Retrospective Analysis of the Results of High-dose Chemotherapy with the Support of Autologous Blood Stem Cells in Patients with Multiple Myeloma. The Experience of a Single Centre

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Abstract: Despite new medical products introduced in multiple myeloma therapy, autologous stem cell transplant (ASCT) remains a standard procedure in younger patients with symptomatic disease. We analyzed a group of 190 patients who underwent ASCT at our clinic for multiple myeloma as primary therapy in years 1995–2008. The total number of transplants performed in this group was 291. 110 patients underwent one ASCT, 59 patients had double transplant, out of which 51 patients underwent tandem transplant, 21 patients underwent triple ASCT, out of which 15 patients were transplanted front-line throughout a clinical trial and 6 patients underwent follow-up transplants due to disease progression. The assessment of the best therapeutic effect of ASCT showed the total rates of patients with complete remission – 22%, very good partial remission (VGPR) – 8%, partial remission – 63%, stabilized disease – 6% and progression – 1%. The transplant related mortality (TRM) was 4.1%. With the median follow-up of surviving patients 2.6 years, the median progression-free survival (PFS) and overall survival (OS) were 21 and 54 months, respectively; the likelihood of a 7-year overall survival was 28%. Comparing tandem versus single transplants, there was

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a significant increase in the median PFS (25.8 versus 20.8 months, respectively); however, there was no difference in overall survivals. The IVE mobilization regimen was found to be more efficacious for PBPC collection than high-dosed cyclophosphamide.

Introduction

A significant progress has been done in multiple myeloma therapy in the past 15 years, which brought a longer overall survival. Randomized clinical trials conducted in 1990s comparing ASCT with conventional therapy demonstrated higher percentage of complete remissions and longer EFS and, in the majority of patients, overall survival (Attal et al., 1996; Child et al., 2003; Blade et al., 2005; Fermand et al., 2005; Barlogie et al., 2006a). Achieving a superior therapeutic response (at least VGPR) is a key prognostic factor of the further survival (Alexanian et al., 2001; Barlogie et al., 2006b). One of the ways to increase the number of complete remissions is the repeated high dose therapy. This procedure has been tested by a number of clinical trials comparing single versus tandem ASCTs. The majority of these trials demonstrated EFS improvement after the tandem transplant; however, significant prolongation of OS was proved in one trial with mature data only (Attal et al., 2003; Cavo et al., 2007). The results show that repeating ASCT is of the biggest importance in patients who did not achieve at least VGPR following first transplant. On the contrary, the tandem procedure does not bring any other benefit to patients achieving remission after the first ASCT. Further improvement will probably come with the use of new drugs (thalidomide, bortezomide, lenalidomide) having been tested in a combination with ASCT, particularly as a part of the induction therapy (Cavo et al., 2005; Harousseau et al., 2006; Rajkumar et al., 2006; Barlogie et al., 2007), resulting in a significantly higher number of quality therapeutic responses, or as consolidation or maintenance therapy after a transplant procedure (Attal et al., 2006).

Methods

The analysis included patients with multiple myeloma undergoing ASCT at our clinic. The total number of patients observed was 190 with 291 ASCTs performed in years 1995–2008. ASCT was indicated as primary treatment in all patients at the beginning of the therapy. It is necessary to remark that out of the whole population 32 patients were treated in the framework of an international randomized clinical trial (Ludwig et al., 2008) comparing tandem ASCT with preparative regimen with melphalan 200 mg/m^2 (17 patients included) and triple ASCT with melphalan 100 mg/m^2 (15 patients included).

   The majority of patients underwent a single ASCT. Besides taking part in the clinical trial, other indications for tandem or lately repeated ASCTs included failing in the achievement of at least VGPR following first transplant or relapsed disease, respectively.

Kořen J.; Špička I.; Straub J.; Vacková B.; Trnková M.; Pohlreich D.; Pytlík R.; Trněný M.

The induction therapy included regimens combining dexamethasone with cytostatics, either VAD (vincristine 0.4 mg/m^2 on days 1–4, adriamycine 9 mg/m^2 on days 1–4 and dexamethasone 40 mg on days 1–4, 9–12 and 17–20) or CD (cyclophosphamide 1 g/m^2 on day 1, dexamethasone 40 mg on days 1–4 and 9–12).

