Autologous stem cell transplantation for mantle cell lymphoma – single centre experience

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Aim of the study: Mantle cell lymphoma (MCL) is a B-cell neoplasm showing resistance to conventional chemotherapy. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) may result in higher progression-free (PFS) and overall survival (OS) when used as a consolidation for younger and fit patients.

Material and methods: We retrospectively evaluated the results of ASCT for MCL. Patients were transplanted after achieving first or subsequent complete or partial response after conventional chemotherapy.

Results: Twenty patients (7 male and 13 female) at median age of 59 years (range 41–68) were included. 90% of transplanted patients had stage III/IV disease at diagnosis and low, intermediate and high MIPI scores occurred in 5, 9 and 6 patients respectively. Induction chemotherapy consisted of the R-CHOP regimen in all patients except one who received R-CVAD. The disease status at transplant was as follows: first complete response (n = 13); second complete response (n = 4) and partial response (n = 3). The conditioning regimen prior to ASCT consisted of CBV and BEAM for 18 and 2 patients, respectively. The transplant-related mortality was 0% at day 100. Median OS and PFS were 48 and 29.8 months, respectively. The estimated 5-year OS and PFS were found to be 52% and 35%, respectively. After median follow-up after ASCT of 36 months (range 11–73), 10 patients were alive with 8 remaining in complete remission (CR) whereas 2 relapsed and received salvage chemotherapy. Ten patients died from disease recurrence and subsequent chemoresistance.

Conclusions: ASCT as a consolidation for MCL patients is found to be an effective and safe procedure.

Key words: mantle cell lymphoma, autologous stem cell transplantation, results.

Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm characterized by monomorphic proliferation of small and medium-sized lymphoid cells expressing mature B-cell markers and IgM and/or IgD surface immunoglobulin. The t(11;14)(q13;q32) between IGH@ and cyclin D1 genes is thought to be the primary genetic event in the pathogenesis of MCL [1]. Mantle cell lymphoma is more frequently seen in males than in females (2 : 1), with a median age of 60 to 65 years [2]. Most patients have an advanced stage of disease at diagnosis with common extranodal involvement including bone marrow, spleen, liver and gastrointestinal tract [3]. The clinical course of MCL becomes aggressive with time and resistant to chemotherapy with a median survival of 3 to 5 years [4]. Mantle cell lymphoma remains incurable with conventional chemotherapy and responses are short-lived. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) may increase progression-free (PFS) and overall survival (OS), but survival curves do not eventually plateau [5]. Herein we report the outcome of ASCT performed in our centre for twenty patients diagnosed with MCL.

Material and methods

Patient selection and characteristics

Twenty patients (7 male and 13 female) at median age of 59 years (41–68 years) received ASCT in our centre between 2004 and 2010. The management of patients after diagnosis followed common standards, but due to the fact that some patients were referred for transplantation from other centres, not all data were available for all patients. A histological diagnosis was established by the local pathologist and overexpression of Cyclin D1 was confirmed by immunochemistry in all patients. The disease stage was evaluated according to the Ann Arbor staging system and the International Prognostic Index for Mantle Cell Lymphoma (MIPI) score was calculated as published elsewhere [6]. The diagnostic work-up included physical examination, blood and serum analysis, chest X-ray, and computed tomography of the neck, chest, abdomen and pelvis. Bone marrow biopsy was taken at diagnosis and then repeated at the time of transplant. Patients were eligible for ASCT if they fulfilled the following criteria:
- first or subsequent complete (CR) or partial remission (PR) after conventional chemotherapy;
- ECOG status 0 to 2;
- age < 70 years;
- adequate hepatic, renal and cardiac function.

All patients signed informed consent. The clinical characteristics of patients are presented in Table 1.

Treatment

Induction chemotherapy consisted of R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) in 19 patients and R-CVAD (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in 1. CR was achieved in 13 cases (65%). Seven patients proceeded to receive second line treatment including different chemotherapeutic schema: R-ESHAP (rituximab, cisplatin, methylprednisolone, etoposide, cytarabine; $n = 3$), R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone; $n = 2$), R-FC (rituximab, fludarabine, cyclophosphamide; $n = 1$) and R-CVAD ($n = 1$). Second CR was demonstrated in 4 out of the 7 patients who achieved less than partial response (PR) after induction. Three remaining patients were given additional regimens and eventually met criteria for PR. Mobilized peripheral blood was the source of stem cells for ASCT in all patients. The IVE (ifosfamide, etoposide, epirubicin) regimen was used for mobilization. Granulocyte colony stimulating factor (G-CSF) at 10 µg/kg/day was started from day +5 until the last day of apheresis. The number of 2×10^6 CD34-positive cells/kg was considered sufficient for ASCT, but in 3 patients the number of transplanted CD34-positive cells was below this threshold. The apheresis product was processed, frozen to –150°C, stored and re-infused after conditioning was completed. The preparative regimens included CBV (cyclophosphamide, BCNU, etoposide) in 18 and BEAM (BCNU, cytarabine, etoposide, melphalan) in 2 patients.

