Early versus delayed autologous stem cell transplant in patients receiving induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) for newly diagnosed multiple myeloma

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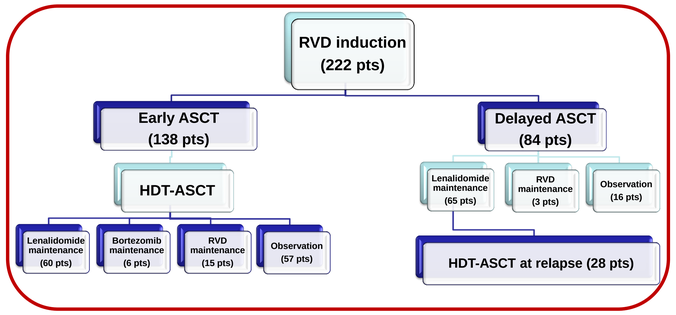
Background

- Prior to the era of novel agents (thalidomide, lenalidomide, bortezomib), the standard approach for treatment of newly diagnosed younger myeloma patients is initial therapy with cytotoxic agents like vincristine, adriamycin, and dexamethasone (VAD), followed by melphalan high dose therapy with autologous stem cell transplant rescue (HDT-ASCT) (Attal, M 1996).
- In phase 2 trials, combination of lenalidomide, bortezomib and dexamethasone (RVD) is an active, tolerable regimen in newly diagnosed myeloma patients with superior response rates (≥VGPR rates of ≈64%) after 4 cycles of induction therapy; surpassing the response rates seen with HDT-ASCT from pre-novel agent era (Richardson, P 2010).
- HDT-ASCT following induction therapy with combination of novel agents bortezomib, thalidomide and dexamethasone (VTD) as induction therapy in phase 3 trials augmented the post-induction response rates (Cavo, M 2010). Similar data from phase 3 trials is unavailable for the RVD as induction therapy.
- In phase 2 trials, HDT-ASCT following induction therapy with RVD induction therapy improves the post-induction response rates (≥VGPR rates of ≈70%; ORR ≈ 100%) (Roussel, M 2010, Richardson, P 2010) suggesting that HDT-ASCT continues to be an important treatment regimen in the armamentarium of myeloma treatments. However, with the increase in the depth of the responses seen with these newer agents, the optimal timing of HDT-ASCT is uncertain, especially in younger patients treated with combination regimens.
- We have evaluated our institutional experience to provide an insight for the best timing of HDT-ASCT, where specific patients were offered delayed HDT-ASCT based on risk, response and toxicity of therapy.

Methods

- 222 transplant-eligible patients with newly diagnosed MM treated with at least 2 cycles of RVD induction therapy and underwent stem cell collection from May 2007 until October 2011 were identified from our myeloma database from our myeloma database.
- 138 patients underwent planned early transplant; 84 patients underwent delayed transplant based on risk, response, toxicity and patient preference. The flow chart illustrates the maintenance approaches before and after HDT-ASCT
- 21 patients were identified with high risk cytogenetics (CTG). High risk CTG were defined as presence of del 17p, t(4;14), t(14;16), by fluorescence in-situ hybridization (FISH) or by conventional CTG.
- All the intended patients qualifying the inclusion criteria underwent HDT-ASCT in the early transplant group. 28 patients underwent HDT-ASCT in the delayed group
- Median follow up for both PFS and OS is 31 months