In the majority of patients, two regimens were used as mobilization chemotherapy for the collection of PBPC (peripheral blood progenitor cells): high-dosed cyclophosphamide (2.5 g/m^2) or IVE chemotherapy (epirubicine 50 mg/m^2 on day 1, iphosphamide 2 g/m^2 on days 1–3, etopozide 150 mg/m^2 on days 1–3). Several patients underwent EDAP chemotherapy (etoposide 400 mg/m^2, cisplatin 80 mg/m^2 on day 1, dexamethasone 40 mg for 4 days and ara-C 1,000 mg/m^2 on day 5). The mobilization chemotherapy was followed by G-CSF stimulation in the dose 10 mcg/kg/day. In 2 patients, PBPC were collected by mobilization with growth factors only after the chemotherapeutic mobilization had failed.

The conditioning regimen included melphalan in a standard dose 200 mg/m^2 except for patients treated by triple transplant in the abovementioned clinical trial who were applied with melphalan 100 mg/m^2. The preparative regimen included whole body radiation in 2 patients, once in combination with melphalan 140 mg/m^2. The dose of melphalan was reduced to 140 mg/m^2 in 6 patients.

The transplant procedure was followed by the administration of G-CSF growth factor (filgrastim) in the dose 5 mcg/kg from day 7 following SCT transfer. The prophylactic security measures included anti-infection therapy with ciprofloxacine 500 mg twice daily plus acyclovir and fluconazole since 1998 and 2000, respectively. The substitution with blood derivatives was indicated in patients with asymptomatic course and Hg and thrombocyte levels under 80 g/l and 20×10^9/l (10×10^9 since 2000), respectively. The formulations administrated were previously deleucotised and irradiated.

Engraftment was defined as the increase in granulocyte and thrombocyte levels exceeding 0.5×10^9/l and 20×10^9/l without following decrease, respectively. The toxicity was assessed according to WHO scale.

The responses were assessed by EBMT criteria (The European Group for Blood and Marrow Transplantation) for the assessment of transplanted patients (Blade et al., 1998). Patients with M-component disappearing at classical electrophoresis but persisting immunofixation are considered as nCR.

Long-term results were analyzed according to Kaplan Meier survival curves. The outcomes that we assessed included overall survival (OS, an interval from blood cell transfer to death or date of the last assessment) and progression-free survival (PFS, an interval from the date of blood cell transfer to progression or the date of the last assessment). The date of ASCT (not the date of diagnosis) was used as the base of the assessment of basic prognostic parameters, because the duration of the induction therapy differs in various periods and its including into analysis could affect the overall assessment. The curves were compared by the log-rank and Gehan Breslow-Wilcoxon tests.

Results

For the population characteristics, see Tables 1 and 2.

The total number of patients having been observed was 190 with 88 (46%) women and 102 (54%) men; the age median at the time of diagnosis was 56 years (range 31–68 years). M-component types of IgA, IgG, IgD and IgM were present in 36 (19%), 118 (64%), 1 (0.5%) and 1 (0.5%) patients, respectively; the production of light chains only was seen in 26 (14%) patients out of which 4 (2%) patients exerted non-secretory myeloma.

Table 1 – Base-line characteristics of the patients (n=190)

		no. of patiens (%)	median	range
Sex (male/female)		102/88 (54%/46%)		
Age (year)			56	(31–68)
M component	IgG	118 (64%)		
	IgA	36 (19%)		
	IgD, IgM	2 (1%)		
	LC	26 (14%)		
	non secretory	4 (2%)		
Induction treatment	no. of lines		1	(1–2)
	no. of cycles		4	(3–11)

Table 2 – Transplant characteristics

		(n)	(%)	median	range
Number of transplants	total	291			
	1 × ASCT	110			
	2 × ASCT	59			
	tandem (up front)	51			
	repeatedly for progression	8			
	3 × ASCT	21			
	triplet (up front)	15			
	repeatedly for progression	6			
Mobilization regimen	CFA	144			
	IVE	41			
	EDAP	3			
	G-CSF only	2			
Conditioning regimen	MEL 200	223	(75.6)		
	MEL 140	6	(2)		
	MEL 100	58	(20)		
	TBI ± CHT	2	(0.7)		
Number of CD34$^+$ graft				6.78×10^{-6}/kg	(2.19–28.9)
Engraftment	Granulocytes ($>0.5 \times 10^9$/l)			+11	(10–28)
	Thrombocytes ($>20 \times 10^9$/l)			+13	(10–45)
Febrile neutropenia	yes	177	(61%)	2 days	(1–19)
	no	114			

Kořen J.; Špička I.; Straub J.; Vacková B.; Trnková M.; Pohlreich D.; Pytlík R.; Trněný M.

