Total-Body Irradiation in the Conditioning Regimens for Autologous Stem Cell Transplantation in Lymphoproliferative Diseases

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Key Words. Total body irradiation · Autologous stem cell transplantation · Lymphoproliferative disease

ABSTRACT

We review the rationale for, and the results of, clinical trials on chemoradiotherapy-based pretransplant regimens for non-Hodgkin’s lymphomas, Hodgkin’s disease and multiple myeloma. What clearly emerges from this review is the lack of any conclusive evidence that total-body irradiation (TBI)-containing regimens are better than chemotherapy alone in diseases which are considered to be radiosensitive. Due to the variety of pretransplant regimens adopted, the relatively low number of patients enrolled in each trial, and the lack of randomized studies, no one conditioning scheme, with or without TBI, could be identified as superior to another. Only randomized clinical studies will indicate whether TBI-containing regimens are superior to chemotherapy-only regimens and whether TBI and/or involved field radiation therapy have a place in autologous stem cell transplantation programs for lymphoproliferative disorders. And finally, the best TBI dose, schedule, and technique should be defined.

INTRODUCTION

High-dose chemotherapy (HDCT) followed by autologous hematopoietic progenitor cell support is effective treatment for patients with hematopoietic malignancies [1, 2], solid tumors [3, 4], and autoimmune diseases [5, 6].

The rationale for using HDCT to overcome drug resistance stems from the dose-response curves of chemosensitive tumors. The safety of the HDCT can be improved by accelerating marrow recovery from near myeloablative or myeloablative treatment with hematopoietic stem cell rescue.

The standard source of repopulating hematopoietic stem cells was bone marrow (BM) aspirated from the iliac bones, but peripheral blood stem cells (PBSCs) are currently replacing marrow [7, 8] because A) hematopoietic recovery is faster after PBSC than after BM support [9, 10]; B) stable hematological reconstitution using PBSCs as rescue has been almost definitively established, and the fear of no long-term hematopoietic reconstitution has been put to flight [11, 12]; C) PBSC rescue shortens hospital stays and reduces transfusion requirements and antibiotic usage [7, 8], and finally, D) multiple leukapheresis procedures are tolerated better than BM harvest [13].

Choosing the proper HDCT scheme is crucial. Over the past 15 years, preparative regimens have been based on chemotherapy alone or on a combination of chemotherapeutic and radiotherapy. High-dose pretransplant chemotherapy regimens include one or more alkylating agents, etoposide, and other drugs such as cytarabine, carmustine, and melphalan (MEL), or platinum. Whether chemotherapy alone or in combination with radiotherapy is best remains to be established.

The results of pretransplant conditioning regimens based only on chemotherapy have been extensively reviewed elsewhere [14, 15].

TOTAL-BODY IRRADIATION IN PRETRANSPLANT REGIMENS

Total-body irradiation (TBI) is commonly used in conditioning regimens before bone marrow transplantation (BMT). In pretransplant regimens for allogeneic BMT, TBI is used to obtain immuno- and myelosuppression and
to create space in the marrow to allow engraftment of transplanted cells.

TBI is not always administered before autologous stem cell transplantation (ASCT) when immunosuppression is not required, despite its antineoplastic action. HDCT alone is often preferred, and radiotherapy is employed in limited fields (such as total nodal irradiation or involved field) in order to reduce toxicity.

The biological and clinical bases for TBI in leukemias and lymphomas have been reviewed extensively elsewhere [16].

TBI added to chemotherapy before ASCT provides the following advantages: A) there is no cross-resistance with chemotherapeutic agents; B) a homogeneous dose of irradiation is administered to the body; C) the dose distribution may be tailored by shields on the more sensitive body areas or by boosts in more resistant areas, and D) there is no sanctuary site sparing [17].

