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Efficacy and safety of high-dose chemotherapy with autologous hematopoietic stem cell rescue for relapsed/refractory Hodgkin's lymphoma patients in former USSR countries. Retrospective analysis of data from four transplantation centers in Belarus, Russia and the Ukraine

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Running title: HDC in patients with HL in former USSR republics

Summary

High-dose chemotherapy (HDC) with autologous stem cell transplantation support is a routine treatment approach for relapsed or refractory Hodgkin's lymphoma (HL) patients. Unfortunately, HDC is much less common in the former USSR republics; among other reasons due to a lack of information about the efficacy and safety of this treatment as performed at local centers.
We analyzed the outcome for 184 HL patients receiving HDC in the former USSR republics between January 1990 and March 2003. Most patients had primary refractory disease (44.8%), early (27.2%) or multiple (21.6%) relapses. Restaging revealed stage III–IV disease in 69%, and B-symptoms in 53% of cases. The patients received a mean of 9 (2 to 34) courses of standard chemotherapy prior to HDC.
HDC yielded complete response or complete response uncertain (CR/CRu) in 68.2% of cases, and the 5-year overall survival (OS) rate was 60%; freedom from treatment failure (FFTF) survival was 41.5% with a median follow-up of 30 months (3 to 139 months). As estimated with respect to disease status, the 5-year FFTF was 35% among patients with primary refractory disease, 46.4% in patients with multiple relapses, and 59.2% in patients with early sensitive relapse. The early death rate was 5.4%, but has demonstrated a considerable decreasing trend over recent years (1.4% in 2000–2003). The HDC with autologous hematopoietic stem cell rescue procedure performed at transplant centers in the former USSR republics is associated with low mortality and satisfactory FFTF for patients with primary refractory or relapsed Hodgkin's disease.

Keywords: Hodgkin's lymphoma, relapse, primary refractory disease, high-dose chemotherapy, stem cell support

Introduction

With modern chemotherapy, the vast majority of HL (formerly, Hodgkin's disease) patients achieve CR, and approximately 70% to 90% will be alive and free of disease at 5 years. However, 10 to 30% of HL patients have primary refractory disease, or relapse after their first CR. Survival rates are significantly worse for these patients.

Treatment with alternative second-line chemotherapy regimens yields 5 to 10-year survival rates of only 20% to 32% [1-6]. Randomized trials confirmed the benefit of HDC as compared to second-line therapy with respect to event-free/FFTF survival [7,8]. In recent years, the use of peripheral blood as a source of autologous hematopoietic progenitor cells, together with advances in supportive care have significantly reduced transplant-associated morbidity and mortality—which further strengthens the appeal of HDC. HDC is currently a standard treatment modality in patients with sensitive relapse of HL [9,10]. The advantages in cases of primary refractory or multiple relapsing HL are questionable, though the use of HDC in this patient category is justified by the absence of effective alternatives.

According to the European Group for Blood and Marrow

Transplantation (EBMT) registry, about 1200–1300 transplants are performed in HL patients in Western Europe annually, in contrast to Eastern Europe and, still more so, to the former USSR republics, where this effective treatment is much less common in spite of a similar proportion of relapsed/refractory HL patients. This situation may in part be explained by a generally low level of transplantation activity due to inadequate technical facilities and funding: cf., the number of transplantations per 10 million population in recent years was 60 in Belarus, 15 in Russia and 1 in the Ukraine (i.e., the total number of transplantations of any kind and for any reason in all 3 countries was approximately 290–300). It should be noted that there are some subjective reasons too, including a lack of information about the efficacy and safety of HDC as performed at local centers.

Materials and methods

The primary objective of this study was to assess the efficacy (OS, relapse-free survival [RFS], FFTF survival) and safety (early post-transplant mortality) of HDC with ASCT for patients with poor prognosis HL at centers of former USSR republics. The secondary objective was to assess the treatment efficacy with respect to the disease course (multiple relapse, primary refractory disease, early relapse).

We analyzed retrospective data of 184 patients who, due to a poor prognosis for HL received HDC with autologous progenitor cells from peripheral blood (PBSC) and/or bone marrow (BM) rescue between January 1990 and March 2003. Only data from centers that met the EBMT criteria for safety and transplantation activity (> 20 autologous transplantations per year) were included in the analysis. The following centers supplied their data:

1. Bone Marrow Transplantation Department, N. N. Blokhin Cancer Research Center, RAMS, Moscow, Russian Federation
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4. Kiev Center for Bone Marrow Transplantation, Kiev, Ukraine.