Single transplants were performed in 110 patients, 59 patients underwent double transplant out of which 51 patients underwent tandem transplant procedure (3–6 months following first ASCT) and 8 patients had double transplant due to disease progression. Triple ASCT was performed in 21 patients with 15 patients transplanted front-line throughout the abovementioned clinical trial and 6 patients undergoing following transplants due to disease progression.

The number of therapeutic lines preceding the first ASCT ranged between 1 and 2; with the median was 1 line. The median of the number of chemotherapy prior to ASCT was 4 (ranged 3–11).

The mobilization chemotherapy with high-dosed cyclophosphamide, IVE chemotherapy and EDAP combination were used in 144, 41 and 3 patients, respectively. PBPC grafts were obtained after mobilization by growth factors only in 2 patients.

PBPCs were used as a source of haematopoietic cells in 189 patients; bone marrow was used in 1 patient only.

The preparative regimen included melphalan 200 mg/m^2 in 223 cases (76.6%), in doses reduced to 140 mg/m^2 in 6 (2%) cases, in doses of 100 mg/m^2 in 58 (20%) cases. Two patients were subjected to whole body radiation, one in combination with melphalan 140 mg/m^2.

The median number of PBPC for transplants was 6.78 × 10^{-6}/kg CD34$^+$ cells (ranged 2.19–28.9). The medians of engraftment defined by ANC increase over 0.5 × 10^{-9}/l and thrombocyte increase over 20 × 10^{-9}/l were 11 days (ranged 10–28) and 13 days (10–45), respectively. Febrile neutropenia developed in 177 (61%) surgeries with the median duration 2 days (1–19). For the incidence of other toxicity symptoms and their severity, see Table 3. The most significant symptom was mucositis with that of grade 3–4 occurring in 23% patients; other severe toxicities (gr 3–4) did not exceed 5%.

The transplant related mortality (TRM, i.e. death within 100 days following ASCT) was 4.1% (12 patients); 8 patients died from infectious complications, 3 from heart complications and 1 from pseudomembranous colitis complications.

Table 3 – Toxicity (according to WHO scale)

Toxicity	Grade				
	0	1	2	3	4
Mucositis	50 (18%)	79 (28%)	86 (31%)	46 (17%)	17 (6%)
Hepatic	172 (62%)	81 (29%)	16 (6%)	5 (2%)	2 (1%)
Renal	126 (46%)	136 (50%)	8 (3%)	4 (1%)	1
Cardiac	196 (71%)	64 (23%)	6 (2%)	4 (1%)	7 (3%)
Pulmonary	261 (95%)	6 (2%)	2 (1%)	1	6 (2%)
Neurotoxicity	264 (96%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)

Therapeutic effect

After induction therapy in the whole patient population CR (complete remission) + nCR was achieved in 23 (12%) patients, VGPR (very good partial remission) in 7 (4%), PR (partial remission) in 117 (62%), MR (minimal response) in 10 (5%) and SD (stable disease) in 10 (5%); PD (disease progression) was seen in 22 (12%) patients. Regardless the number of ASCT, the assessment of the best therapeutic response achieved in all patients showed CR+nCR in 40 (22%) patients, VGPR in 15 (8%), PR in 114 (63%), SD in 10 (6%) and progression in 2 (1%) patients, see Table 4.

