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AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA

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Summary

Substantial number of patients who present with non-Hodgkin's lymphoma cannot be cured of their disease by conventional dose therapy. New data on treatment results in the past decade elucidate the role of high-dose therapy (HDT) and autologous bone marrow or peripheral blood stem cells in the treatment of malignant lymphomas. There is evidence from randomized studies that high-dose therapy followed by autografting for relapsed chemosensitive patients is superior to conventional chemotherapy in terms of disease-free and overall survival. For this group of patients autografting became a standard approach to therapy. Also the increasing evidences indicate that high-dose therapy and autotransplantation in first remission improves survival in high-risk patients. The toxicity of the procedure is substantially reduced in recent years. Several new methods are under investigation, like various forms of immunotherapy and radioimmunotherapy, with the aim to reduce the incidence of relapse following transplantation.

KEY WORDS: *non-Hodgkin's lymphoma, autotransplantation*

TRANSPLANTACIJA AUTOLOGNIH MATIČNIH STANICA U LIJEČENJU NE-HODGKINOVOG LIMFOMA

Sažetak

Brojne bolesnike s ne-Hodgkinovim limfomom nije moguće izliječiti terapijom konvencionalnih doza. Novi podaci o rezultatima liječenja u posljednjem desetljeću rasvjetljavaju ulogu terapije velikim dozama i matičnih stanica autlogne koštane srži ili periferne krvi u liječenju zloćudnih limfoma. U randomiziranim je ispitivanjima dokazano da je terapija velikim dozama nakon koje slijedi autotransplantacija primijenjena u kemosenzitivnih bolesnika s relapsom uspješnija od konvencionalne kemoterapije s obzirom na sveukupno preživljenje bez znakova bolesti. Za tu je skuppinu bolesnika autotransplantacija postala standardna terapijska metoda. Sve je više dokaza koji pokazuju da se terapijom velikim dozama i autotransplantacijom kod prve remisije bolesti postiže bolje preživljenje u bolesnika izloženim velikom riziku. Toksičnost postupka posljednjih je godina znatno smanjena. Ispituje se nekoliko novih metoda, poput raznih oblika imunoterapije i radioimunoterapije, s ciljem da se pojavnost relapsa nakon transplantacije smanji.

KLJUČNE RIJEČI: *ne-Hodgkinov limfom, autotransplantacija*

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is the most commonly occurring hematological malignancy. 85% of NHLs are B cell lymphomas; the most common occurring varieties include the diffuse B cell large cell lymphomas, while the second most common type of NHL is follicular lymphoma. Its incidence has risen by 150% from 1950 until 1990, and it is still rising, at the speed greater than in other malignancies. Although considerable progress has been made in the understanding of etiology and pathogenesis of the disease, and in

treatment as well, there are still questions that need to be addressed.

RECENT ADVANCES IN CONVENTIONAL LYMPHOMA THERAPY

Even though for most of aggressive non-Hodgkin's lymphomas complete remission (CR) can be achieved with combined cytostatic therapy containing anthracyclines, like CHOP, less than 50% of patients are cured of their illness (1). Using more intense chemotherapy combinations like MACOP-B, ProMace-CytaBOM or m-BACOD, did not prove superior to CHOP in achieving CR, in disease-free survival (DFS) or overall survival (OS) of patients (2-4) The value of adding rituximab, a chimeric anti-CD20 monoclonal antibody that displays intrinsic anti-lymphoma effect but also initiates complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, was confirmed in the pivotal study of 166 patients with refractory or relapsed indolent lymphoma achieving an overall response rate od 48% and a median time to progression of 13 months, with negligible side-effects profile (5). Its value has been proved since in younger population as well (6), and especially strong evidence for that has been provided by the study of Sehn and others that showed a profound effect on survival achieved by addition of rituximab therapy to all newly diagnosed patients with advanced diffuse large B cell lymphoma in British Columbia (7). The study showed that both progression-free survival (PFS) and overall survival were significantly improved in the post-rituximab group, and the effect was present regardless of the age group of the patient. The addition of rituximab to standard chemotherapy now represents the standard of care in the first line treatment of CD20+ lymphoma.

