a 100% response rate (CR, 95%; PR, 5%), and a 3-year actuarial freedom from relapse rate of 56%. Slater et al reported similar results in 51 patients treated on successive ALL protocols at Memorial Sloan-Kettering Cancer Center, with a CR rate of 78% and 5-year actuarial overall survival rate of 45%. However, these favorable results have not been reported in all of the

Fig 6. Actuarial overall survival for patients randomized to ASCT (—) or conventional-dose consolidation/maintenance therapy (---).

Fig 7. Actuarial overall survival for patients receiving allogeneic BMT in first remission.

Fig 8. Actuarial overall survival for randomized patients according to number of risk factors in age-adjusted IPI. — = 0 risk factors; . . . . . = 1 risk factor; --- = 2 risk factors; --- = 3 risk factors.
published single-center series. In addition, in a recent retrospective report from the International Lymphoma Study Group that included 26 patients with lymphoblastic lymphoma as defined by the Revised European-American Lymphoma classification, the 5-year actuarial overall survival rate was only 22%.²⁰

In view of the relatively high relapse rates reported among patients with this disease, the use of high-dose therapy and stem-cell transplantation was introduced in an attempt to consolidate first remission after standard induction therapy. This has now been the subject of several reports, most of which have used autologous stem cells as the source of hematopoietic rescue, although small numbers of patients receiving allogeneic BMT in first remission have also been reported.⁹-¹⁴ In general, the results of this approach have seemed superior to those achieved with conventional-dose therapy alone, with 60% to 80% of patients achieving long-term disease-free survival. For example, Milpied et al⁹ reported 25 adult patients with LBL treated with TBI-based high-dose regimens in first remission, with either autologous or allogeneic BMT.⁹ The 4-year actuarial disease-free survival rate was 69%. More recently, Bouabdallah et al¹⁴ reported results in 62 adult patients treated with French Multicenter Acute Lymphoblastic Leukemia protocols or NHL protocols. Forty-six patients achieved a CR, of whom 30 proceeded to high-dose therapy and autologous (n = 18) or allogeneic (n = 12) stem-cell rescue. The 5-year actuarial overall survival rate for patients treated with high-dose therapy and stem-cell transplantation was 60%, compared with only 30% in those who received conventional-dose consolidation/maintenance therapy (P = .005). However, because this analysis was conducted retrospectively, it is possible that the patients proceeding to high-dose therapy represent a selected group, and the impact of the high-dose therapy on subsequent survival cannot be determined.

We previously reported results from the European Bone Marrow Transplantation lymphoma registry for 105 adult patients with LBL who underwent high-dose therapy and ASCT in first CR.¹² The 6-year actuarial overall and progression-free survival rates were 64% and 63%, respectively. In contrast to these results, a single-center study from Switzerland in which adult patients with LBL received chemotherapy with MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) or VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) followed by high-dose therapy and ASCT reported 3-year actuarial overall and event-free survival rates of only 48% and 31%, respectively.¹³ Furthermore, many of these studies only examined outcome from the time of attainment of remission or the date of ASCT. In studies in which an intent-to-treat analysis from the date of diagnosis has been possible, results in patients receiving high-dose therapy in first remission have not seemed superior to those treated with conventional therapy alone.

In view of the potential selection bias inherent in all of the retrospective series discussed above, the present randomized trial was undertaken to determine the effect of high-dose therapy and ASCT in first remission on subsequent relapse and survival rates.

It was unfortunate that this trial was terminated because of low accrual. However, our post hoc power calculations have shown that even if the planned accrual of 200 randomized patients had been achieved, it is unlikely that a different result would have been observed. The trial was designed to detect an increase in 5-year overall survival from 30% to 60%, corresponding to a hazards ratio of 0.42. With 65 patients entered onto the study, the power to detect this difference in survival is 65%. Based on the comparisons at 3 years, the study has a 56% power to detect a relative risk of 0.42 or less.

Despite the early closure of this trial, it is the largest prospective trial conducted for adult patients with LBL and the first study to collect prospective data on the use of autologous and allogeneic stem-cell transplantation and prognostic information based on the IPI.

The overall response rate to induction therapy of 82% is comparable to that of previous series. Although the complete response rate is apparently lower than in previous studies, this may be due to the fact that response assessment took place relatively early to allow adequate time for stem-cell collection in those patients randomized to high-dose therapy. The 3-year actuarial overall survival rate of 48% is comparable to previous studies in which patients were treated with conventional-dose therapy only and almost identical to the series reported by Jost et al.,¹¹ in which all patients underwent first-remission ASCT, but the survival analyses were based on intention to treat. The selection bias that is introduced into retrospective series of first-remission transplantation is underscored by the fact that in the present study, of 119 patients entered onto this study, only 69 (58%) were eligible for randomization and an additional 12 patients received allogeneic BMT. Therefore, only 69% could potentially have undergone stem-cell transplantation. Early disease progression or death, severe toxicity, or patient refusal were the main reasons for failure to proceed to randomization or allogeneic BMT. The failure to be randomized in this study was not related to prognostic groups according to the IPI. The proportions of patients in each of the IPI risk groups was the same in the randomized patients as in the entire presenting population, indicating that the induction therapy was equally equivalent in all risk categories.