Patients were selected for this study if they received HDC within the above-mentioned interval (01.1990–03.2003) due to poor-prognosis HL. The patients‘ mean age at the time of ASCT was 27 years (11 to 56 years). The study group consisted of 89 males and 95 females.

Most of the patients had primary refractory or early relapsing disease. Patient characteristics are shown in tables 1 and 2.

Of 50 patients with early relapses, 27 received HDC after the failure of one or more second-line regimens. Because there were few patients (9) receiving HDC after their first late relapse, they were joined into a single group together with patients having multiple relapses.

Most patients (n=156; 85%) were treated with one of the second-line combination chemotherapy regimens for disease „debulking“ before HDC (remission reinduction). The reinduction consisted of (hereinafter total doses per chemotherapy cycle are specified): dexamethazone, carmustine 60 mg/m^2, etoposide 800–1000 mg/m^2, cytarabine 800–1000 mg/m^2, melphalan 20 mg/m2 (dexa-BEAM) in 100 (54%) patients, and dexamethazone, cisplatin 100 mg/m2, cytarabin 4 g/m2 (DHAP) in 31 (17%). The remaining 25 (14%) of patients were treated with other regimens.

The majority of patients (149 from 184; 81%) received conditioning chemotherapy with BEAM (carmustine 300 mg/m^2, etoposide 1 g/m^2, cytarabine 1 g/m^2, melphalan 140 mg/m^2), 20 patients (11%) received CBV (cyclophosphamide 6 g/m^2, carmustin 350–500 mg/m^2, etoposide 1–1.5 g/m^2 + mitoxanthrone 50 mg/m^2), and 11 (6%) received other high-dose regimens; 4 (2%) of patients were given two HDC courses.

Most of the patients (152/184) were rescued with peripheral blood progenitor cells (n=99; 54%) or a combination of PBSC and BM (n=53; 29%). BM was the only source of autologous stem cells in the remaining 32 (17%) patients. BM as a source of stem cells was used (solely or in combination with PBSC) basically before PBSC mobilization, and collection became a routine procedure in the transplant center (1990–1995 y.y.). After this period PBSC mobilization (G-CSF with or without chemotherapy) and collection were performed in all patients, and combined transplant (BM + PBSC) was used only in poor-mobilized patients.

Definitions and statistical analysis

Primary refractory disease was defined as disease progression on adequate first-line chemotherapy, inability to achieve a CR/CRu

Table 1. Distribution of cases with respect to disease course

Disease course	n (%)
Primary refractory disease	82 (44.8)
Early relapse	50 (27.2)
Multiple/early relapses	49 (26.6)
Consolidation of first CR	3 (1.4)
Total	184 (100)

Table 2. Characteristics of patients before inclusion in chemotherapy schedules planned for the preparation of HDC / autologous stem cell support

Characteristics	
Disease stage	
I	7 (4%)
II	50 (27%)
III	48 (26%)
IV	79 (43%)
B-symptoms	98 (53%)
Mean number of conventional chemotherapy cycles prior to HDC (range)	9 (2 to 34)

Figure 1. Overall survival

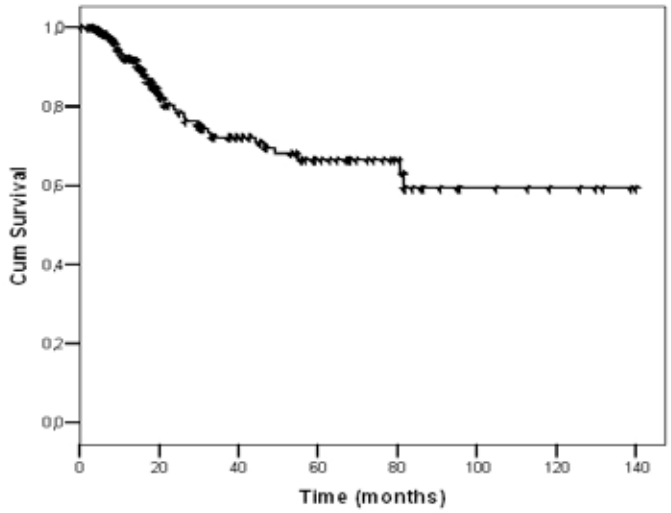
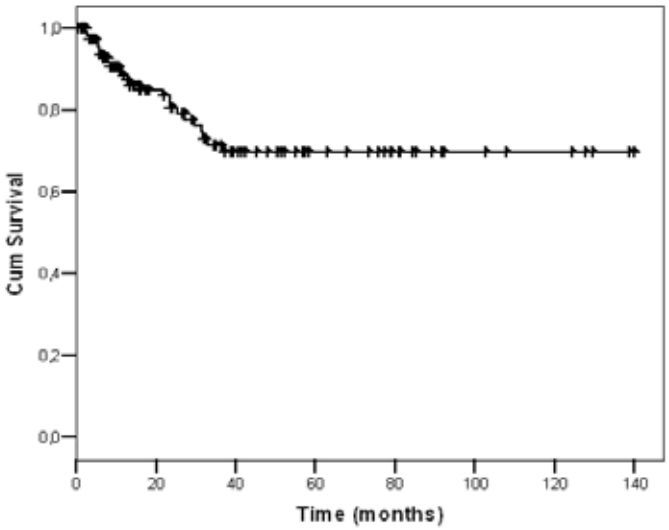


