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ORIGINAL ARTICLE

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Treatment of relapsed aggressive lymphomas: regimens with and without high-dose therapy and stem cell rescue

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Abstract Treatment of aggressive lymphoma in relapse is difficult. Patients who initially present with these diseases often know they have a malignancy considered curable in many cases, and diagnosis of relapse can be devastating. For this reason, it is useful to know the individual patient's risk of relapse prior to starting initial therapy, since it may be appropriate to treat patients with poor prognoses with intensive programs or investigational studies. In the private practice setting, most patients with these diseases receive CHOP or similar cyclophosphamide and doxorubicin-containing regimens at the time of initial diagnosis. However, there are certain disease-related features which determine whether these patients have a high or low risk of relapse, and investigators are now using combinations of these features to determine which patients may be safely treated with CHOP and which may benefit from more intensive chemotherapy management. For example, the International Prognostic Factor Index system, now in common usage, delineates four different groups of patients with differing complete remission, freedom from progression, and overall survival rates. The Tumor Score System, developed at MDACC, delineates only two groups with very different survival rates, and may be a better scoring system for patients with diffuse large cell lymphomas, primarily because of its inclusion of the serum beta$_2$-microglobulin level prior to treatment, an important predictor of relapse. In addition to pretreatment features, certain treatment-related factors are also important in determining the risk of relapse, including the dose of chemotherapy administered and the rapidity of response. Results of a gallium scan with SPECT imaging may be an important method of confirming complete response, and should be incorporated into treatment programs, whether the treatment is standard CHOP or an investigational program. For the patient with relapse or progressive disease following induction with CHOP or a similar regimen, the type of response to initial therapy plays an important role in determining potential response to salvage therapy, including high-dose therapy followed by stem cell rescue. Patients for whom initial treatment fails to achieve any response have a very poor chance of responding to any currently used standard-dose program for relapse. Those with partial responses have a better chance of responding to relapse therapy, but a high risk of disease progression or early relapse, and those with a prior complete response to initial therapy have a good chance of responding to relapse therapy, especially those in whom the complete response lasted more than a year. For these reasons, stem cell transplant (SCT) protocols routinely require complete response with initial therapy as a requirement for entry, although "good partial remission" may be acceptable at certain centers. Other limitations for SCT protocols include age greater than 60 or 65 years, significant chronic obstructive pulmonary, renal, or cardiac disease, a poor performance status, and central nervous system or marrow involvement. For these reasons, there is a continued need for newer treatment programs which offer the potential for higher response rates and better survival rates, not only for those for whom SCT is not an option, but also for those who must have an adequate response to "standard dose therapy" prior to selecting SCT as a treatment option. Three broad groups of relapse therapy for aggressive lymphoma have been described, based upon the drugs contained within these regimens. These include platinum-based, mitoxantrone-based, and ifosfamide-based chemotherapy regimens. Results with these programs vary widely and are likely different because of

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tumor-related features prior to relapse therapy, including size of mass, beta$_2$-microglobulin level, LDH level, and type of response to initial therapy. Other features, such as dose of therapy, specific drugs utilized, and number of prior treatments also play important roles in determining results with relapse therapy. In a study of DHAP followed by transplant or more DHAP, DHAP induced a response in 56% of patients, and at 5 years, significantly more of the responders to DHAP who were subsequently treated with high-dose therapy and bone marrow transplant were free of disease compared to those who continued to receive DHAP after response to this regimen. Therefore, high-dose therapy is clearly better for DHAP responders than is continued DHAP. However, results for the overall population are still not good when non-responders are included in the analysis, and DHAP, a first-generation platinum regimen, may not be the optimal regimen to use prior to high-dose therapy followed by peripheral stem cell rescue. At MDACC, we have extensively investigated various combinations containing ifosfamide and etoposide. The most recently reported regimen, MINE-ESHAP, contains mesna, ifosfamide, mitoxantrone, and etoposide, followed after adequate response with etoposide, methylprednisolone, high-dose cytarabine, and continuous infusion as cis-platinum, a second-generation platinum regimen. This strategy resulted in a complete response in 47% of the patients treated, with a 44% complete response in patients with intermediate-grade lymphoma, 56% in those with low-grade lymphoma and 36% in those with transformed lymphoma. Results varied according to type of response achieved with initial therapy, and serum LDH and beta$_2$-microglobulin levels prior to treatment with MINE-ESHAP. Using more intensive doses of ifosfamide and etoposide, we have described therapy for 36 patients with relapsed aggressive lymphomas, prior to pheresis and SCT. Results of this study are encouraging: 42% entered complete response with ifosfamide-etoposide and the overall survival was 52%, with a progression-free survival of 32%. Therapy with a similar regimen, combining ifosfamide, carboplatin, and etoposide in standard doses (ICE) has also been described. This regimen has been extensively studied in patients with relapsed aggressive lymphomas and Hodgkin's disease, followed by SCT. In patients with relapsed lymphomas, ICE has achieved a 66% complete response rate, with 89% undergoing transplant. Overall survival in these studies is affected by the quality of the response to ICE. The same program was used to treat 65 patients with Hodgkin's disease. The response rate to ICE was 88%, and the 5-year event-free survival for those transplanted was 68%. These factors predicted outcome: B symptoms, extranodal disease, and complete response less than 1 year. Finally, we have recently studied paclitaxel in combination with topotecan for relapsed and refractory aggressive lymphomas. These and newer combinations should be further developed to treat patients in relapse of aggressive lymphomas.