There has been a lot of debate and a fair amount of clinical data addressing the issue of dose intensification in induction therapy. Dose escalation with granulocyte colony-stimulating factor (G-CSF) support has been investigated, rationale being that with G-CSF support higher doses can be delivered. After showing that maximum tolerated dose (MTD) of cyclophosphamide in the CHOP regimen can be increased by the factor of 1.8 (up to 2750/m^2) with acceptable toxicity using G-CSF support (8, 9), and that also significant dose-escalation of epirubicin and cyclophosphamide in CEOP regimen is possible with filgrastim support (10), following studies looked at the survival benefit of escalated doses. Using escalated doses of CHOPE regimen where MTD for cyclophosphamide was 1500mg/m^2 and 160mg/m^2 for etoposide respectively response and survival rates of patients, even with the addition of G-CSF, appear similar to the rates reported with standard-dose CHOP. Another study by Gordon and others also confirmed that, albeit feasible, dose escalation with G-CSF support does not offer considerable survival benefit (11, 12). Recently the focus has shifted more towards increasing dose density of chemotherapy. Two important studies have been published as result of work done by German High-Grade Non-Hodgkin's Lymphoma Study Group, showing that reducing the interval between CHOP cycles on two instead of three weeks is not only feasible with G-CSF support, but also improves overall survival in both younger and older patient group. This approach could be considered as the new standard chemotherapy regimen (13, 14).

MYELOABLATIVE HIGH-DOSE CHEMOTHERAPY (HDT) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR RELAPSED NHL

Substantial number of patients who present with non-Hodgkin's lymphoma cannot be cured of their disease by conventional dose therapy. Even though the addition of rituximab has remarkably improved event-free survival (EFS) for patients with aggressive NHL, there is still a considerable portion of patients that will relapse after achieving remission, or those with primarily refractory disease that will need additional therapy. In the PARMA study, 109 patients with chemosensitive relapsed disease were assigned to receive four additional cycles of chemotherapy or HDT followed by bone marrow transplantation, HDT yielded considerably better EFS and OS. (15). EFS after a 5-year period was 46% in the transplantation group and 12% in the group receiving only chemotherapy (p=0.001), while overall survival was 53 and 32 percent, respectively (p=0.038). There were also other clinical data that showed 22-53% EFS after ASCT (16, 17), so this approach became a standard of care for relapsed chemosen-

Table 1.

RANDOMIZED STUDIES OF THE EFFICACY OF STANDARD THERAPY VERSUS ASCT IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA IN FIRST REMISSION

Authors	Therapy	No of patients	Prognostic group, stage	Disease-free survival	Overall survival
Haioun et al 1994.	Stand. LNH-84 CVB-ASCT	234 230	I CR (all types)	52% - 3 y 59% - 3 y (p=0.46)	71% - 3 y 69% - 3 y (p=0.06)
Haioun et al 1997. (22)	Stand. LNH–84 CVB-ASCT	55 77	IPI H/I, H	39% - 5 y 59% - 5 y (p=0.01)	52% 65% (p=0.06)
Santini et al. 1998 (24)	Standard therapy ASCT	124	.I CR (all types) IPI H/I, H	NS 48% - 3 y stand th. 87% - 3 y ASCT (p=0.008)	
Gianni et al 1997 (25)	MACOP-B. ASCT	50 48	I/II bulky III/IV	76% 49% (p=0.004)	81% 55% (p=0.09)
Haioun 2000. (23)	CVB-ASCT vs. Stand. LNH-84	451 (277)	IPI H/I, H	55% - 8 y 39% - 8 y (p=0.02)	64% - 8 y 49% - 8 y (p=0.04)
Gisselbrecht et al 2002 (28)	ACVBP vs. shortened induction + ASCT	181 189		52% 39% (p=0.01)	60% 46% (p=0.007)
Martelli et al 2003 (29)	MACOP-B vs. MACOP-B abbr + ASCT	75 75	H/I, H	65% - 5 y 77% (p =0.22)	65% - 5 y 64% (p =0.95)
Milpied at al 2004 (30)	CHOP vs. HDT + ASCT	99 98	II bulky, III, IV	37% - 5 y 55% (p=0.037)	56% - 5 y 71% (p=0.076)
Sebban C et al (31)	CHVP + IFN vs. CHOP + ASCT	209 192		p= 0.11 NS	p=0.53 NS

CVB – ciclophosphamide, etoposide, carmustin, BEAM – carmustin, etoposide, cytarabine, melphalan, IPI – international prognostic index, H/I – high/intermediate, H – high risk, BM- bone marrow, PBSC- peripheral blood stem cell, BEAC- carmustin, etoposide, cytarabine, cyclophosphamide, P-cisplatinum, TBI-total body irradiation, CTX - cyclophosphamide, VP-16 etoposide, ASCT – autologous stem cell transplantation, NS – non significant

sitive aggressive NHL. In addition, the technology of transplantation has improved considerably. With the introduction of peripheral blood stem cells, and better supportive care in the last 10 years, the mortality of procedure has decreased considerably, and now is around 5%, which in conjunction with decrease of procedure costs represents another argument in favor of considering ASCT in this group of patients (18).

AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST LINE THERAPY

After initial success of ASCT in relapsed disease, recent studies focus to evaluate its value in an earlier phase of aggressive NHL, predominantly in patients with high risk features.

International Prognostic Index (IPI) (19) stratifies patients at the time of diagnosis in four different groups according to the number of adverse prognostic factors present at the diagnosis (age, performance status, LDH, extra nodal disease): low risk with 73% expected 5-year survival, intermediate low risk with 51%, intermediate high risk with 43% and high risk with 26% 5-year survival, respectively. Patients in latter two groups (intermediate high and high risk) with expected survival lower than 50% are potential candidates for HD therapy followed by ASCT as consolidation therapy in first CR. Haioun and others (20, 21) showed for the group of high risk patients (IPI 3-5), a clear benefit of dose intense consolidation approach with ASCT over sequential chemotherapy, with 8-year DFS rates of 55% and 39%, respectively (P =0.02; relative risk, 1.56), and 8-year OS rate 64%

and 49% (P =.04; relative risk, 1.51). No difference in outcome was found when looking at low and high risk groups combined. In other clinical studies, a significant difference was also noted in survival of patients only in intermediate high and high risk according to IPI (22, 23). Another prospective randomized study was done by EORTC in which patients diagnosed with aggressive NHL received three cycles of CHVmP/BV polychemotherapy, after which patients that showed at least partial remission were assigned to receive further three cycles of CHVmP/BV followed by high-dose BEAC chemotherapy and ASCT (ASCT arm) or five more cycles of CHVmP/BV (control arm). Intention-to-treat analysis showed no statistical difference between ASCT group and control group in respect to the time to disease progression and overall survival at 5 years. A subset analysis on IPI risk groups, although too small for reliable statistical analysis, yielded similar results (24). Similarly designed study of German High Grade Lymphoma Study Group also showed no benefit in using ASCT in the early phase of treatment after 3 cycles compared to receiving 5 cycles of conventional therapy (25). A study form French GELA group clearly showed inferior results for patients randomized to receive ASCT after shortened intensified induction treatment consisting of 3 cycles of chemotherapy, in comparison to classical ACVBP induction therapy followed by sequential consolidation in a poor prognosis aggressive lymphoma patients younger than 60 yrs (5-year overall survival for ACVBP and ASCT was 60% and 46% (P =.007), while event-free survival was 52% and 39% (P =.01), respectively (26). Another Italian multicenter randomized trial also showed that abbreviated chemotherapy followed by intensification with ASCT is not superior to conventional chemotherapy in intermediate high and high risk group according to the intention-to-treat analysis (27). Recently, a study was published that compared ASCT versus CHOP chemotherapy (28). It showed estimated event-free survival rate at 5 years significantly higher among patients who received high-dose therapy than among patients receiving CHOP (55±5% vs. 37±5%, P=0.037). Among patients with a high intermediate risk of death, according to the age-adjusted International Prognostic Index, the five-year survival rate was significantly higher after high-dose therapy than after CHOP (74±6% vs. 44±7%, P=0.001). Also, in a recent study done by Sebban and others (29) a standard CHVP regimen plus interferon was compared with 4 courses of CHOP followed by high-dose therapy with autologous stem cell transplantation in treatment-naïve patients with advanced follicular lymphoma. Intent-to-treat analysis after a median follow-up of 7.5 years showed that there was no difference between the 2 arms in OS (P = 0.53) or event-free survival (EFS) (P = 0.11). These contradictory results can be in part explained by different inclusion criteria and chemotherapy regimens, and also different time to ASCT procedure and the number of cycles given before myeloablative procedure, not to mention response to previous therapy given. ASCT was more efficient after completely administered induction therapy, while negative results mainly came from studies that evaluated ASCT in the earlier phase after only 3 cycles of chemotherapy. Tandem transplantation was also evaluated as a treatment option (30). Thirty-six patients received induction with four cycles of ACVBP, after which peripheral blood stem cells were collected, and then two consecutive HDT with peripheral ASCT. Among the 29 patients responding to induction, 28 received the first HDT and 24 the second. Three-year EFS and OS was 47% and 50%, respectively, suggesting that tandem transplant did not improve the results of the study in which patients received a single consolidative HDT done by the same group (21).