TBI can be administered in a single dose (STBI) or in fractionated (one fraction a day for more days) or hyperfractionated (two or three fractions a day for more days) schemes. TBI was originally given in a single dose. Later experimental data showed that leukemia and lymphoma cells, like normal lymphocytes, have a narrow shoulder or no shoulder on the radiation survival curve, which indicates their low capacity for repairing sublethal damage [18-21]. Consequently, variations in dose intensity (dose rate) or use of fractionated schemes do not modify the antineoplastic effect of any given dose. In order to decrease toxicity without influencing the antineoplastic activity, both an STBI at low-dose rate and fractionated or hyperfractionated schemes have been proposed [18-22]. STBI at a low dose rate takes a very long time, so fractionated schemes have become more widespread.

Transplant-related morbidity and mortality can also be decreased by using shields to reduce the dose to the lungs, the major dose-limiting organ. In some centers, the ribs are then boosted with electrons to compensate for the lower dose given to the area under the shields [23].

More recently, some studies have observed a normal cell-like shoulder on radiation survival curves in some acute leukemia, non-Hodgkin’s lymphoma, and myeloma cells [24-27], indicating a capacity for repairing the sublethal damage. When an effective dose is delivered in a fractionated scheme, fewer malignant cells are killed than with a single dose. Consequently, modification of currently used TBI regimens may be required to lower the probability of relapse.

Several TBI schemes have indeed been designed, but despite different doses, dose rates, and fractionations, the best schedule still remains to be defined.

Many techniques for TBI have been described with the aim of achieving a uniform dose distribution to the entire body with a variation of ±10% in the dose given to the prescription point. Nonhomogeneous distribution may affect disease control as well as complications and side effects.

### ASCT for Low-Grade Non-Hodgkin’s Lymphomas

With standard chemotherapy, the median survival of patients affected by advanced-stage, low-grade non-Hodgkin’s lymphomas (NHLs) is 7-10 years [28]. Despite a high complete remission rate, a continuous pattern of relapse is seen, and there is little evidence that patients can be cured. Transformation of low-grade lymphomas into intermediate- or high-grade malignancies worsens prognosis even more. Consequently, innovative therapy for these patients continues to be explored.

Studies in the 1980s and the early 1990s on high-dose therapy followed by autologous BMT in patients with follicular low-grade NHL in first or subsequent relapses, partial remission (PR), or second or subsequent remissions showed a complete remission (CR) rate ranging from 40% to 88%, a disease-free survival (DFS) rate between 18% and 60%, and an overall survival (OS) between 37% and 83%, with a median follow-up of two to four years [29-35] (Table 1). On the basis of these early studies, predictive factors for OS and DFS have been identified as the number of chemotherapy regimens before transplantation, pretransplant disease status, chemoresistant disease, and elevated serum lactic dehydrogenase (LDH) levels [30, 31, 33, 35, 36]. Transformed follicular lymphomas are associated with poor prognosis in some, but not all, studies [29, 34, 37, 38].

These promising results encouraged clinical trials including autologous stem cell transplantation (ASCT) as initial therapy after standard induction chemotherapy [39-41]. At two to five years post-transplant, event-free survival (EFS) is 63%-76%, and the incidence of relapse is 21%-55%. However, few patients have been treated, and the follow-ups are not long enough to assess the efficacy of this procedure in patients in first remission.

The rationale for using TBI in high-dose therapy protocols for low-grade NHL is that the disease is highly sensitive to radiotherapy. Studies in patients at stages I and II have reported a high percentage of cures [42]. On the other hand, low-dose TBI in patients with advanced-stage disease provided a 74%-84% clinical response rate, which was, however, followed by a very high incidence of relapse [43, 44].

TBI can be given in a single dose but is usually administered in a hyperfractionated scheme of 2 Gy twice a day for three days until a total dose of 12 Gy is reached [29-31, 34, 35, 41]. Higher doses, up to 13.2 and 14.4 Gy, have been employed [33, 40]. Cyclophosphamide (Cy) and etoposide are most commonly combined with TBI (Table 1).