Keywords Ifosfamide · Aggressive lymphoma · Relapse therapy · Stem cell rescue

Introduction

Although patients with lymphomas of aggressive histology are regarded as having curable malignancies, only 40–50% are expected to be alive 5 years after treatment with CHOP chemotherapy. In the randomized United States Intergroup trial, patients who received Pro-MACE-CytaBOM, MACOP-B, and M-BACOD had results similar to those who received CHOP, although they generally had more toxicity and the combinations were more expensive than CHOP [1]. Therefore, although CHOP may not be an optimal regimen, it became the standard of care for patients with aggressive lymphomas.

Identification of the risk of relapse

Shipp et al. have described five adverse prognostic features in the International Prognostic Factors Index Project (IPI), which has been used to predict those patients at high risk for relapse following treatment with standard regimens. This index, which can be remembered by the mnemonic "APELS", can reliably predict which patients have a poor chance of surviving their disease [2], and includes age 60 years or greater, WHO performance status of 2 or more, two or more extranodal sites, elevated serum LDH, and stage III or IV disease. The Southwest Oncology Group treated patients with stage I and II aggressive lymphomas with three cycles of CHOP followed by involved field radiation therapy or eight cycles of CHOP. Using a "stage-modified" IPI system which includes age, LDH, and stage, this group defined three different populations of patients with varying prognoses [3]. In this series, only those with stage I disease who were under the age of 60 years and had a low serum LDH had a survival rate above 80%, representing only a small proportion of patients with early-stage disease [4]. Therefore, the relapse rates for patients with stage I disease with adverse prognostic features and all of those with stage II disease who receive one of these two therapies remain high, necessitating the need for better programs.

At M.D. Anderson Cancer Center, prognostic factors other than those in the IPI have also played an important role in predicting outcome, including size of tumor mass and serum beta$_2$-microglobulin, the latter of which was first reported as important in 1989 [5]. Using the Tumor Score, comprising prognostic factors remembered by the mnemonic "BuBBLS" (bulky disease $\geq$7 cm, B symptoms, beta$_2$-microglobulin $>10\%$ above normal, LDH $>50\%$ above normal, stage III or IV disease), patients with up to two factors have an 80% survival rate at 5 years compared to less than 20% for

patients with three or more factors [6]. Future studies to treat patients with aggressive histology lymphomas should include serum beta$_2$-microglobulin and other biologic factors to determine the benefit of these programs. Besides these pretreatment factors, there are other ways to predict which patients have a high risk of relapse. For example, investigators have reported that the gallium or PET scan can predict outcomes of patients with aggressive histology lymphomas [7, 8]. Spaepen et al. have described the results for 93 patients who received standard therapy: all patients with positive PET scans after treatment developed relapse, whereas only 11 of 67 patients with negative PET scans developed progressive disease [9]. Survival results in this study were not correlated with the results of CT scans. Clearly, treatment-related features should be taken into account in determining which patients will ultimately develop progressive disease.