The effect of tandem ASCT was assessed individually; the total number of patients observed was 66 (including those with planned triple ASCT). Following the induction therapy, this group achieved CR+nCR in 4 (6%), VGPR in 1 (1.5%), PR in 49 (74%), MR in 1 (1.5%) and SD in 3 (5%) patients; progression was seen in 8 (12%) patients. After the first ASCT CR+nCR was achieved in 11 (17%) patients, VGPR in 3 (4.5%), PR in 44 (66%) and SD in 3 (4.5%) patients; progression was seen in 5 (7%) patients. Following the second ASCT, CR+nCR was achieved in 14 (20%) patients, VGPR in 3

Table 4 – Results of all patients (n=190)

	After induction therapy	Best response achieved
CR	23 (12%)	40 (22%)
VGPR	7 (4%)	15 (8%)
PR	117 (62%)	114 (63%)
MR	10 (5%)	0 (0%)
SD	10 (5%)	10 (7%)
PD	22 (12%)	2 (1%)

Table 5 – Patients who underwent tandem ASCT (n=66)

	After induction therapy	After 1. ASCT	After 2. ASCT
CR	4 (6%)	11 (17%)	14 (20%)
VGPR	1 (1.5%)	3 (4.5%)	3 (4.5%)
PR	49 (74%)	44 (66%)	45 (68%)
MR	1 (1.5%)	0 (0%)	0 (0%)
SD	3 (5%)	3 (4.5%)	3 (4.5%)
PD	8 (12%)	5 (7%)	1 (2%)

Table 6 – Patients who underwent single ASCT (n=110)

	After induction therapy	Best response achieved
CR	17 (15.4%)	24 (21.8%)
VGPR	5 (4.5%)	8 (7.2%)
PR	60 (54.5%)	61 (55.4%)
MR	9 (8.1%)	0 (0%)
SD	5 (4.5%)	7 (6.4%)
PD	14 (12.7%)	1 (0.9%)

Kořen J.; Špička I.; Straub J.; Vacková B.; Trnková M.; Pohlreich D.; Pytlík R.; Trněný M.

(4.5%), PR in 45 (68%) and SD in 3 (4.5%) patients; progression was observed in 1 (2%) patient, see Table 5.

In patients with single ASCT, the induction therapy resulted in CR+nCR in 17 (15.4%) patients, VGPR in 5 (4.5%), PR in 60 (54.5%), MR in 9 (8.1%) and SD in 5 (4.5%) patients; progression was seen in 14 (12.7%) patients. Following single ASCT, CR+nCR was achieved in 24 (21.8%) patients, VGPR in 8 (7.2%), PR in 61 (55.4%) and SD in 7 (6.4%) patients; progression was seen in 1 (0.9%) patient and the response was not assessed in 9 (8.1%) patients (TRM in 6 patients and the data are not available in 3 patients), see Table 6.

Long-term follow-up
The median follow-up of surviving patients is 2.6 years (0.4–11.5).

According to the analysis of the whole patient population, the median PFS and OS were 21 and 54 months, respectively. The estimated 7-year overall survival is 28% (Figure 1).
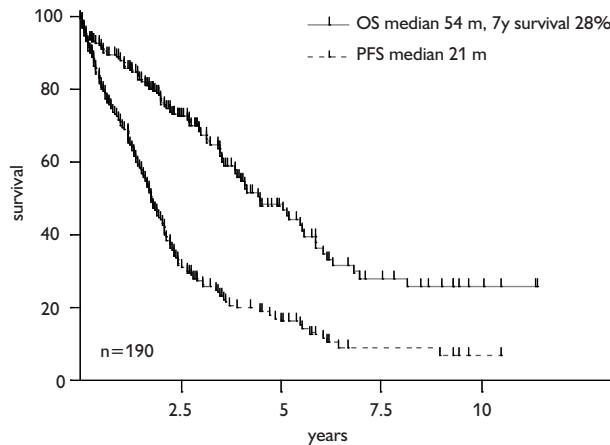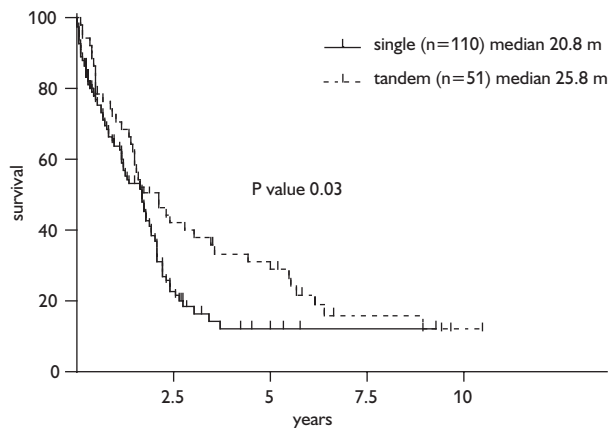

Figure 1 – PFS and OS – all patients.

