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Malignant Lymphomas

High-dose therapy with autologous stem cell transplantation in first response in mantle cell lymphoma

We retrospectively investigated the outcome of 30 newly diagnosed patients with mantle cell lymphoma treated with high-dose therapy and autologous stem cell transplantation in first response. With a median follow-up of 55 months, the 5-year overall-survival is 62%, the 5-year progression-free-survival is 40% and no secondary malignancy has occurred.

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We performed a retrospective analysis of patients under 65 years of age diagnosed with mantle cell lymphoma (MCL) in our department between 1990 and 2003. Our therapeutic strategy for these patients always included autologous stem cell transplantation (ASCT) in first response. Thirty-five patients were diagnosed as having MCL in this period. However, five patients were excluded from the study: one because he received an allogeneic stem cell transplantation and four because they had progressive disease after initial chemotherapy.

The induction therapy consisted of three to four courses of increased CHOP-like or CHOP regimen. The DHAP or an ESHAP regimen was used to obtain a response before ASCT in patients with stable disease following the CHOP or CHOP-like regimen. Response was assessed by physical examination, hemogram and blood chemistry analysis, chest X-ray, thoracic, abdominal and pelvic computed tomography, and bone marrow biopsy if positive at diagnosis. The response was evaluated after the initial chemotherapy, 3 months after ASCT, twice a year for 5 years, and then yearly up to 10 years. Complete response was defined as the complete disappearance of lymphoma. Regression of at least 50% of all measurable disease was defined as a partial response. Minimal response and stable disease were defined as reductions of all measurable lesions of, respectively, 25% to 50% and 0% to 25%.

The patients' initial characteristics are listed in Table 1A and the characteristics of their transplants are summarized in Table 1B. The median follow-up is 55 months (range: 13-149 months). As shown in Figure 1A, the 5-year overall

Table 1A. Initial patient characteristics.

	n (%)
Age (years)	
Median	53
Range	40-63
International Prognostic Index	
Low-risk	10 (33)
Low-intermediate risk	13 (43)
High-intermediate risk	4 (14)
High-risk	2 (7)
Unknown	1 (3)
Sex	
Male	23 (77)
Female	7 (23)
Ann Arbor stage	
III	4 (14)
IV	26 (86)
B symptoms	
Present	8 (27)
Absent	19 (63)
Unknown	3 (10)
Performance status	
<2	30 (100)
≥2	0 (0)
Lactate dehydrogenases	
Normal level	17 (57)
Above normal	12 (40)
Unknown	1(3)
Dimension of the largest tumor mass	
≥10 cm	5 (17)
<10 cm	23 (77)
Unknown	2 (6)
Site of extra-nodal disease	
Bone marrow	23 (77)
Blood	15 (50)
Gastrointestinal tract	11 (37)
Liver	7 (23)
Lung	1 (3)
Extranodal sites	
0	4 (13)
1	14 (47)
2	6 (20)
3	6 (20)

Table 1B. Characteristics at transplantation.

	n (%)
Time from diagnosis to transplantation	
Median	5 months
Source of stem cells	
Peripheral blood	27 (90)
Bone marrow	3 (10)
Conditioning regimen	
TBI+Cy	23 (77)
BEAM	5 (17)
TBI+CBV	1 (3)
TBI+Mel	1 (3)
Post-transplant growth factors	
G-CSF	22 (72)
GM-CSF	4 (14)
None	4 (14)
Number of chemotherapy lines before transplantation	
1	23 (77)
2	6 (20)
3	1 (3)
Status at transplantation	
Complete response	5 (17)
Partial response	24 (80)
Minimal response	1 (3)
Response 90 days after transplant	
Complete response	26 (87)
Partial response	3 (10)
Progressive disease	1 (3)

TBI+Cy: total body irradiation of 12 Gy in 6 fractions over 3 days plus cyclophosphamide (60 mg/kg/day for 2 consecutive days); BEAM: BCNU: 300 mg/m² day 1; etoposide: 200 mg/m² days 2-5; aracytine: 400 mg/m² days 2-5 and melphalan: 140 mg/m² day 6; CBV: cyclophosphamide: 1500 mg/m² days 1-4; BCNU: 300 mg/m² day 1 and etoposide: 200 mg/m² days 2-4; Mel: melphalan 140 mg/m².