The Perugia BMT Unit used a high-dose therapy scheme based on 8 Gy STBI and 12 mg/Kg thiotepa (TT). STBI was
delivered at a medium dose rate ranging from 18.8 to 8.00 cGy/min/midplane (median 10.11). The dose to the lungs was reduced from 7.5 to 6 Gy. Thirty patients were treated. The five-year actuarial EFS was 64.3% ± 9.2%, and the probability of relapse at five years was 25.5% ± 9.1% at a median follow-up of surviving patients of 41 months (range 11-72).

There were four deaths due to toxicity, two (6.0%) within 100 days of transplantation due to septic shock and interstitial pneumonia from cytomegalovirus (CMV). The two (7%) cases of chronic lethal toxicity occurring in patients in CR were due to interstitial pneumonia and hepatitis B [45]. With the aim of reducing relapses, we recently replaced TT with fludarabine, which is known to be extremely effective in chronic lymphoproliferative diseases. So far, 16 patients have been treated, and although the regimen was well tolerated, the main drawback was the delayed immunological recovery. This was responsible for life-threatening infections, which were fatal in three cases (19%). The median follow-up is too short to define the impact of fludarabine on the EFS [46].

Acute lethal toxicity after ASCT for low-grade NHL is about 5%, while the total incidence of toxic deaths, whether acute or chronic, ranges from 4% to 12%. Infections, and less often, hemorrhage, are the most frequent causes of treatment-related mortality (TRM).

Late complications include the minor ones (cataract, hypothyroidism, renal impairment) and the major ones (myelodysplasia [MDS] and/or acute myeloid leukemia [AML]). The actuarial risk at five to six years has been reported to range from 14.5% ± 11.6% to 18% ± 9% [47-49]. The most important predictive factors for the development of MDS/AML in the series reported by Stone et al., with all patients receiving TBI, are radiotherapy to the pelvis and the interval between first treatment and ASCT [49]. Darrington et al. showed a higher risk of MDS/AML in patients aged 40 or more at the time of transplant who received TBI [48].

No definitive conclusions on the best conditioning regimens can be drawn from the results cited so far. Although TBI is widely used in pretransplant schedules, similar results in terms of OS, relapse-free survival (RFS), progression-free survival (PFS), or freedom from survival (FFS) have been obtained with regimens containing chemotherapy alone [32, 34, 36]. However, it should be noted that results are from retrospective analyses, that the number of patients is too small to have statistical significance, and that no study was designed to ascertain the best conditioning scheme. However, Darrington et al. [48] reported a better FFS when the conditioning regimen employed TBI.

ASCT FOR INTERMEDIATE/HIGH-GRADE NON-HODGKIN’S LYMPHOMAS

Under 50% of patients with aggressive NHL are cured with standard chemotherapy regimens [50], and few patients who relapse are curable with conventional doses of chemotherapy or radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>n Patients</th>
<th>Pretransplant regimen</th>
<th>Early TRM pts</th>
<th>OS (%)</th>
<th>EFS (%)</th>
<th>DFS (%)</th>
<th>Relapse n pts</th>
<th>Median follow-up</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Freedman et al. [29]</td>
<td>51</td>
<td>Cy-TBI</td>
<td>1.96%</td>
<td></td>
<td>47%</td>
<td>18</td>
<td></td>
<td></td>
<td>DFS actuarial at 4 years</td>
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<tr>
<td>Colombat et al. [32]</td>
<td>42</td>
<td>CT alone* 22 pts TBI-Cy + other drugs 20 pts</td>
<td>7.14%</td>
<td>83%</td>
<td>58%</td>
<td>14</td>
<td>43 months</td>
<td>Actuarial OS, EFS RFS 66%</td>
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<tr>
<td>Cervantes et al. [33]</td>
<td>34</td>
<td>Cy-TBI</td>
<td>11.76%</td>
<td>37%</td>
<td></td>
<td>18%</td>
<td>75%</td>
<td>40 months</td>
<td>OS at 5 years, DFS and probability of relapse at 2 years</td>
</tr>
<tr>
<td>Rohatiner et al. [31]</td>
<td>64</td>
<td>Cy-TBI</td>
<td>4.69%</td>
<td>69%</td>
<td></td>
<td></td>
<td>24</td>
<td>3.5 years</td>
<td></td>
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<tr>
<td>Rohatiner et al. [30]</td>
<td>121</td>
<td>Cy-TBI</td>
<td>3.3%</td>
<td>69%</td>
<td></td>
<td></td>
<td>43</td>
<td>3.5 years</td>
<td></td>
</tr>
<tr>
<td>Bastion et al. [34]</td>
<td>60</td>
<td>Cy2VP16+TBI 46 pts CT alone 14 pts</td>
<td>8.33%</td>
<td>88%</td>
<td></td>
<td>53%</td>
<td>21 months</td>
<td>OS and DFS actuarial at 2 years</td>
<td></td>
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<tr>
<td>Bierman et al. [35]</td>
<td>100</td>
<td>Cy-TBI 75 pts CT alone 23 pts* Cy+TBI 2 pts</td>
<td>6%</td>
<td>65%</td>
<td></td>
<td>44%</td>
<td>2.6 years</td>
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</tbody>
</table>