Figure 2 – PFS single vs. tandem ASCT.

Up-front ASCT for Multiple Myeloma, Single Center Experience

The comparison of survival curves between a group of patients with single transplant and a group of patients with tandem transplant showed the median PFS in tandem transplanted patients and those with single ASCT – 25.8 months and 20.8 months, respectively, which is a statistically significant difference (P=0.03). On the contrary, the median OS was shorter in the tandem ASCT group (54 months) compared with 61 months in patients with single ASCT; however, the difference was not statistically significant (Figures 2 and 3).

The analysis of long-term results in terms of the best therapeutic response to ASCT showed that the median PFS in patients achieving CR+nCR, VGPR, PR and response worse than PR were 23.5, 29.6, 21 and 6.7 months, respectively; however, the differences were not statistically significant (Figure 4). Comparing OS in patients with CR+nCR, VGPR and PR, the medians were 71.2, 62.8 and
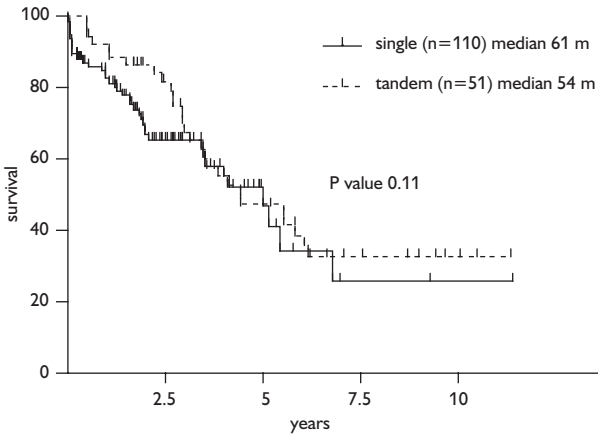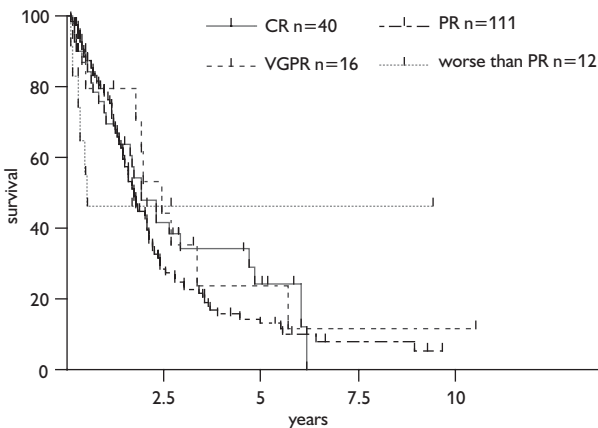

Figure 3 – OS single vs. tandem ASCT.

Figure 4 – PFS according to response achievement.

Kořen J.; Špička I.; Straub J.; Vacková B.; Trnková M.; Pohlreich D.; Pytlík R.; Trněný M.

50 months, respectively; the median was not achieved in patients with neither PR due to their low number. However, the differences were not statistically significant, either (Figure 5).

Results of mobilization chemotherapy
A subanalysis of the patient population included the comparison between the results of peripheral stem progenitor cell collection following two different mobilization regimens. This analysis included 176 patients. The standard mobilization regimen with high-dosed cyclophosphamide (2.5 g/m^2) was applied in 135 (77%) patients, whereas mobilization chemotherapy with IVE was used in 41 (23%) patients – particularly in those treated throughout the above mentioned clinical study (Ludwig et al., 2008). G-CSF stimulation was performed with the same doses – 10 mcg/kg/day – from day 3 following CFA or day 4 after chemotherapy with IVE. Following CFA mobilization, the median number of collected PBPCs was 11.6 × 10^{-6}/kg CD 34$^+$ cells (range 2.2–68.2), whereas the median following mobilization with IVE was 26.3 × 10^{-6}/kg (range 5.4–93).

Discussion
The achievement of a quality therapeutic response (CR$^+$ VGPR) has a fundamental prognostic influence on the improvement of overall survival. High-dose therapy with autologous transplant has been proved as an efficacious therapeutic method resulting in a high number of quality responses and remains a standard therapeutic modality for younger patients with symptomatic disease. On the base of randomized trials, the tandem transplant is recommended for patients who do not achieve at least VGPR after their first transplant.