The overall survival for patients randomized to ASCT is also comparable to that of previous series. For the randomized patients, there was a trend for superior progression-free sur-
vival in those treated with high-dose therapy and ASCT compared with those receiving conventional-dose consolidation and maintenance therapy, although this did not achieve statistical significance at the 95% level. No difference in overall survival was observed. The relatively small number of randomized patients in this study makes definitive conclusions regarding the effectiveness of ASCT difficult to reach. However, the absence of a difference in overall survival despite a trend for superior progression-free survival in the ASCT arm may be due to the fact that some patients who experienced relapse after conventional therapy were successfully treated with salvage therapy by the use of ASCT in second remission.

To date, reliable and reproducible prognostic factors for adult LBL have not been described. This is mainly because of the small sample size of previous single-center series and the variable criteria for distinguishing between LBL and ALL. Until recently, the most widely used prognostic factors for adult LBL were those described by Coleman et al. In their series, they identified a poor-risk group with elevated LDH levels and Ann Arbor stage IV disease with bone marrow or CNS infiltration in whom the 5-year freedom from progression was only 19%. However, these factors have not been identified in all series. Following the description of the IPI for intermediate-grade NHL, this has been applied to other subtypes of NHL by several groups. In a recent report from the International Lymphoma Study Group, the IPI was not predictive of either overall or progression-free survival in 26 adult and pediatric patients with LBL. In contrast, the present study shows a significantly poorer progression-free and overall survival with an increasing number of risk factors. The total number of randomized patients was too small to determine whether a significant difference in progression-free or overall survival according to randomized arm could be determined in any of the IPI risk groups.

The 3-year actuarial overall survival rate of 58% for patients receiving allogeneic BMT is also comparable to that of previous reports and to the outcome for patients on this study receiving autologous stem cells. Two previous series suggested that patients with HLA-identical siblings who undergo allogeneic BMT have a superior outcome to those treated with ASCT. However, these studies are retrospective, and patients proceeding to allogeneic BMT are likely to represent a favorable subgroup in terms of age, performance status, and so on, which may influence their long-term overall and disease-free survival. In this prospective series, analyzed by intention to treat, there was no apparent improvement in outcome for patients receiving allogeneic compared with autologous stem cells.

In conclusion, the use of high-dose therapy and ASCT in adult patients with LBL in first remission after intensive remission induction therapy did not improve overall survival compared with conventional-dose therapy in this randomized trial.

Patients receiving high-dose therapy and ASCT complete their entire treatment in a shorter period than those receiving prolonged maintenance therapy. This may be another important factor in management decisions in this disease, although long-term follow-up will be required to explore potential long-term toxicities of these approaches, and quality-of-life studies may also be required.

Although this study was able to confirm the predictive value of the IPI, it was not possible to determine whether any subgroup of patients stratified by risk had superior outcome after ASCT.

New treatment strategies are required for this disease. The use of more dose-intensive induction may increase the complete response rates. Further attempts to reduce relapse rates after conventional-dose or high-dose consolidation, such as the use of mini-allograft strategies, should also be investigated.

**APPENDIX**

*The following physicians participated in this trial: R. Centurioni (Università di Ancona, Ancona); S. Tura and F. Gherlinzoni (Ospedale S. Orsola, Bologna); P. Coser (Ospedale Generale Regionale, Bolzano); A. Gallami (Divisione di Ematologia, Cuneo); G. Santini (Ospedale S. Martino, Genova); G. Lambertenghi (Ospedale Maggiore di Milano, Milano); G. Torreli (Divisione di Ematologia/Oncologia Policlinico, Modena); O. Vinante (Centro Oncologico Multizonale, Venezia); S. Montafoni (Az. Ospedale di Padova, Padova); I. Maiddino (Ospedale V. Cervello, Palermo); F. Mandelli, V. De Sanctis, and M. Martelli (Università La Sapienza, Roma); M. Tribalto (Ospedale S Eugenio, Roma); T. Chiesi (Ospedale Civili di Venezia, Venezia); L. Trentin (Ospedale Civile S Bortolo, Vicenza); A. Chierichini (Ospedale Sta M. Garetti, Latina); M. Brugiatelli (Ospedale Civili Regionale, Reggio Calabria); M. Carotenuto (Ospedale Casa Sollievo Della Sofferenza, San Giovanni Rotondo); U. Vitolo (Ospedale Le Molinette, Torino); A. Novarino (Az. Ospedale S Giovanni, Torino, Italy); J. Radford and D. Crowther (Christie Hospital, Manchester); D.C. Linch and R.L. Souhami (University College Hospital, London); B.W. Hancock (Weston Park Hospital, Sheffield); T.A. Lister (St Bartholomew’s Hospital, London); D. Cunningham (Royal Marsden Hospital, Sutton); J. Fletcher (Nottingham City Hospital, Nottingham); C. Poynton (University Hospital Wales, Cardiff); J. Sweetenham and G.M. Mead (Southampton University Hospitals, Southampton); R. Clark (Royal Liverpool University Hospital, Liverpool); P.J. Selby (St James’ Hospital, Leeds); G. Smith (Leeds General Infirmary, Leeds); N. Stuart and H. Parry (Ysbyty Gwynedd); C. Littlewood (John Radcliffe Infirmary, Oxford); R. Sheppard (Northampton General Hospital, Northampton); S. Johnson (Musgrove Park Hospital, Taunton, United Kingdom); A. Nagler (Hadasah University Hospital, Jerusalem, Israel); S. Brunet (Hospital St Pau, Barcelona, Spain); and H. Holte and A. Kolstad (Norwegian Radium Hospital, Oslo, Norway).*
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