TRM = treatment-related mortality.
* BEAM = 17 patients; BEAC = 1 patient; CBV = 3 patients; TACC = 1 patient.
** BEAC = 21 patients; CBV = 1 patient; Carmustine, Etoposide, Cyclophosphamide, Hydroxyuria = 1 patient.
Cy = cyclophosphamide; TBI = total-body irradiation; CT = chemotherapy; VP16 = etoposide; BEAM = carmustine, etoposide, cytarabine, melphalan; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; CBV = cyclophosphamide, carmustine, etoposide; TACC = thioguanine, cytarabine, lomustine, cyclophosphamide.
Myeloablative doses of chemotherapy with or without TBI and BM or PBSC transplantation have been used to treat patients with aggressive NHL in relapse or with primary refractory disease [51-64]. At a median follow-up of two to five years, OS ranges from 20% to 54%, DFS from 45% to 57%, and EFS from 11% to 53%. The results of some of these studies are reported in Table 2.

Predictive factors for DFS and OS are tumor size, chemosensitive disease, and status of disease at transplantation [61, 63, 65-67].

High-dose consolidation therapy with BM or PBSC support is currently being evaluated as initial therapy or in patients in first CR or PR with poor prognostic factors [68-78]. The results of some trials are reported in Table 3. Actuarial OS

| Table 2. Results of ASCT in relapsed or refractory intermediate/high-grade NHL |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Author                                         | n Patients    | Pretransplant regimen | Early TRM pts | OS (%) | EFS (%) | DFS (%) | Relapse n pts | Median follow-up | Comments |
| Takvorian et al. [51]                          | 49            | Cy-TBI                 | 4.08%          | 65%    |         |         | 13           | >11 months        | 16 pts low-grade/DFS actuarial |
| Petersen et al. [53]                           | 101           | Various with or without TBI | 20.8%         | 20%    | 11%   |         | 62           | 26 months        | OS-EFS-5 years actuarial |
| Phillips et al. [54]                           | 54            | Cy-TBI                 | 20.37%         |        |       |         | 27           | 5.3 years        | 9 low-grade DFS actuarial |
| Gulati et al. [55]                             | 44            | TBI-VP16-Cy            | 34.09%         | 57%    |       |         | 3            | 42 months        | DFS actuarial |
| Verdonck et al. [57]                           | 17            | Cy-TBI                 | 5.88%          | 62%    |       |         | 2 (1 non-responder) | 41 months        | |
| Horrow et al. [58]                             | 72            | TBI-VP16-Cy            | 11.11%         | 55%    | 53%   |         | 21           | 2.5 years        | 10 low-grade 3-year actuarial |
| Rapoport et al. [63]                           | 136           | BEAC or TBI+Cy ± other drugs | 4.41%         | 34%    |       |         | 66           | 3 years          | EFS actuarial at 5 years |
| Stiff et al. [64]                               | 94            | Cy-VP16-TBI or BCV    | 10.64%         | 43%    |       |         | 47           | OS actuarial at 3 years PFS 33% at 3 years |

TRM = treatment-related mortality.