Special consideration might be paid to mantle cell lymphoma, in which a remission can be achieved in a considerable number of patients, but they relapse quite fast and frequently. Recently published study showed excellent results, with CR achieved in 92% patients after hyper-CVAD + rituximab, followed by ASCT after Bu/Mel conditioning. With a median follow-up from diagnosis of 36 months, authors observed OS and EFS both to be 92% for the whole cohort (31).

With respect to all the data collected in the field, a panel of experts within the American Society for Blood and Marrow Transplantation, after an analysis of studies published from 1980 until 2000, published an *evidence based review* (32). On the basis of evidence of benefits of transplantation in aggressive lymphomas (diffuse large cell B-cell non-Hodgkin's lymphoma, DLCL) following recommendations have been summarized: transplantation in DLCL is more efficient than conventional therapy and is recommended as treatment of

choice in treating patients during first, chemosensitive relapse, for patients in first complete remission that according to IPI are considered intermediate high or high risk, as well as a sequential high-dose therapy in previously untreated patients of same risk groups according to IPI. Transplantation is not more efficient than conventional chemotherapy and therefore is not recommended for patients in first complete remission that are considered to be of intermediate low or low risk according to IPI. Also, it is not recommended in treating patients that have received only shortened induction therapy: 6 or less CHOP cycles, or 12 or less MACOP-B or VACOP-B cycles, which means that transplantation should be done only after completely administered induction therapy. Recommendations are not given for indications that have not been thoroughly researched, like chemoresistant relapse, or primarily refractory disease, first partial remission after completely administered induction therapy or for sequential high-dose therapy in patients with lower risk according to IPI. It has been suggested that further studies need to be done.

ALLOGENEIC STEM CELL TRANSPLANTATION AS AN OPTION

There have not been many studies evaluating efficacy of allogeneic transplantation in NHL. Several retrospective studies comparing alloBMT and ASCT showed no significant benefit of allogeneic transplantation (33, 34). A large retrospective study of transplantations reported to EBMT showed that, even though allogeneic transplantation appears to be superior to autologous in terms of a lower relapse rate, the toxicity of allogeneic procedures overcomes its benefits and results in OS that was better for autologous than for allogeneic transplantation (34). Since there is no clear benefit of allogeneic transplantation over autologous one, patients should receive this therapy only in the context of a research study.

Allogeneic transplantation is also being used quite frequently in patients with available donors that relapse after autologous transplantation. So far, there has been little data to support this approach. A retrospective analysis by Freytes and others (35) evaluated 114 patients in relapse after ASCT treated with myeloablative allogeneic SCT. Three-year probabilities of OS and PFS were 33% and 25%, respectively, but with a prolonged follow-up nearly all patients experienced disease progression, and 5-year OS and PFS probabilities were 24% and 5%, respectively. Complete remission at the time of allo-HSCT and the use of total body irradiation (TBI) in patients with non-Hodgkin lymphoma (NHL) were associated with lower rates of disease progression and higher rates of OS. They found allogeneic transplantation feasible for patients with lymphoma who have relapsed after ASCT, this procedure can prolong survival for a subset of patients, but it is not considered a curative method.

There are studies currently underway to evaluate whether allogeneic SCT after non-myeloablative conditioning (mini-transplant) could be the treatment option as a way to harness graft-versus-lymphoma effect that is undoubtedly present, avoiding toxicity of high-dose therapy that compromise conventional approach.

FUTURE DIRECTIONS

Primary concern regarding treatment of malignant lymphoma with ASCT is still relatively high incidence of disease relapse after transplantation. Besides better selection of patients, and use of transplantation earlier in the course of the disease, future studies will be focused on increasing the antitumor potential of whole treatment strategy. Further increase in the dose of cytotoxic agents administered might not be an option, since current myeloablative protocols are already at the limit of tolerance. There are many studies underway trying to harness the potential of immune response, especially in the phase of minimal residual disease, such as α-interferon, interleukin-2 (IL2), anti-CD19 immunotoxin, or tumor-reactive T lymphocytes. Specific monoclonal antibodies, like anti-CD20 or anti-CD25, are being evaluated as therapy before or after autotransplantation. A group from Stanford evaluated efficacy and safety of adding rituximab in maintenance therapy after HDT and ASCT in 35 patients with B-cell lymphoma. Rituximab was administered in 4 weekly infusions (375 mg/m^2) starting at day 42 after HCT and, for 20 patients, a second 4-week course was given 6 months after HCT. Toxicity profile was expected and acceptable. A prospective study of immune reconstitution included measurements of lymphocyte sub-