Figure 2. Relapse-free survival



at the completion of first-line chemotherapy+/-radiotherapy, or a relapse within 3 months after CR/CRu achievement. Early relapse was defined as a relapse occurring within 3 to 12 months after CR or Cru; late relapse was defined as a relapse occurring at >12 months after attainment of CR or CRu. Multiple relapses were defined as more than one relapse in the same patient. Patients with one relapse receiving HDC after failure of one or more second-line regimens were defined as those having resistant relapse even if they responded to a reinduction of remission.

OS was defined as the time from the date of remission reinduction (if any) or HDC initiation (in the remaining patients) until death from any cause, or until the last follow-up visit. FFTF survival was estimated from the same date until the first event (failure to achieve CR or CRu after HDC, death from any cause, relapse) or until the last follow-up visit. RFS was calculated only in patients achieving CR/Cru, and was defined as the time from CR/CRu until relapse or the last follow-up visit.

Survival time distributions were calculated using the productlimit method of Kaplan and Meier. Comparisons of this time to event distributions were made using the log-rank test.

Results

Response to chemotherapy and survival rates

Following the reinduction of chemotherapy 33 from 156 (21.2%) patients were in CR, 6 (3.8%) were in CRu and 73 (46.8%) achieved partial response (PR). Stabilization was achieved in 20 (12.8%), and disease progression in 24 (15.4%) patients. HDC increased CR and CRu rates to 57.4% (106 from 184 patients) and 10.8% (20/184), respectively. PR rate was 15.9% (29/184). Disease stabilization and disease progression were reported in 10.8% (n=20) and 5.1% (n=9) of patients, respectively.

At final analysis after a median follow-up of 30 months (3 to 139 months) the 5-year OS was 60%, RFS was 69.7% and FFTF survival was 41.5%. All participating centers had comparable results in respect of long-term outcomes (Figs. 1–3).

The analysis showed a difference in FFTF with respect to disease status (p=0.029). However, the 5-year survival reached 35% even in patients with primary refractory disease. In patients with early relapse and with multiple relapses/late relapse, the 5-year survival

Figure 3. Freedom from treatment failure survival

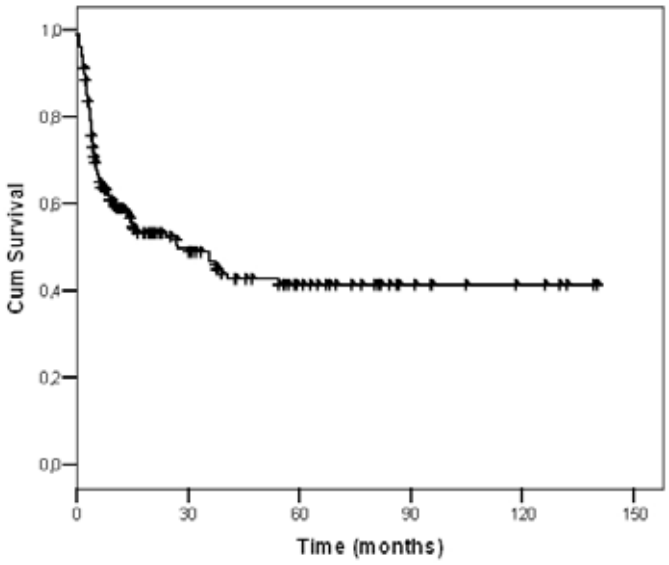
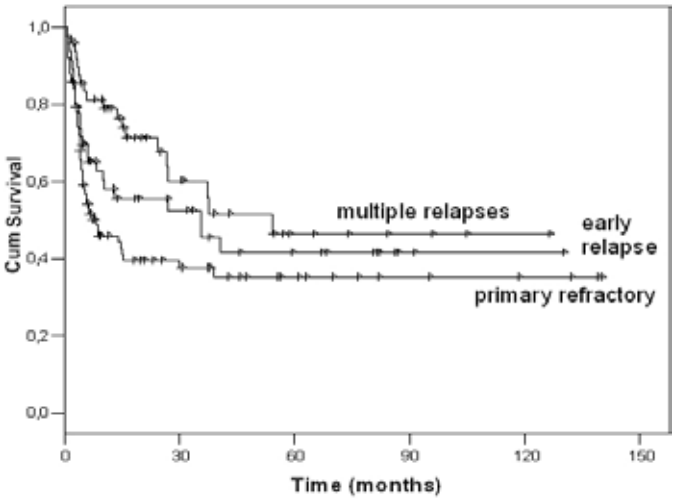