In order to prevent disease progression, investigators have developed programs which intensify doses of the drugs in the standard CHOP regimen. Gregory et al. have described a dose-intensified CHOP program for lymphomas of aggressive histology, which involves the administration of standard doses every 2 weeks for six cycles [10]. Patients received growth factors in order to keep treatment on schedule and more than 70% of patients completed all six cycles on time, regardless of their age. At 3 years, 53% of patients over the age of 60 years were alive compared with 52% of those who were 60 years or younger, suggesting that dose intensification is possible for patients over the age of 60 years, and that the prognostic significance of age can be averted by administering full-dose therapy to such patients. Itoh et al. have also described a biweekly CHOP regimen randomized against a dose-intensified CHOP regimen in which 1000 mg/m^2 of cyclophosphamide and 70 mg/m^2 of doxorubicin were administered every 3 weeks [11]. For eligible patients in this study, 3-year progression-free survival rates were 42% for those receiving biweekly CHOP and 35% for those receiving dose-intensified CHOP, with overall survivals of 42% and 48%, respectively.

The results in these two studies appear similar to those reported with CHOP chemotherapy given at full doses every 3 weeks. However, more significant escalation of therapy doses could potentially reduce the risk of disease progression. Gordon et al. have reported results using 200% ProMACE-CytaBOM for diffuse aggressive lymphomas [12]. Time-to-treatment failure results at 5 years were 58% for those patients with IPI scores of 0–1 compared with 55% for those with IPI scores of 2–4, suggesting that intensification of therapy may improve results for those patients with IPI scores of 2–4, but not for those with low IPI scores. More recently, studying a larger number of patients than those reported by Gregory et al., Pfreundschuh et al. have reported that dose escalation of chemotherapy with CHOP given every 2 rather than 3 weeks can significantly improve response and freedom from progression rates for patients over the age of 60 years with high serum LDH, although the same strategy was not true for patients under 61 years [13, 14]. Instead, the addition of etoposide in modest doses to the CHOP regimen improved results for patients under 61 years. These two studies may prompt an intergroup trial in the United States which should be performed to verify these findings.

Standard-dose relapse therapy

EPOCH chemotherapy

Investigators at the National Cancer Institute (NCI) developed the EPOCH regimen as therapy for relapsed or refractory lymphomas [15, 16]. This regimen, in which drugs are administered as continuous infusions, was expected to be good relapse therapy for patients who had previously received standard-dose CHOP. However, most of the patients treated with this program developed progressive disease within 1 year from initiating therapy. Patients with lymphomas considered resistant to initial chemotherapy had a very low chance of remaining free of disease, with the best results achieved for patients who underwent high-dose therapy followed by stem cell rescue (SCT) following response to EPOCH.

Ifosfamide-containing regimens at M.D. Anderson Cancer Center

At our center, we have evaluated ifosfamide and etoposide combinations for more than 20 years in both standard-dose and high-dose therapy programs prior to SCT [17]. Using a standard-dose program, MINE-ESHAP, in the therapy of 153 patients, we found at 5 years that 15% were alive, and only 10% were free of disease [18]. Adverse prognostic factors for time to relapse for patients treated with MINE-ESHAP included high tumor burden, high serum LDH levels, and high serum beta$_2$-microglobulin levels. Survival rates were also strongly associated with the tumor score value achieved by adding these factors. By 2 years, 8 of 20 patients had developed progressive disease with a tumor score of 0, compared with 18 of 22 with 1, 13 of 18 with 2, and all 14 progressing who had three adverse tumor score features (score 3).

Newer drugs also appear to produce good responses in patients with relapsed lymphomas. These include paclitaxel and topotecan, which have produced response rates of 15% and 12%, respectively, in patients with primary refractory disease and 50% and 43%, respectively, in patients who developed relapse following response to initial therapy [19, 20]. In combination, these drugs appear to be additive, and have produced overall response rates of 31% in patients with primary refractory disease and 65% in relapse from complete response [21]. Corresponding complete response rates were 6%

and 18%. When rituximab was added to this combination, overall response and complete response rates were 55% and 25%, respectively, for patients with refractory and 80% and 60% for those with relapsed disease, respectively [22].

Gemcitabine may also be an important drug in the management of relapsed lymphomas, and although it has been tested in multiple studies as a single agent, and has recently been approved for therapy in relapsed lymphomas in the United States, the best method of administration of this drug has yet to be determined [23, 24, 25]. Standard doses range from 750 to 1250 mg/m^2, given weekly for as many as 3 weeks in a row, with cycles repeated every 28 days. Complete response rates have ranged from 0% to 14%, with overall response rates from 5% to 59%. Investigators have combined this drug with vinorelbine in the treatment of patients with relapsed lymphomas [26]. Liposomal encapsulation of drugs has also been recently considered a potentially more effective method of delivering the drugs. The use of liposomal vincristine (2 mg/m^2 at full doses every 2 weeks) has been reported in the treatment of 68 patients with relapsed or refractory lymphomas [27]. In this study, the serum beta$_2$-microglobulin was high in 55%, and the LDH high in 45%, with an age range from 19 to 86 years. Responses occurred in all histologies, but 17 of 38 patients (45%) with aggressive lymphomas had a response. Complete remissions also occurred in this latter group suggesting that this might be an important drug to incorporate as initial treatment of patients with aggressive histology lymphomas. Trials are ongoing at M.D. Anderson Cancer Center to evaluate the efficacy and patient's tolerance of this drug in combination with cyclophosphamide, doxorubicin, and prednisone.