Cy = cyclophosphamide; TBI = total-body irradiation; VP16 = etoposide; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; BCV = carmustine, cyclophosphamide, etoposide; FFP = freedom from progression.

| Table 3. Results of ASCT as initial therapy in intermediate/high-grade NHL |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Author                                         | n Patients    | Pretransplant regimen | Early TRM pts | OS (%) | EFS (%) | DFS (%) | Relapse n pts | Median follow-up | Comments |
| Freedman et al. [68]                           | 26            | Cy-TBI                 | 0%            | 84%    |         | 85%    | 19           | 32 months        | 5 years actuarial OS 5 years actuarial PFS 69.7% |
| Sweetenham et al. [69]                         | 118           | various with or without TBI | 3.39%         | 70%    |         |         | 19           | 45 months        | OS-EFS-DFS actuarial at 4 years* |
| Sweetenham et al. [70]                         | 70            | various with or without TBI | 2.86%         | 72%    |         |         | 9            | 23 months        | OS and EFS actuarial at 7 years PFS 84% |
| Verdonck et al. [71]                           | 34            | Cy-TBI                 | 5.88%         | 56%    | 41%   | 60%    | 7            | OS-EFS-DFS actuarial at 4 years* |
| Gianni et al. [74]                             | 48            | high-dose sequential chemotherapy with or without TBI | 16.67%        | 81%    | 76%   | 3 + 2 NR | 55 months | OS and DFS actuarial at 3 years |
| Nadeemanee et al. [77]                         | 52            | TBI-VP16-Cy            | 1.92%         | 84%    | 82%   |         | 6            | 44 months        | OS and DFS actuarial at 3 years |

TRM = treatment-related mortality.

*8 pts did not received ASCT but were considered in the results.

Cy = cyclophosphamide; TBI = total-body irradiation; VP16 = etoposide; NR = nonresponders; FFP = freedom from progression.
ranges from 56% to 81%, DFS from 59% to 85%, and EFS from 41% to 76% at a median follow-up of 31-55 months. However, great caution must be used in assessing these results, for several reasons: A) “high-risk” disease is defined on the basis of several different criteria; B) a selection bias may be present, as mean age tends to be relatively low; C) few patients are enrolled in each trial, and finally, D) results are compared with historical controls. Four of these trials [71, 72, 74, 76], two of which contained TBI in the pretransplant regimens [71, 74], were randomized and designed to compare conventional treatment with high-dose chemotherapy followed by ASCT. All conclusions are extremely divergent.

Analyzing the pretransplant regimens in greater depth shows that TBI is generally associated with Cy alone or with Cy and etoposide or cytarabine [51, 53-55, 57-59, 64, 68-70]. It is almost always administered in hyperfractionated schemes with different doses, with the single dose ranging from 1.2 to 2 Gy and the total dose ranging from 12 to 15.75 Gy. Only a few centers delivered STBI; Verdonck et al. gave 8 Gy at a dose rate of 16 cGy/min, with the dose to the lungs reduced to 7 or 6 Gy [57, 71]. In some other studies, STBI was employed only in a small number of patients, generally the first enrolled [51, 54, 77].

In many centers, TBI is not currently used in pretransplant regimens for aggressive NHL because of a concern for increased acute toxicity and possibly (although not clearly substantiated) a higher risk of MDS/AML toxicity. Others were concerned that it is impossible to reach the optimal dose for bulky eradication with TBI alone [54], although the addition of involved field boost may solve this concern.

One alternative to TBI is pre- or post-transplant involved field radiotherapy [56, 61, 63, 72-75, 78-80] to areas of symptomatic, bulky, or persistent disease, or to all previous sites of disease to consolidate a complete response. The rationale for involved field radiotherapy is the high incidence of relapse in sites of prior disease [51, 53, 61, 66, 68, 79]. Although involved field radiotherapy decreases the risk of local recurrence, it is not clear whether it improves outcome. In one of the few retrospective studies examining the contribution of involved field radiotherapy after autologous transplant for NHL, Fouillard et al. showed involved field radiotherapy increases EFS and OS in patients transplanted in first response [80]. Involved field radiation therapy has been given to patients submitted to TBI, but toxicity may be increased with the combination of TBI and involved field [53-55, 81].

