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HIGH EFFICACY AND SAFETY OF VTD AS AN INDUCTION PROTOCOL IN NEWLY DIAGNOSED MM PATIENTS ELIGIBLE FOR HDT/AUTOSCT A REPORT OF POLISH MULTIPLE MYELOMA STUDY GROUP

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INTRODUCTION

The three drug bortezomib-based regimens are nowadays generally recommended standard induction therapy for transplant-eligible patients with newly diagnosed multiple myeloma. The choice between different regimens depends on drug availability in particular countries, their toxicity profile and local preferences. So far, only one phase 3 clinical study comparing three drug-bortezomib-based protocols was published showing higher efficacy of VTD (bortezomib, thalidomide, dexamethasone) comparing to VCD (bortezomib, cyclophosphamide, dexamethasone) protocol and their different toxicity profile (Moreau et al.). Observations from routine practice might have also significant clinical importance.

OBJECTIVES

The aim of this retrospective analysis was to evaluate the efficacy and safety of VTD regimen in newly diagnosed MM patients eligible for HDT/autoSCT in routine clinical practice.

METHODS

We collected the clinical data of 169 patients qualified to HDT/autoSCT treated with VTD as an induction regimen in 14 Polish hematology/oncology centers. VTD protocol recommended by Polis Multiple Myeloma Study Group was as follows: bortezomib: 1.3 mg/m^2(days 1, 4, 8, 11), thalidomide: 100 – 200 mg a day (days 1-21), dexamethasone 20 mg a day (days: 1 ,2, 4, 5, 8, 9, 11, 12) or 40 mg a day (days 1 - 4), every 21 days. Patients were included into analysis if ≥1 cycle of VTD was administered. Adverse events (AEs) were graded according to CTCAE v4.0. The analysis involved also the impact of VTD regimen on efficiency of stem cells mobilization as well as high dose therapy/ autologous stem cell transplantation (HDT/autoSCT) procedure.

RESULTS

In the cohort of 169 patients, median age was 59 years (range 36 – 70). ISS stage 1 was found in 30.8% of patients, ISS 2 and 3 in 20.7% and 45.5%, respectively. Characteristics of patients are presented in Table 1.

Table 1. Clinical charecteristics of patients treated with VTD regimen

Age; years, median (range)		59 (36-70)	
		N	%
Sex	F	86	51
	M	83	49
M-protein type	IgG	91	54
	IgA	34	20
	LCD	38	22.5
	other (IgM, NS, PCL)	6	3.5
	Kappa	67	40
	Lambda	86	58

Abbreviations: LCD, light chain disease; NS, non secretory; PCL, plasma cell leukemia

RESULTS

Median number of VTD cycles was 5. In 81.6% of patients bortezomib was administered subcutaneously. Thalidomide dose was 100 mg a day in 85.1% of patients.

Efficacy of VTD regimen as induction therapy

Response ≥ PR was achieved in 95% of patients and ≥ VGPR in 65% of patients (Figure 1).

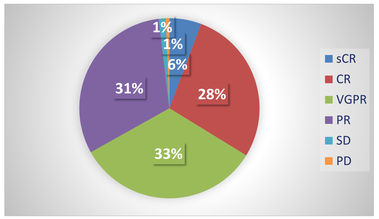

Figure 1. Response rates in patients with MM treated with VTD as an induction regimen.

Toxicity of VTD as an induction regimen

The most common grade 3/4 adverse event was polyneuropathy, observed in 20 patients (11.8%). Neutropenia was the most common hematological toxicity, though it was noted only in 5 patients (3%) (Table 2 and Table 3).

Table 2. Hematological toxicity of VTD regimen

Hematological toxicity	1 – 2 grade acc. CTCAE v4.0		3 – 4 grade acc. CTCAE v4.0	
	N	% (169)	N	% (169)
Neutropenia	1	0,6	5	3,0
Thrombocytopenia	4	2,4	1	0,6
Anemia	12	72	-	-

Table 3. Non hematological toxicity of VTD regimen

Non hematological toxicity	1 – 2 grade acc. CTCAE v4.0		3 - 4 grade acc. CTCAE v4.0	
	N	% (169)	N	% (169)
Polyneuropathy	8	4,8	20	11,8
Infections	10	6,0	1	0,6
Thrombosis	3	1,8	-	-
Constipations	2	1,2	-	-
Skin changes	8	4,8	-	-

Bortezomib dose was reduced in 43 patients (25.4%) with peripheral polyneuropathy as the most common reason (75%). Early discontinuation of induction therapy was noted in 36 of patients (21.3%) with adverse events as a reason of discontinuation in 23 patients (64%) including polyneuropathy in 15 patients (42%).

Results of stem cell mobilization after VTD as an induction regimen

So far, stem cell mobilization was performed in 110 patients. Most commonly used protocols were cyclophosphamide (42.9%) and cytosine arabinoside (36.2%).

In 69.3% of patients one apheresis allowed to obtain the number of stem cells sufficient for transplantation. Median yield of CD34+ cells was 11 x 10^6/kg (max 55.7 x 10^6/kg) that was sufficient for two transplantations in the majority of patients.

RESULTS

Results of HDT/autoSCT after VTD as an induction regimen

HDT/autoSCT was performer so far in 89 patients with Melphalan 200 mg/m2 protocol as conditioning regimen in 77.6% of patients.

Median number of transplanted CD34+ cells was 4.4 x 10^6/kg. Median time to reach ANC Mount > 0.5 G/L and PLT count> 20 G/L was 11 days and 12 days, respectively.

Evaluation of response 100 days after HDT/autoSCT performed in 81 patients, showed ≥ PR in 49.4% of patients and ≥ VGPR in 83.5% of patients (Figure 3). There was an increase of sCR rate from 5.6% to 12.7% and CR from 27.1% to 36.7%

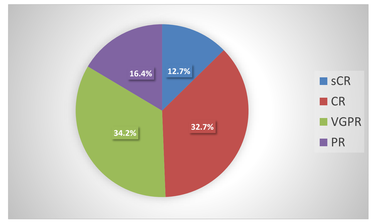

Figure 3. Response rates in MM patients in evaluation performed 100 days after HDT/autoHSCT.

CONCLUSIONS

- VTD regimen (with dexamethasone dose of 20mg a day and thalidomide dose of 100mg a day in majority of patients) allowed to achieve ≥ PR in 95% of patients including ≥ VGPR u 64.8% of patients as compared to 73.5% ≥ PR including 36% of ≥ nCR achieved in patients treated with CTD in our previous study (Dmoszynska et al. Leuk Res 2010).
- Treatment was safe and well tolerated with polyneuropathy and neutropoenia as the most common grade≥ 3 adverse events (12% and 3%, respectively).
- Inductiontherapy with VTD regimen allowed to obtain sufficient number of CD34+ cells Turing first procedure in 96% of patients subsequently undergoing stem cell mobilization (median 11.0 mln/kg).
- HDT/autoSCT procedure further increased response rate after VTD induction (≥ CR up to 43.5%, ≥ VGPR up to 83.5%).

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