Rituximab for relapsed lymphomas

Single-agent rituximab may well be valuable for indolent histologies, but half of the patients with intermediate-grade lymphomas who receive this drug will develop disease progression by 60–90 days, and most have had progression at a year of follow-up [28]. However, in combination with chemotherapy, rituximab appears to increase response rates in patients with chemotherapy-naive disease [29]. In the study reported by Coiffier et al., rituximab-CHOP proved to be better than CHOP alone for previously untreated diffuse large-cell lymphoma [30, 31]. This group treated 400 patients over the age 60 years, 60% of whom had an IPI of 2 or 3. Other adverse prognostic factors included an elevated serum LDH level in 65%, stage IV disease in 63%, and a performance status of 2 or more in 19%. Nonetheless, rituximab-CHOP induced complete response in 76% compared with only 60% obtained with CHOP alone ($P = 0.004$); there were also significant differences between event-free survival rates at 1 year (69% versus 49%, $P = 0.0005$) and overall survival rates (83% versus 63%, $P < 0.01$).

At the NCI, rituximab was combined with EPOCH as therapy for 23 patients with previously untreated diffuse large-cell lymphoma, and the results compared with those in similar patients who had received EPOCH alone [32]. Overexpression of BCL-2, a protein which prevents apoptosis and confers chemotherapy resistance on lymphoma cells, was an adverse prognostic factor in patients who were treated with EPOCH, but was not in those who had received rituximab-EPOCH. Progression-free survival results at 1 year for those receiving EPOCH whose tumor cells expressed BCL-2 were only 56% compared with 82% for those whose tumors had low expression of BCL-2. However, when this group were given rituximab-EPOCH, the results were 87% and 78%, respectively.

In the treatment of patients with relapsed disease, when we combined rituximab with paclitaxel and topotecan, the complete response rate as well as the overall response rate improved. This was evident in the therapy not only of patients with relapsed lymphomas after initial complete response, but also in patients with chemotherapy-refractory disease. Therefore, in new studies, it may now be difficult to design programs which do not include rituximab for aggressive lymphomas. The United States Intergroup trial randomizes treatment with CHOP versus CHOP and high-dose therapy for previously untreated patients less than 66 years old with intermediate/high or high IPI scores and does not include rituximab. Enrollment on this study continues, but investigators have considered adding rituximab to this program. However, the same group has completed a study of patients over the age of 65 years randomized to treatment with CHOP-rituximab or CHOP, followed by a second randomization to rituximab maintenance or no therapy. The results of this study may or may not corroborate the findings of the European trial.

Ifosfamide and high-dose therapy followed by stem cell rescue for relapsed lymphomas

The results of the PARMA trial have demonstrated that patients who undergo high-dose therapy followed by SCT after an adequate response to DHAP chemotherapy (dexamethasone, cytarabine, platinol) have better failure-free survival (FFS) and overall survival (OS) rates than patients who receive only DHAP [33]. However, participation in the PARMA trial was limited to patients with disease in relapse from complete response following anthracycline regimens without a history of bone marrow involvement. Only patients responding to second-line therapy with DHAP were analyzed, comprising 58% of the population, and the investigators did not address the outcomes of enrolled patients on an intend-to-treat basis, nor the possible role of SCT as therapy for primary refractory disease. After the publication of this trial, the only reported study of patients treated with randomized therapy for relapsed disease, investigators assumed that all regimens were equivalent

to DHAP in achieving remissions, and that any regimen which would induce a response in a patient with relapsed disease would have results as good as those for DHAP followed by SCT. However, there may be regimens that are better than DHAP in achieving remissions in patients with relapsed aggressive lymphomas.