Response criteria

The response to therapy was evaluated at 1, 3 and 6 months after ASCT and 6 months thereafter. CR was defined as the disappearance of all disease-related symptoms and measurable lesions for at least 4 weeks; PR was defined as a > 50% decrease in the sum of the products of the two largest diameters of all measurable lesions for at least 4 weeks. Progressive disease was defined by any increase > 25% in the sum of the diameter of any measurable lesions or the appearance of a new lesion.

Statistical methods

The OS and PFS rates were calculated according to the Kaplan-Meier method. All calculations were made from the date of transplantation. Comparisons between the variables were carried out by log-rank test. Statistical significance was defined at a p value < 0.05. Transplant-related mortality (TRM) was defined as death within 100 days of high-dose therapy not related to the disease, relapse and progression.

Results

Cell dose and engraftment

The median number of transplanted nucleated cells was 2.6×10^8/kg (range 1.6–13.0) and the median number of CD34-positive cells was 5.5×10^6/kg (range 1.1–22.8). All patients engrafted. The median time to neutrophil recovery was 14 days (range 10–18) and platelet count $> 50 \times 10^9$/l was

Table 1. Patient and transplant characteristics

Variable	MCL ($n = 20$)
Male/Female; no.	7/13
Median age; years (range) at diagnosis at transplant	59 (41–68) 60 (42–69)
Bone marrow involvement at diagnosis	12 (60)
Stage; no. (%) I/II III/IV	2 (10) 18 (90)
MIPI; no. (%) low intermediate high	5 (25) 9 (45) 6 (30)
B symptoms; no. (%)	10 (50)
Median treatment lines pre-ASCT (range)	2 (1–4)
Median number of treatment cycles (range)	7 (6–15)
Radiotherapy prior to ASCT; no. (%)	6 (30)
Median time to ASCT; months (range)	13.7 (7.4–57.8)
Disease status at ASCT; no. (%) CR1 PR	13 (65) 7 (35)
Type of conditioning; no. (%) CBV BEAM	18 (90) 2 (10)
Median days of post-ASCT hospitalization; range	26 (21–45)
Median number of post-ASCT blood transfusions; range	1 (0–5)
Median number of post-ASCT platelet transfusions; range	2 (0–5)

ASCT – autologous stem cell transplantation; CR – complete remission; PR – partial remission; CBV – cyclophosphamide, BCNU, etoposide; BEAM – BCNU, etoposide, cytarabine, melphalan; MIPI – Mantle International Prognostic Index

noted after a median of 14 days (range 10–22). No patient died within 100 days after the transplant.

Adverse events and supportive care

Thirteen patients demonstrated infectious complications in the post-transplant period. Grade 3 or 4 non-hematological adverse events were not observed. Five patients developed fever with negative bacterial and fungal cultures and mucositis of grade 1 or 2 were noted in 4 cases. The other complications included proctitis ($n = 2$), gastritis ($n = 10$), pneumonia ($n = 1$) and laryngitis ($n = 1$). Five patients required G-CSF to speed up post-transplant regeneration. Median time of post-transplant hospitalization was 26 days (range 21–45).

Outcome and prognostic factors

The transplant-related mortality was 0% at day 100. Median OS and PFS were 48 and 29.8 months, respectively. The estimated 5-year OS and PFS were found to be 52% and 35%, respectively (Fig. 1). There was no significant difference in OS
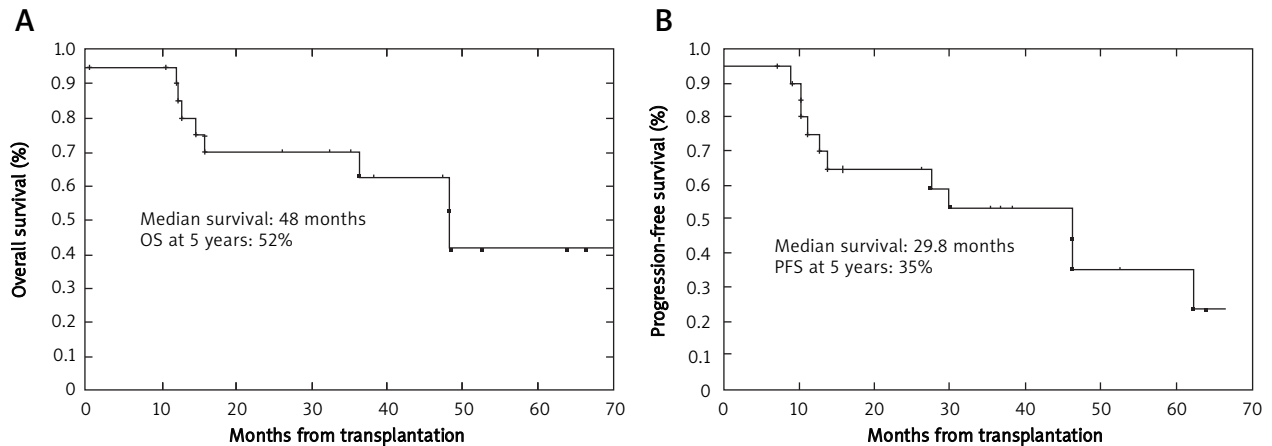
A

B

Fig. 1. Overall survival (A) and progression-free survival (B) for study group

and PFS in terms of MIPI score and disease status at transplant. Median follow-ups from diagnosis and from ASCT were 51.5 months (range 20.8–112.7) and 36 months (range 11–73), respectively. Median time to relapse was 13 months (range 7–62). Ten patients died from disease recurrence and subsequent chemoresistance. Ten patients are alive: 8 in CR, whereas 2 patients relapsed and receive salvage regimens.