### ASCT FOR HODGKIN’S DISEASE

ASCT has become a frequent salvage procedure for patients with a very poor prognosis, i.e., for whom projected survival is less than 20% at five years, those with refractory disease, those relapsing within 12 months of a CR, or those suffering a second relapse [14, 82]. Several studies showed that the overall response rate was between 80% and 86%, the CR rate between 46% and 80%, DFS between 25% and 62%, and EFS between 32% and 53%, with follow-ups ranging from 19 to 77 months [83-96] (Table 4). The efficacy of HDT in refractory relapsed Hodgkin’s disease was confirmed in a randomized trial comparing HDT (BEAM) with conventional-dose salvage chemotherapy (mini-BEAM). The actuarial three-year EFS (53% versus 10%, \( p = 0.0025 \)) and PFS (\( p = 0.005 \)) were significantly better in patients who received HDT [97].

Pretransplant prognostic factors include disease status, performance status and B symptoms at the time of

<table>
<thead>
<tr>
<th>Table 4. Results of ASCT in poor prognosis Hodgkin’s disease</th>
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<tr>
<td>Author</td>
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<tr>
<td>Phillips et al. [85]</td>
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<td>Gianni et al. [89]</td>
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<td>Horning et al. [91]</td>
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<td>Nademanee et al. [95]</td>
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<td>Anderson et al. [96]</td>
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TRM = treatment-related mortality.

Cy = cyclophosphamide; TBI = total-body irradiation; VP16 = etoposide; BCU = carmustine; CCNU = lomustine; Bu = busulfan; FFP = freedom from progression.
transplantation, the number of prior chemotherapy regimens, and response to rescue protocols before transplantation [95, 98-100].

Radiotherapy is given to patients undergoing ASCT for Hodgkin’s disease because it is the single most effective agent. In fact, with high-dose chemotherapy alone, the incidence of relapse is high in primary disease sites [85, 87, 94, 96, 101, 102].

Few centers employed TBI in pretransplant regimens. Always delivered in hyperfractionated schemes, the single dose ranged between 1.2 Gy and 2.5 Gy, and the total dose between 12 Gy and 14.4 Gy [85, 89, 91, 94, 96]. Since April 1987 in the John Hopkins Oncology Center, 3 Gy once a day have been delivered up to a total dose of 12 Gy [94]. Because of the high rate of pulmonary toxicity in patients previously irradiated on the mediastinum and doubts about the tumoricidal potential of the relatively low doses of radiation, use of TBI has been discouraged [85, 101, 103]. The drugs most commonly combined with TBI are Cy alone or Cy and etoposide.

Another strategy is high-dose chemoradiotherapy, i.e., rapid sequential administration of high doses of Cy, methotrexate, etoposide, and TBI plus MEL. The probability of EFS at six years was 78% in patients transplanted in relapse following initial complete response and 31% for refractory patients [89].

To reduce toxicity, Yahalom et al. designed a regimen employing 18 Gy total lymphoid irradiation (TLI) before etoposide and high-dose Cy followed by ASCT. The advantages of TLI are that it is possible to deliver doses above the TBI limits (which correspond to effective doses to lymph nodes) and selected extranodal sites of disease can be effectively irradiated. At a median follow-up of four years, 50% of patients are alive and disease-free, and the transplant-related toxicity has dropped from 24% to 5% [104-105].

As described for high grade NHL, radiotherapy can also be delivered as pre- or post-transplant involved field treatment, which unlike TBI or TLI, is suitable for most patients, even if they have been previously irradiated. Administering involved field radiotherapy before ASCT reduces the neoplastic burden, and patients with minimal disease have a better prognosis than patients with residual bulky disease. Another advantage is that recently engrafted cells are not exposed to myelosuppressive and potentially leukemogenic agents. The disadvantages are that during the interval between radiotherapy and ASCT, patients risk relapse in untreated sites, and the peritransplant morbidity is high [106]. Involved-field radiotherapy is reported to lower relapse rates [101, 107, 108] but does not appear to have an impact on survival.