In an attempt to improve results for patients who undergo SCT, at M.D. Anderson Cancer Center we designed a treatment program, known as High-Dose Ifosfamide/VP-16, in which 10 g/m^2 of ifosfamide and 900 mg/m^2 of etoposide were administered, both in one cycle as continuous infusions over 3 days, along with continuous infusion mesna [34]. Following this cycle, patients underwent pheresis of stem cells. In this program, patients who achieved complete response with this one cycle of therapy underwent BEAM and SCT. Patients in partial response underwent a second cycle of therapy with high-dose ifosfamide/mitoxantrone, followed by SCT if complete response was obtained and high doses of cyclophosphamide, etoposide, and platinol if partial response was obtained. This was followed by SCT, using half of the pheresis product obtained with ifosfamide-etoposide; a second cycle of high-dose therapy (tandem) transplant was then given, using BEAM and the remainder of the stem cells. On an intend-to-treat basis for 44 patients, the overall survival rate at 4 years was 52%, and the failure-free survival rate was 32%. The apheresis product was excellent with a median of 13.1 (4.1–148) $\times 10^6$ of CD34-positive cells per kilogram collected. The median number of CD34-positive cells per liter of blood processed was 44.8 (2.9–613.6) $\times 10^6$ cells [35].

Wilson et al., at the NCI, first described treatment with ifosfamide, etoposide, and carboplatin (ICE), using 2.5–4.0 g/m^2 ifosfamide, 100–300 mg/m^2 etoposide and 500–600 mg/m^2 carboplatin for patients with relapsed disease without bone marrow transplant [36]. Moskowitz et al. at the Memorial Sloan-Kettering Cancer Center have also described the use of this regimen, administering 5 g/m^2 of ifosfamide and mesna, given together as a 24-h infusion on day 2, the same dose as in MINE, etoposide 300 mg/m^2 in three divided doses on days 1, 2, and 3, and carboplatin in a dose which takes into account the AUC, based upon creatinine clearance, given on day 1 [37]. This dose was calculated using the formula: $\text{AUC} = 5 \times (\text{creatinine clearance} + 25)$. All patients also received G-CSF 5 μg/kg per dose on days 5–12, there were no dose reductions allowed, and the treatment was given every 14 days or when the absolute neutrophil count was greater than 1000/mm^3 and the platelet count greater than 50,000/mm^3. Patients accepted for this study had biopsy-proven refractory or relapsed disease, a cardiac ejection fraction and DLCO of more than 50%, and a creatinine clearance of more than 60ml/min. Patients over the age of 60 years also received this therapy as long as their Karnofsky performance status was more than 70 and they had less than two extranodal sites of disease.

All patients on the ICE program received three cycles of ICE chemotherapy, with peripheral blood stem cells collected after cycle 3. If a partial response or complete response was obtained, involved field, accelerated fractionation radiation therapy was administered followed by high-dose chemotherapy and PSCT. Patients less than 60 years of age also received total body irradiation. Only patients achieving a complete or partial response were eligible for transplant, although, in this study, some patients who had only minor response or stable disease also underwent high-dose therapy followed by SCT. All patients were eligible for analysis of results, regardless of whether a SCT was administered.

The overall response rate to ICE for aggressive non-Hodgkin's lymphomas was 71.4%, 83% for patients with relapsed disease and 50% for patients with primary refractory disease. A median of 8.4×10^6 CD34-positive cells per kilogram were collected, and patients experienced minimal extramedullary toxicity. The overall survival for all patients enrolled on this study on an intend-to-treat basis was 38%, and for those undergoing high-dose therapy followed by SCT, it was 48%. There was a difference in overall survival rates according to type of response: only 14 of the 39 (36%) achieving a complete response with ICE died following all therapy compared to 46 of the 69 (67%) achieving a partial response, and 46 of the 55 (84%) who failed ICE. By multivariate analysis, advanced stage, high LDH, poor Karnofsky performance status, and refractory disease prior to ICE were adverse prognostic factors. Features which were not significantly important in predicting event-free survival rates were age, stage at relapse, number of extranodal sites, histology, and presence of bone marrow involvement. By the age-adjusted IPI, the results were significantly affected by the number of adverse features: at 5 years approximately 70% of the patients with an IPI of 0 were projected to be alive, compared with 53% of those with one adverse feature, and 25% of those with two, and 12% of those with three at 40 months ($P < 0.0001$).