Flowchart

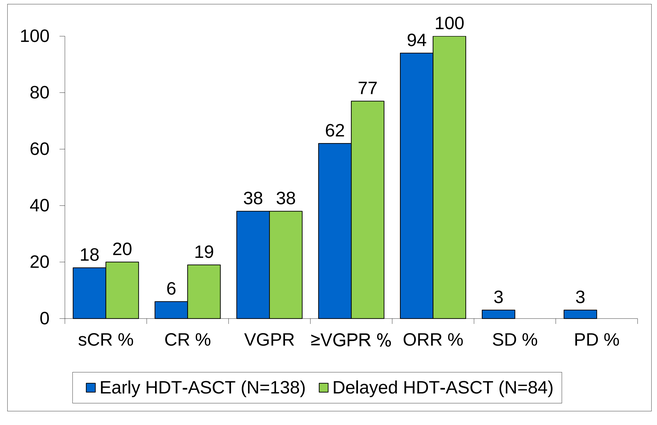


Patient Characteristics

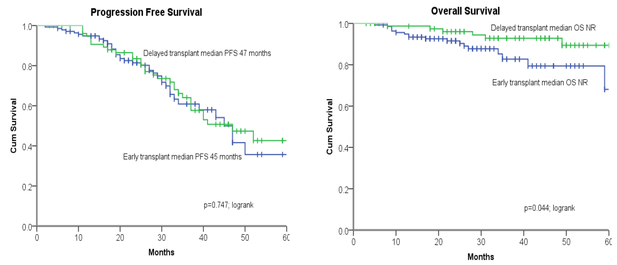
Patient Characteristics	Early HDT-ASCT (N-138)	%	Delayed HDT-ASCT (N-84)	%
Sex (Male/female)	78/60	56.5/43.5	45/39	54/46
Race (White/AA/Hispanic/Asian)	88/45/4/1	63.5/32.5/3/1	56/21/3/5	67/25/3/5
Isotype (IgG/IgA/FLC/IgM)	83/28/27/0	60/20/20/0	53/14/16/1	63/16/19/1
ISS Stage (I/II/III/unknown)	27/31/26/54	20/22/19/38	21/32/6/25	25/38/7/30
Risk del 17/t (4;14)/t (14;16)	6/7/2	4.5/5/1.5	3/3/0	3.5/3.5/0
Median Age at dx, years (Range)	60.5 (32-77)		60 (22-73)	
Median Age at HDT, years (Range)	61 (33-78)		63 (43-72)*	
Median no of RVD cycles (Range)	4 (2-9)		6.5 (2-8)	
Median β-2 microglobulin (Range)	3.8 (0.94-17.10)		2.57 (0.8-21.3)	
Median Albumin (Range)	3.6 (1.3-4.9)		3.7 (2.6-5.3)	
Median Hemoglobin (Range)	10.6 (5.0-15.60)		11.2 (7.0-16)	
Median Creatinine (Range)	1.10 (0.50-16.1)		1.05 (0.40-6.0)	
Median Calcium (Range)	9.1 (7.6-16.1)		9.2 (8.3-19.2)	
Median LDH (range)	150 (70-363)		142 (79-146)	
Median plasma cells in BM (range)	40 (1-100)		33 (1-100)	
Median KPS (range)	80 (40-100)		90 (60-90)	
Median time from diagnosis to therapy, months (Range)	1 (0-9)		0 (0-7)	
Median time from diagnosis to HDT-ASCT, months (Range)	7 (3-17)		26.5 (14-42)*	
Median time from therapy to HDT-ASCT, months (Range)	5 (3-12)		26 (13-41)*	

*in patients that underwent HDT-ASCT

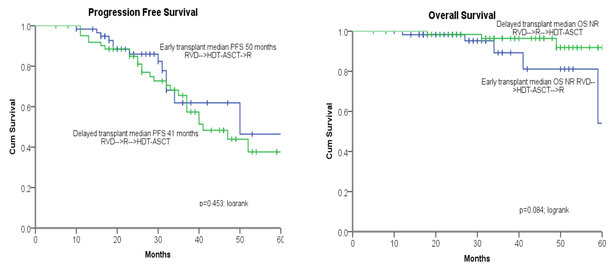
Post induction response rates



PFS and OS - entire cohort



PFS and OS - selective cohort (lenalidomide maintenance)

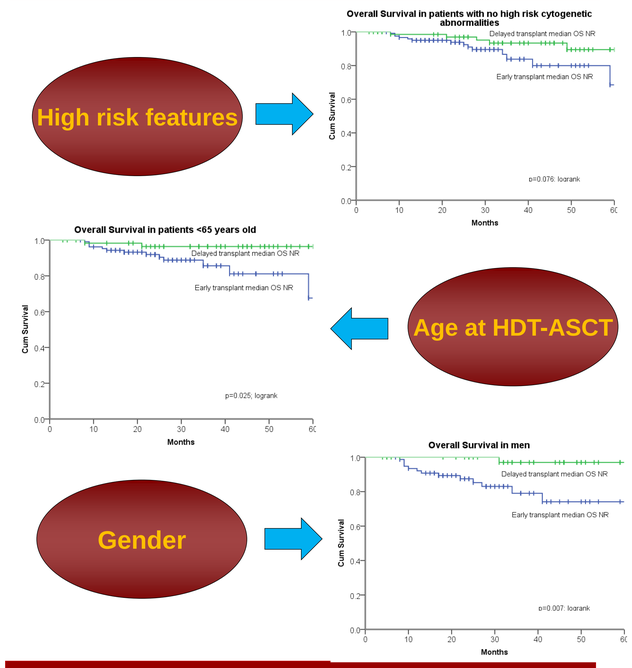


Survival by risk, response, demographics

Survival by risk, response, demographic variables - Univariate analysis

	PFS			OS		
	Early	Delayed	p-value	Early	Delayed	p-value
ISS stage I/II	47 months	40 months	0.280	NR	NR	0.741
ISS stage III	31 months	-	0.731	NR	NR	0.938
No high risk	47 months	47 months	0.987	NR	NR	0.076
High risk	25 months	28 months	0.797	NR	NR	0.181
Plamsa cells ≥50%	43 months	37 months	0.914	NR	NR	0.574
Plasma cells <50%	45 months	52 months	0.855	NR	NR	0.124
sCR	NR	NR	0.160	NR	NR	0.857
≥CR	45 months	47 months	0.747	NR	NR	0.535
≥VGPR	47 months	47 months	0.691	NR	NR	0.526
≥PR	47 months	47 months	0.689	NR	NR	0.206
<PR	11 months	-	-	13	-	-
Male	47 months	-	0.529	NR	NR	0.007
Female	39 months	40 months	0.849	NR	NR	0.900
White	47 months	40 months	0.653	NR	NR	0.267
Black	39 months	52 months	0.181	NR	NR	0.240
Age ≥65	45 months	-	0.724	NR	NR	0.526
Age <65	47 months	41 months	0.579	NR	NR	0.025

OS - subsets



Conclusions

- Transplant eligible myeloma patients receiving RVD as induction regimen results in prolonged PFS, OS.
- Selection bias exists for head to head comparison of outcomes; but our analysis suggests that delayed HDT-ASCT is a feasible option in selected newly diagnosed myeloma patients receiving RVD induction therapy and achieve >PR.
- Males, patients under the age of 65, and those not exhibiting high risk cytogenetics have better outcomes with delayed HDT-ASCT approach.
- Until phase 3 data available, our institutional experience could provide a perspective that delayed HDT-ASCT following RVD induction therapy is a feasible approach in selected patients

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