### ASCT FOR MULTIPLE MYELOMA

MEL combined with prednisone has become the standard treatment for multiple myeloma (MM) over the last 30 years; it is associated with a median survival of two to three years. Although other chemotherapeutic combinations have sometimes provided better remission rates, they have not prolonged overall survival [109-111]. These disappointing results led to a search for alternatives, such as high-dose therapy followed by autologous BM [112-117] or PBSC transplantation [115, 118-122]. The efficacy of high-dose therapy was demonstrated in a randomized trial conducted by the Intergroupe Français du Myélome to compare conventional-dose chemotherapy and 140 mg/m² MEL plus TBI (8 Gy in four fractions administered in four days) followed by ASCT. The results showed that the CR rate was higher (22% versus 5%), and the EFS (28% versus 10%, p = 0.01) and OS (52% versus 12%, p = 0.03) were better after high-dose therapy [123].

Different pretransplant regimens have been assessed in patients with MM, the more common ones employing high-dose MEL, which is more efficacious than other alkylating agents, whether alone [112, 113, 116, 121, 124-128] or with TBI [114, 121, 126-128]. The rationale for using TBI is based on the high radiosensitivity of human clonogenic myeloma cells [27] and the known efficacy of radiotherapy in patients with MM.

Barlogie et al. first introduced TBI into the conditioning regimen in a small group of chemoresistant patients. Response rate was better than after MEL alone (72% versus 50%), although remission durations and survival times overlapped [129]. Since then, TBI has been used with extremely different schemes and doses, 10 Gy being the most common dose in STBI [118, 128] and 8-15 Gy in fractionated or hyperfractionated schedules [112, 113, 116, 118, 120, 124-126, 128]. At median follow-ups ranging from 12 to 35 months, the overall response rate is between 68% and 98%, the CR rate between 37% and 73%, and the OS between 43% and 88% (Table 5). The response rate, PFS, and OS tend to overlap with pretransplant regimens either with or without TBI [112-114, 116, 118, 121, 126-128].

No study has specifically assessed the role of TBI. The ongoing trial designed by the Intergroupe Français du Myélome will evaluate the role of TBI in the conditioning regimen. Patients aged 60 to 65 years are randomized to receive MEL 140 mg/m² plus TBI or MEL 200 mg/m². The results will perhaps provide a definitive statement on the efficacy of TBI in patients with MM. Unfortunately, many patients are ineligible for TBI because of previous radiotherapy, often to the spine.

Other major obstacles to TBI are: A) local disease control requires higher doses of radiotherapy than can be delivered during TBI [115], and B) TBI-related toxicity. To overcome
this last problem, the Seattle group used a modified TBI with lung and liver shields. In order to avoid underdosages to the ribs which are covered by the lung shields, electron boost was given [122].

More recently, the Arkansas team proposed a “total therapy” protocol [130, 131] to increase the response rate and obtain better EFS and OS in newly diagnosed MM patients [132]. After non-cross-resistant remission induction regimens, patients received a tandem transplant followed by interferon α maintenance therapy. In the first pretransplant regimen, 200 mg/m² MEL are given. In cases of sustained PR or CR, patients receive the same regimen followed by a second transplant after three to six months. In nonresponsive patients, the second conditioning regimen is MEL 140 mg/m² plus TBI or Cy. Results show an increase in the CR rate after the two high-dose therapy cycles. The contribution which TBI or Cy makes to disease control in nonresponding patients at the time of second autotransplant is difficult to assess. Although these are encouraging results, the treatment needs further evaluation. The ongoing randomized trial by the Intergroup Français du Myélome comparing a single with a double transplant in patients under 60 years of age may provide more conclusive evidence.