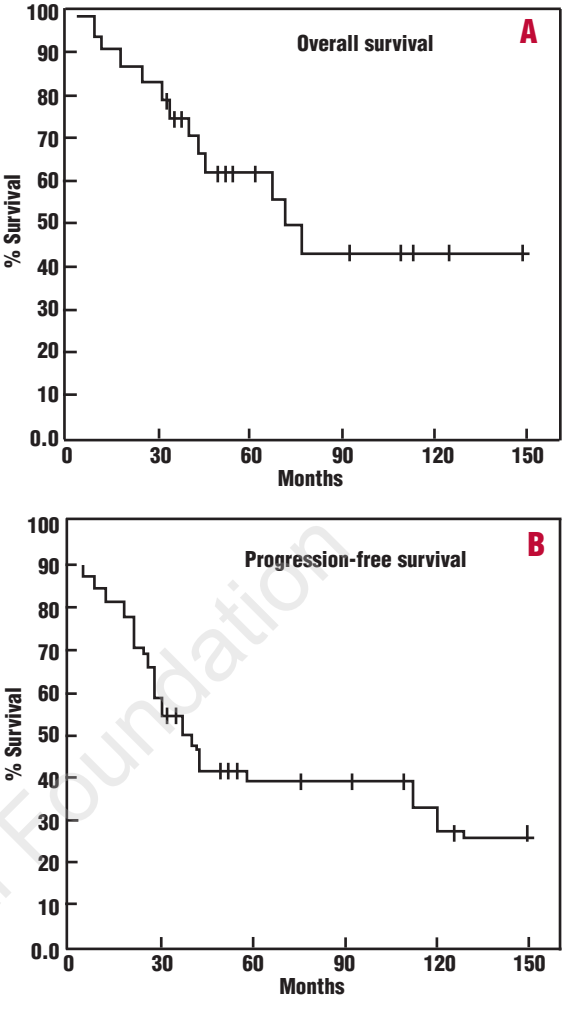

Figure 1. A. Overall survival of the studied population. **B.** Progression-free survival of the studied population.

Table 2. Extra-hematological toxicity of ASCT.

	n
Toxic death	0
Secondary malignancy	0
Herpes zoster infection	4
Localized basal cell skin carcinoma	2

survival is 62% and the median overall survival is 72 months. Thirteen patients have died at a median time of 34 months (range: 6-75 months): 11 from lymphoma and 2 from bacterial sepsis. As shown in Figure 1B, the 5-year progression free survival is 40% and the median progression-free survival is 37 months. Seventeen patients have relapsed or progressed at a median time of 22 months (range: 3-111 months). Among these, 13 relapsed from a complete remission at a median time of 22 months (range: 7-111 months). These 13 patients were treated with conventional chemotherapy (n=9) or allogeneic stem cell transplantation (n=4). Three patients in partial remission after ASCT progressed at 4, 10 and 26 months and were treated with conventional chemotherapy. One patient progressed immediately after transplantation and was treated with conventional chemotherapy. Among the 17 relapsing or progressing patients, 13 had died by the time of analysis. High-dose therapy was well tolerated without any toxic deaths during the 3 months following transplantation. The toxicity of the therapy is summarized in Table 2. With a long median follow-up of 55 months, our study shows that patients under 65 years of age responding to initial chemotherapy and subsequently autografted can achieve 5-year progression-free survival and overall survival of, respectively, 40% and 62%, with an acceptable toxicity profile. These results update our previous report on 17 MCL patients who showed 4-year disease-free and overall survivals of, respectively, 49% and 81%.[1] It must be emphasized that 15% of patients (5 out of 35) were not eligible for ASCT because of a poor response to initial chemotherapy. It is also noteworthy that 83% of patients received a conditioning regimen based on total body irradiation and that none developed a secondary malignancy. However, this finding should be viewed cautiously because of the limited size of our study and because a recent prospective study reported an actuarial