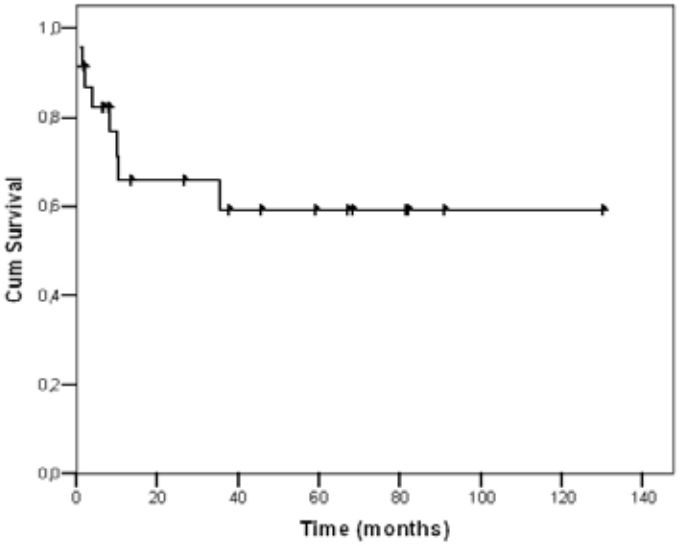
Figure 4. FFTF survival with respect to disease course



rates were 41.6% and 46.4%, respectively (Fig. 4).

We analyzed the FFTF for a small group of 23 patients receiving HDC separately, according to the most accepted standard indication

Figure 5. FFTF survival of patients receiving high-dose chemotherapy in first sensitive early relapse



i.e., the first early sensitive relapse (CR or PR achievement after reinduction of remission in the absence of any other second-line chemotherapy). The 5-year FFTF in this cohort of patients was 59.2% (Fig. 5).

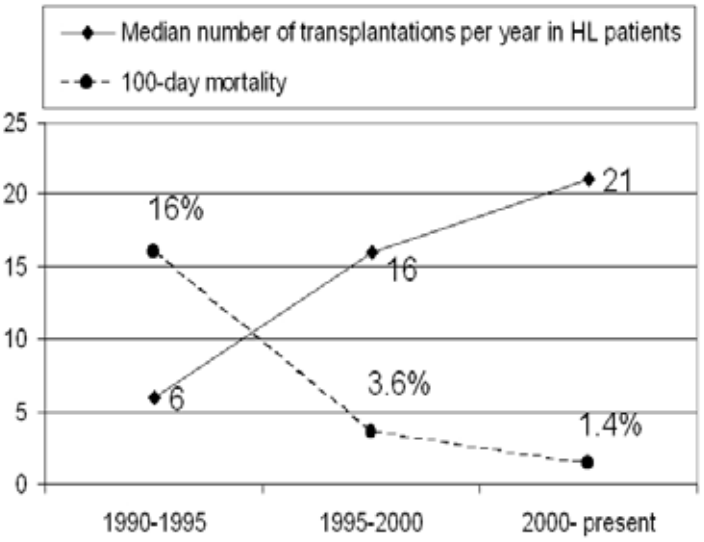
Hematological recovery

Median duration of neutropenia < $0.5x10^9$/l was 13 days (8 to 90 days), and was different (p=0.0035) with respect to the type of transplant (22 days in patients receiving BM transplant vs. 13 days in patients receiving PBSC vs. 16 days in the combined transplant group). The median time to platelet transfusion-independent recovery status was 13 days (6 to 90 days), and also dependant on the transplant type (23, 14 and 18 days for BM, PBSC and combined transplants, respectively, p=0.015).