Our results of high-dose therapy with autologous transplant in multiple myeloma correspond with the results related to this issue and published in literature.
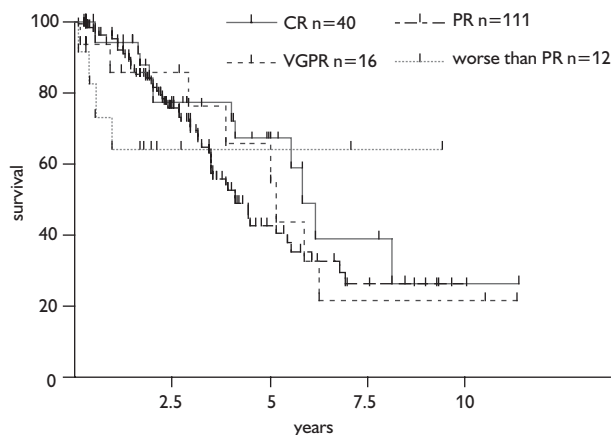

Figure 5 – OS according to response achievement.

Up-front ASCT for Multiple Myeloma, Single Center Experience

Regarding retrospective assessment of the ASCTs performed within 13 years, the population is appreciably heterogeneous in terms of various induction therapy and indications for multiple high-dose therapy; last but not least, the overall survival in the last decade is probably affected by the therapy of relapses and progressions after transplantation therapy depending on the use of new drugs.

The comparison of tandem versus single transplant showed significant prolongation of EFS; however, the overall survival was rather better with single transplant (the median OS was 61 versus 54 months, respectively); nevertheless, the difference was not statistically significant. This can be partially explained by the fact that the majority of indications for the tandem transplant was defined as failure in achieving of at least VGPR following the first transplant; thus, it was performed in patients with less chemosensitive disease, which is also demonstrated by a lower number of CR after the induction phase of the therapy in this group of patients compared with the whole population (CR rate 6% versus 12%, CR$^+$ VGPR 7.5% versus 16%, respectively). However, the efficacy of multiple transplants is demonstrated by an increase in the number of quality responses (CR$^+$ VGPR) following the second (tandem) transplant.

The comparison of results of long-term progression-free survival and overall progression based on the best response suggested a trend towards better results, particularly that of overall survival in patients achieving CR and VGPR (OS median 71.2 and 62.8 months, respectively) versus PR group (OS median 50 months); however, the difference was not of statistical significance. This can be explained by a relatively low number of patients in the groups compared and by the heterogeneity of the tested group, particularly in terms of various post-transplant therapies throughout the years.

Moreover, the mobilization chemotherapy with high-dosed cyclophosphamide and chemotherapy with IVE were compared in terms of the efficacy of the stimulation of peripheral haematopoietic cells; the mobilization regimen with IVE was significantly more efficacious in the population analyzed. This difference can be partially explained by the fact that the mobilization therapy with IVE was administrated after 3 VAD cycles (throughout the abovementioned clinical trial), whereas the mobilization therapy with high-dosed cyclophosphamide usually followed in 4 cycles of chemotherapy with VAD which could result in potentially bigger damage of stem cells. Nevertheless, it seems probable that chemotherapy with IVE has bigger potential in this issue. Although multiple myeloma belongs to the diseases with a high number of patients with successful stem blood stem cell collection in the vast majority of patients, the results of this analysis can be of significance, particularly in patients with border PBPC collection following mobilization with cyclophosphamide.

The determination of the position of autologous transplant in the era of new drugs is a subject of clinical testing. The induction therapy with new drugs leads to the results which are comparable with those of ASCT and induces complete

remission in a high number of patients. Clinical trials suggest that a combination of new drugs with following ASCT could bring further improvement of the results (Barlogie et al., 2007). Higher percentage of quality responses could result in the reduction of tandem transplants. It begs a question whether ASCT performed as consolidation therapy brings further benefit in terms of the duration of survival to patients achieving complete remission after the induction with new drugs or if ASCT can be delayed until the therapy of relapse. These questions will be answered after further study of the results of ongoing trials and other randomized trials which compare the effects of new drugs with or without ASCT and which can help determine its role in the new era of modern drugs.

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