Discussion

Mantle cell lymphoma remains incurable with conventional chemotherapy including anthracycline-based chemotherapy or monoclonal antibody treatment [5]. Autologous stem cell transplantation has become an encouraging therapeutic option based on the results from small series of patients. Namely, it was documented that nine patients with recurrent MCL who underwent ASCT had superior OS and failure-free survival than 14 patients treated with anthracycline-containing combinations [7]. Another small retrospective study reported the outcome of ASCT in 8 MCL patients transplanted in CR or PR. After a median follow-up of 22 months all patients were in CR and toxicity related to ASCT was manageable [8]. In the largest retrospective study to date, which analyzed 195 patients with MCL reported to the European Blood and Bone Marrow Transplant (EBMTR) and Autologous Blood and Marrow Transplant (ABMTR) registries, the median survival of transplanted patients was 6 years with 5-year OS and PFS of 50% and 33% respectively. More EBMTR patients received total body irradiation (TBI) as part of conditioning and conditioning regimens varied between registries. The BEAM protocol predominated in EBMTR whereas the BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) regime predominated in ABMTR. CBV conditioning was used in about 5% of EBMTR and ABMTR patients and it did not influence survival in multivariate analysis. Only disease status at transplant affected survival; patients had superior OS and PFS if transplanted in CR1 compared with those beyond CR1 [9]. The above-mentioned results were in line with our data; the 5-year OS and PFS were 52% and 35%, respectively. In contrast, we found that disease status (CR1 vs CR2/PR) did not influence OS and PFS.

It should be noted that our patients received uniform induction chemotherapy with the R-CHOP regimen and CR1

was achieved in 65% of patients. The median survival for the transplanted cohort was 5 years, which is 2 years longer than for historical series of patients treated with conventional chemotherapy [10]. Most patients from our cohort were transplanted after CBV conditioning with TRM at day 100 of 0%. However, one should realize that the CBV preparative regimen was found to be less favorable in terms of TRM and OS than BEAM for Hodgkin's and non-Hodgkin's lymphomas in some previous studies [11, 12]. Due to the low number of patients transplanted after the BEAM protocol in our study, a comparison between protocols was not performed.

There are also several prospective studies showing the results of ASCT consolidation in first-line MCL. Most studies recruited between 20 and 62 patients and used different induction regimens. The results of these studies may suggest that patients in the ASCT arm had significantly higher PFS if compared with historical controls, but the effect on OS needs to be determined. Based on the above-mentioned studies, we may conclude that a disease-free plateau was not reached and all patients eventually will relapse [13–15]. In contrast, a recently published report by the Nordic Lymphoma Group [16] showed no relapses occurring after 5 years, which may suggest that we can cure a proportion of MCL patients. However, it should be mentioned that these patients received intensive front-line immunochemotherapy with in vivo rituximab-purged stem cell rescue. The 6-year OS and PFS were 70% and 54% respectively. It seems that the addition of rituximab and high-dose cytarabine may improve the final outcome. The same was also concluded by Tam et al. [17]. They found that a major improvement in the approach for MCL patients was associated with the addition of rituximab to CVAD combined chemotherapy. This therapy resulted in a 90% CR rate. It was demonstrated that ASCT in CR1 after R-CVAD resulted in PFS and OS at 6 years of 39% and 61%, respectively. Even better results after R-CVAD were also reported by others; OS was 78% at 5 years [18]. It was suggested that cytarabine remained the most active agent in CVAD treatment, but the optimal dose needs to be determined [19].

In our study, the median time to relapse was 13 months from ASCT, 50% of relapses occurred within the first 2 years from transplant, and there was only one disease recurrence after 5 years.

We did not find any difference in OS and PFS depending on MIPI score. It was probably due to the small number of patients in each subgroup. A more recent publication showed similar outcomes between good and intermediate risk groups whereas poor-risk patients were found to have significantly inferior survival [20]. It is noteworthy that ASCT for MCL was found to be a well-tolerated procedure and only mild infectious complications were observed in our study cohort. Post-transplant recovery was rapid and only a small proportion of patients required growth factors in order to accelerate neutrophil regeneration.

In conclusion, ASCT as a consolidation treatment for advanced-stage MCL seems to be an effective procedure with manageable adverse events. Recent studies suggest that intensive immunochemotherapy followed by stem cell rescue may result in the improvement of OS and PFS in MCL with a proportion of patients being cured.

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