Toxicity

Early post-transplant mortality (100-days) was 5.4 % (10 patients), and decreased considerably in patients receiving HDC over recent years: cf. 16% during 1990–1995 versus 3.6% in 1995–2000 and 1.4% in 2000–2003 (Fig. 6).

Figure 6. Early (100-day) post-transplant mortality rate with respect to timeframe of HDC performance.



Discussion

In most economically developed countries HDC is given mainly to patients with the highest chance of cure (patients in first sensitive relapse). Unfortunately, in the former USSR republics this treatment modality was until recently either not offered to patients at all or was considered by physicians as the „last chance" to be taken after the failure of all other salvage modalities. Today we have sufficient reason to revise this approach shared by the oncologists and hematologists of former USSR countries, and to adjust the indication of HDC to worldwide standards (use of HDC mainly in patients in first sensitive relapse). The HDC performed at selected transplant centers of former USSR countries resulted in long-term FFTF survival in 35%–46.4% of patients with poor-prognosis HL, depending upon disease course. As previously suggested by others [11], HDC is a preferred treatment modality not only for patients with sensitive relapse, but also for patients with primary refractory HL, because there is no alternative effective treatment yet. Our results have shown that a proportion of patients with primary refractory HL (5-year FFTF survival 35%) or multiple relapses of HL (5-year FFTF survival 46.4%) do well. However, we should like to mention that the prevalence of patients with primary resistance, multiple relapses, and resistant relapses reflects to a certain extent the opinion of oncologists and hematologists from former USSR republics about HDC. Unfortunately, HDC (especially as conducted at local clinics) is considered in these countries a highly toxic and „experimental" therapy that is indicated only in cases of absolute resistance to standard salvage treatment. As demonstrated by our findings, the experience of actively functioning transplantation centers in former USSR republics together with an improvement in supportive care have led to a considerable reduction in early post-transplant death rates.

Conclusion

Our analysis demonstrated that a more than 10-year experience in HDC in HL patients with poor prognosis at certified clinics of former USSR countries resulted in treatment outcomes that were compatible with those achieved at leading centers.

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Эффективность и безопасность высокодозной химиотерапии с аутологичной трансплантацией гемопоэтических стволовых клеток (ауто-ТГСК) у больных с рефрактерными/рецидивирующими лимфомами в республиках бывшего СССР. Ретроспективный анализ данных из четырех центров трансплантации в Беларуси, России и Украине

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Резюме

Высокодозная химиотерапия (ВХТ) с поддерживающей аутологичной трансплантацией гемопоэтических стволовых клеток (ауто-ТГСК) является рутинным подходом к лечению рецидивирующей или рефрактерной к лечению больных с болезнью Ходжкина (лимфогранулематозом). К сожалению, ВХТ с ТГСК нечасто проводится в республиках бывшего СССР, в частности, из-за отсутствия информации об эффективности и безопасности такого лечения при его проведении в местных центрах.

Мы проанализировали исходы лечения 184 больных, получавших ауто-ТГСК в наших центрах с января 1990 г. по март 2003 г. У большинства больных была установлена первично-рефрактерная болезнь (44,8%), ранние (27,2%) или множественные (21,6%) рецидивы заболевания. Рестадирование выявило заболевание III—IV степени в 69%, В-симптомы – в 53% случаев. До проведения ауто-ТГСК больные получали, в среднем, 9 (от 2 до 34) курсов стандартной химиотерапии.

Высокодозная химиотерапия приводила к полному или предположительно полному ответу (CR/CRu) в 68,2% случаев, при общем 5-летнем выживании у 60% больных, выживаемость без неудачи лечения (FFTF) составляла 41,5% при среднем сроке наблюдения 30 мес. (от 3 до 139 мес.). При оценке статуса заболевания, средние показатели пятилетнего FFTF была 35% среди больных с первично-рефрактерной болезнью, 46,4% - у больных с множественными рецидивами, и 59,2% у больных с ранними химиочувствительными рецидивами. Частота ранней гибели больных была 5,4%, но продемонстрировала тенденцию к значительному снижению в течению последних лет (1,4% в 2000-2003 гг.). Таким образом, ВХТ с поддерживающей ауто-ТГСК, проведенная в трансплантационных центрах республик бывшего СССР, связана с низкой смертностью и удовлетворительными показателями выживаемости у больных с первично-рефрактерной или рецидивирующей болезнью Ходжкина.

Ключевые слова: лимфома Ходжкина, рецидивирование, первичная рефрактерная болезнь, высокодозная терапия, трансплантация стволовых гемопоэтических клеток