CONCLUSIONS

Unequivocal evidence that TBI-containing regimens are better than chemotherapy alone in cases of advanced-stage low-grade NHL did not emerge from this review. In our view, TBI-containing regimens are preferable, because this form of malignancy is particularly sensitive to radiotherapy. This opinion is shared by Darrington et al., who showed a better FFS in patients treated with TBI and chemotherapy.

In patients with high/intermediate-grade NHL, TBI-containing regimens offer no clear advantages over chemotherapy. Some authors reported a higher transplant-related mortality; CR rates overlap, and no data have reported conclusively that TBI significantly improves clinical outcomes. Furthermore, not all hospitals are equipped with a radiotherapy unit, and chemotherapy-based regimens may be easier to administer.

Hodgkin’s disease has long been recognized as extremely radiosensitive, but the high toxicity in pretreated patients reduced the use of TBI in conditioning regimens. This is why many centers include less extensive irradiation fields rather than TBI. This strategy reduces toxicity and at the same time provides an approach which is efficacious in disease control.

Even though the radiosensitivity of neoplastic plasma cells has long been recognized, the role of TBI in pretransplant regimens in patients with MM is much more difficult to establish because of the heterogeneity of the doses, the relatively low doses used in some studies, the relatively low number of patients, and the lack of randomized studies.

In conclusion, what clearly emerges from this review is the lack of any conclusive evidence that pretransplant TBI-containing regimens are better than chemotherapy alone in diseases which are considered to be radiosensitive. Acute and chronic treatment-related toxicity rates have been significantly reduced, prevalently through modifications in autologous transplant strategies, i.e., using PBSCs instead of BM and improvements in supportive care. On the other hand, the relapse rate has remained almost unchanged in the last 15 years. Thus, improvement in conditioning regimens, including the incorporation of TBI, has to be more seriously explored.

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Table 5. Results of ASCT in multiple myeloma

<table>
<thead>
<tr>
<th>Author</th>
<th>n Patients</th>
<th>Pretransplant regimen</th>
<th>Early TRM pts</th>
<th>Response rate</th>
<th>CR rate</th>
<th>OS</th>
<th>Median follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal et al. [113]</td>
<td>35</td>
<td>TBI-MEL</td>
<td>2.86%</td>
<td>83%</td>
<td>43%</td>
<td>81%</td>
<td>15.5 months</td>
<td>OS actuarial at 42 months; at 33 months PFS 55%</td>
</tr>
<tr>
<td>Anderson et al. [116]</td>
<td>26</td>
<td>MEL-TBI or Cy-TBI</td>
<td>3.85%</td>
<td>96%</td>
<td>42%</td>
<td>70%</td>
<td>24 months</td>
<td>PFS 40%; PFS-OS actuarial</td>
</tr>
<tr>
<td>Fermand et al. [118]</td>
<td>63</td>
<td>BCNU-VP14-MEL or Cy-TBI</td>
<td>11.11%</td>
<td>91%</td>
<td>19.6%</td>
<td>69%</td>
<td>OS after 3 years</td>
<td></td>
</tr>
<tr>
<td>Marit et al. [121]</td>
<td>73</td>
<td>MEL-TBI or Bu-MEL</td>
<td>1.37%</td>
<td>96%</td>
<td>47%</td>
<td>66%</td>
<td>27 months</td>
<td>OS actuarial at 3 years</td>
</tr>
<tr>
<td>Harousseau et al. [128]</td>
<td>133</td>
<td>Various with or without TBI</td>
<td>3.76%</td>
<td>83%</td>
<td>37%</td>
<td>43%</td>
<td>35 months</td>
<td>OS actuarial at 5 years; at 4 years RFS 35%</td>
</tr>
</tbody>
</table>

TRM = treatment-related mortality.
TBI = total-body irradiation; MEL = melphalan; MP = methylprednisone; Cy = cyclophosphamide; Bu = busulfan.
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83 Jagannath S, Dicke KA, Armitage JO et al. High-dose cyclophosphamide, carmustine, and etoposide and autologous