sets, immunoglobulins, and response to vaccination. Despite delayed B-cell recovery and suppressed immunoglobulin G (IgG) levels and low pneumococcus antibody titers, serious infections were not observed (36). Recently published study compared rituximab maintenance versus observation after ASCT in patients with aggressive NHL achieving remission after induction therapy. A trend towards better 3-year survival for rituximab arm has been demonstrated (80% vs. 72%) (37). Since early after ASCT the immune system is not very active and this immune incompetence could thus result in decreased ability for immune-mediated tumor eradication, early addition of immunotherapy after ASCT might decrease the incidence of relapse and prolong survival. Based on this hypothesis a study was conducted testing feasibility of adding IL-2 to rituximab in maintenance therapy after ASCT. The treatment was reported feasible, with manageable toxicity with 18 of 20 patients reported alive in complete remission, with a median follow-up of 55.5 months (38). Another approach used in vivo purging with rituximab prior to autologous PBSCT. Fourteen patients with relapsed follicular, marginal zone and mantle cell lymphoma, with a detectable molecular marker in peripheral blood received therapy with rituximab prior to mobilization chemotherapeutic regimen, and also HDT and ASCT (39). PCR analysis was performed before rituximab, in stem cell harvest and during follow-up, and it showed that after rituximab harvests were free of molecular marker in 9/11 cases studied; clinical remission was obtained in 13 (93%), and molecular remission in 11 patients (79%).

Based on the success of radioimmunotherapy (RIT), namely monoclonal antibodies combined with a radionuclide that delivers radiation at the site of disease, in treating relapsed and high risk patients, the benefit of using RIT as a part of preparative regimen for ASCT has been evaluated in several studies. Two forms of RIT are presently available on the market, i.e. ^{90}Y-ibritumomab tiuxetan (Zevalin) and ^{131}I-tositumomab (Bexxar). A phase I/II trial, 52 patients with relapsed B-cell lymphoma were transplanted using preparative regimen that combined ^{131}I-tositumomab with etoposide and cyclophosphamide. Estimated OS and PFS at 2 years were 83% and 68%, respectively, which was superior to nonrandomized comparable group of patients treated with total body irradiation, etoposide and cyclophosphamide (40). In another study 125 patients were treated with high-dose RIT using ^{131}I-tositumomab, and compared to a historical group of patients that received conventional high-dose chemotherapy and ASCT (41). The estimated 5-year OS and PFS were 67% and 48%, respectively for high-dose RIT, and 53% and 29%, respectively for conventional high-dose therapy. A 100-day treatment-related mortality was higher in the conventional therapy arm. 3.7% vs. 11%, respectively.

CONCLUSION

Using high-dose therapy with ASCT it is possible to provide cure for a substantial number of patients with non-Hodgkin's lymphoma, who are not cured using conventional chemotherapy. Based on the data from studies presented here, ASCT has become a standard of care for patients with relapsed, chemosensitive disease, and this treatment should be strongly considered in first remission in patients with high risk disease. ASCT has not yet proved to be a curative measure for advanced chemoresistant disease. Treatment-related mortality has decreased considerably during the last few years, and the risk of undergoing ASCT is not much greater than from conventional chemotherapy. Low risk of treatment further establishes this method as a treatment option even in earlier phases of disease.

Despite the success of ASCT, the incidence of relapse after treatment is still high. Clinical research in the last couple of years has been oriented towards investigating new approaches that would possibly decrease relapse incidence after ASCT. There has been some progress using immunotherapy before, during or after the transplantation. The use of monoclonal antibodies, predominantly anti-CD20, rituximab, has been thoroughly investigated, and some exciting results have been made. However, besides a better selection of patients and using ASCT in the earlier phases of the disease, further controlled, randomized, prospective clinical trials will clarify some unresolved clinical questions in the treatment for malignant lymphoma. The possibilities of further increasing the efficacy of chemotherapy are limited, since it is already at the edge of acceptable toxicity. The use of immunotherapy is so far the most promising option, especially in the phase of minimal residual disease.

This include alpha interferon treatment, IL-2, monoclonal antibodies such as anti-CD20 (rituximab), anti-CD52 (alemtuzumab), anti-CD22 (epratuzumab), all proved to be promising in further advancing the efficacy of the treatment. A more of research is needed in the evolving field of autologous stem cell transplantation to further advance curative potential of this treatment strategy.

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