risk of 18.6% at 5 years in 86 follicular lymphoma patients autografted in first response.[2] In our study, 23 patients out of 35 (65%) responded to an initial anthracycline-based chemotherapy (CHOP or CHOP-like) while 7 patients needed salvage treatment with high doses of cytarabine before ASCT and 5 patients never obtained a response good enough for ASCT. This proportion of MCL patients responding to an anthracycline-based chemotherapy is consistent with other results reported in the literature.[3] Rituximab is likely to play an important role in association with anthracycline-based chemotherapy by effectively clearing blood and bone marrow lymphoma cells.[4] However, the observation that addition of rituximab to induction therapy does not translate into prolonged progression-free survival supports the role of using ASCT in first response.[5,6]

In a recent landmark study, Dreyling *et al*.[7] demonstrated that ASCT prolongs progression-free survival in MCL. They reported 3-year overall survival and progression-free survival rates of 83% and 54%, respectively. The corresponding 5-year rates in our study, dealing with a comparable population of patients, were 62% and 40%, respectively, thus confirming after an extended follow-up that ASCT in first response is an effective and safe treatment for MCL patients under 65 years of age.

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Stem Cell Transplantation

Development of functional *Haemophilus Influenzae* type b antibodies after vaccination of autologous stem cell transplant recipients

Sixteen autologous stem cell transplant recipients received three vaccinations with conjugated *haemophilus influenzae* type b vaccine. Quantitative and qualitative aspects of the antibody response were studied. The vaccination schedule resulted in high antibody response rates and functional maturation of antibodies, as measured by antibody avidity and phagocytosis-inducing capacity.

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Infections are a major source of morbidity in patients undergoing autologous stem cell transplantation and are frequently caused by encapsulated bacteria such as *Haemophilus influenzae* type b (*Hib*) and *Streptococcus pneumoniae*.[1,2] Therefore, vaccination of stem cell transplant recipients with *Hib* and pneumococcal vaccine has been recommended.[3,4] A response to vaccination is often quantitatively expressed as antibody titers, but determination of avidity and phagocytosis-inducing capacity of antibodies can provide important information regarding the functional activity of antibodies.[5,6] For instance, an increase in antibody avidity during the year following *Hib* vaccination with a concurrent decrease in antibody levels, has been described in children.[7] We conducted a prospective follow-up study to determine quantitative and qualitative aspects of the humoral immune response to multiple vaccinations with conjugated *H. influenzae* type b vaccine in 16 adult patients with non-Hodgkin's lymphoma (n=3) or multiple myeloma (n=13) who underwent autologous stem cell transplantation. Patients with multiple myeloma received high dose melphalan, whereas patients with non-Hodgkin's lymphoma received the BEAM regimen as conditioning therapy. At 6, 8 and 14 months after transplantation, patients were vaccinated with *Hib* (PRP-T vaccine: polyribosylribitolphosphate conjugated to tetanus toxoid). Serum samples were taken before vaccination and 3 weeks after each vaccination. For each patient, sera taken at all time points were analyzed simultaneously for all techniques. IgG antibody levels to *H. influenzae* were measured by ELISA as described previously.[8] An adequate antibody response was defined as a 4-fold or greater increase in antibody levels in addition to a minimal titer of 50 U/mL corresponding to 18.8 µg/mL, which is 50% of the titer in the reference serum. Avidity indices of IgG anti-*Hib* antibodies were measured by a modification of the sodium thiocyanate (NaSCN) elution method described by Pullen *et al*.[9] Antibody avidity can only reliably be determined in sera with a minimal optical density value of 1.0 at a 1:50 dilution, corresponding to a minimal *Hib* antibody concentration of 25 µg/mL. The relative