More recently, ICE has been used as part of initial therapy for 39 patients at Memorial Sloan-Kettering Cancer Center. Of the 39 patients, 35 had further response to ICE after achieving a response to initial CHOP therapy. All patients on this study had aggressive lymphomas, and 25 received doxorubicin-vincristine induction therapy and 14 received four doses of accelerated CHOP therapy. This study continues to accrue patients. Rituximab has been added to the ICE program for relapsed disease. Primary endpoints include complete response rate determined by CT and PET scans, number of CD34-positive cells per kilogram collected, and toxicity. To date, 23 patients have been enrolled and of the 20 evaluable, 17 (85%) have had a response, ten of which were complete and seven of which were partial, and 14 have completed SCT of which 9 are event-free. There has been one case each of cardiac ischemia, occurring in a 71-year-old male with coronary artery disease, and hemorrhagic cystitis. Peripheral blood stem cells were collected from 19 patients: a median of 6.6×10^6 CD34-positive cells/kg were collected. Three

patients failed to have mobilization, defined as less than 2×10^6 cells/kg collected. Studies with RICE continue at this institution, and all results will be analyzed on an intend-to-treat basis.

ICE and autologous stem cell transplant for relapsed Hodgkin's disease

Investigators have made certain assumptions regarding relapsed Hodgkin's disease and SCT: (1) multiple components appear to affect the success of SCT, but patients with disease refractory to relapse therapy should not undergo SCT; (2) patients with marrow involvement are generally excluded for fear that Hodgkin's cells might contaminate the stem cell product; (3) SCT is assumed to be better therapy than standard-dose therapy for relapsed disease, although no modern, randomized study has been attempted.

At Memorial Sloan-Kettering Cancer Center, investigators have administered ICE followed by SCT to 65 patients with relapsed or refractory Hodgkin's disease, refractory being defined as development of progressive disease while on initial therapy [38]. On an intend-to-treat basis, and with a median follow-up of 48 months, the 5-year overall survival was projected at 72%, with an event-free survival of 59%. By multivariate analysis for event-free survival, adverse prognostic factors included presence of extranodal involvement, B symptoms before ICE was administered, and the presence of refractory disease. Using these factors, the investigators developed a model which defined three different groups of patients: those with zero or one adverse factor had an 82% chance of being event-free at 5 years, whereas only 23% of those with two adverse features were free of disease at 48 months, and all patients developed progressive disease when they had three adverse features.

Based on their experience with ICE, investigators at Memorial Sloan-Kettering have designed a new study which treats patients according to their prognostic factor group. Group 1, which includes patients with zero or one factor, and comprises 65% of the patient population, receives ICE with no change in the high-dose therapy regimen. Of 31 patients so treated, 16 had a complete response to ICE and 12 had a partial response. Of the 31 patients, 24 (77%) are event-free post-transplant. Patients in group 2, with two adverse factors, represent 25% of the population. Of these patients, 80% responded to ICE in earlier studies, but most responses were partial. In the new study, doses of ICE are escalated in cycle two to 10 g/m^2 of ifosfamide and 600 mg/m^2 of etoposide, and the BCNU dose in BEAC is increased to 360 mg/m^2, with doses of cyclophosphamide and etoposide being increased to maximally tolerated doses. For 22 patients, 17 have had a response, with 3 complete responses and 14 partial responses, and 11 (50%) are event-free post-transplant. In group 3, representing 15% of the population, 50% of the patients had a partial response to ICE in the original study. These patients undergo double autologous SCT or allogenic SCT if a matched donor is available, with 4.5 g/m^2 of cyclophosphamide used for mobilization. Of nine patients treated, only two have completed therapy and are free of disease.

Future directions

Investigators have developed simple, reliable models on which to base therapy for patients with previously untreated aggressive lymphomas and Hodgkin's disease. Selection of therapy for patients with "good-risk" disease, especially those with diffuse large B-cell lymphomas, should probably include CHOP, although the use of radiotherapy for all patients has remained controversial. Patients with previously untreated advanced "poor-risk" disease, who represent more than 60% of the patient population in Europe and the United States, should undergo investigational programs designed to improve results. For patients with relapsed or refractory disease, ifosfamide-based combinations are efficient mobilizers of stem cells prior to high-dose therapy followed by SCT. These regimens are also tolerable and effective at obtaining cytoreduction, even for those who may not be eligible for SCT at the time of relapse. Response to ifosfamide-based regimens also can predict ultimate results for those patients who may ultimately undergo SCT, and have become a standard of care at many centers. Newer drugs and combinations, including dose escalations and monoclonal antibodies, should be incorporated into these and newer therapies for patients at high risk of relapse.

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