[haematologica reports]
2006;2(5):2

An update of the APEX study

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APEX, a pivotal phase III, randomized, multicentre trial was the largest performed in relapsed multiple myeloma (MM) to date, comparing Bortezomib (Velcade®) with high dose dexamethasone (Dex). The initial results of this important study were published by Paul Richardson and colleagues in the New England Journal of Medicine (NEJM) in 2005.[1]

Since these results were published, all Velcade patients who were ongoing at the time of the NEJM publication have completed study participation (i.e. completed all cycles or discontinued the study). However, because of dexamethasone arm was halted early, the results, apart from overall survival, have only been updated for Bortezomib (Velcade®) patients. The median follow-up time has extended from 8.3 months to 22 months giving a better indication of the impact of Bortezomib (Velcade®) monotherapy in relapsed or refractory multiple myeloma patients.

In the APEX trial, 669 patients with MM relapsed after 1-3 prior therapies were randomized to receive Bortezomib (Velcade®) or Dex according to the schedule reported in Figure 1.

Patients previously resistant to Dex were excluded from the study, and those with progressive disease on Dex were eligible to cross over to Bortezomib (Velcade®).

In the APEX study published on NEJM, Bortezomib (Velcade®) has proven to be superior to high-dose dexamethasone in terms of response rate, time to progression, and overall survival. The overall response rate (CR+PR) was 38% for Bortezomib (Velcade®) and 18% for Dex (p=0.001); median time to progression was 6.2 months for Bortezomib (Velcade®) and 3.5 months for Dex (p=0.001); survival rate at 1 year was 80 vs 66% (p=0.003) for Bortezomib (Velcade®) and Dex respectively. APEX trial demonstrated a superiority of bortezomib also in patients with only 1 prior line of therapy. Importantly, the efficacy of Bortezomib (Velcade®) is maintained in elderly patients and patients at high-risk[2] (β2 microglobulin level > 2.5 mg/L, refractory to previous therapy, and > 1 previous line of therapy).

Updated APEX results

Patients receiving Bortezomib (Velcade®) achieved significant improvement in time to progression (TTP, primary end point), response rate (CR + PR using EBMT criteria), and survival. In this analysis, updated response rates, time to response (TTR), DOR, survival, and TTP are presented after extended follow-up.[2]

A summary of the updated APEX results can be seen in Table 2. as shown a longer follow up confirms the efficacy of Bortezomib (Velcade®) reported in the NEJM article for time to progression (TTP) and duration of response (DoR). Importantly, the overall response rate (CR+PR) has improved from 38 to 43% and the CR/nCR rate increased to an impressive 16%. This is important since, as already demonstrated for stem cell transplant, a CR represents a significant prognostic factor for overall survival. Median DoR was longer in patients achieving CR and near CR than in those with PR.

Of note, Bortezomib (Velcade®) continues to demonstrated superior overall survival compared to dexamethasone, with a 1-year survival rate stable on a 80% of patients even though over 62% of patients in the high-dose dexamethasone arm crossed over to receive Bortezomib (Velcade®) due to progressive disease. The improvement in response rate and DoR did not imply a higher toxicity. In fact, infections grade 3, time to skeletal events, grade 4 adverse events (AE), serious AE, and discontinuations due to AE were similar in the 2 treatment arms.

Bortezomib (Velcade®) is associated with a rapid time to response. The median time to first response was 43 days (within to first 2 cycles of therapy) in the APEX trial in both the final and updated analysis. In the APEX

Table 1. Baseline characteristics of patients.

	Bortezomib (N=333)	*Dexamethasone (N=336)*
Median age, yrs	62	61
Male sex, no. (%)	188 (56)	200 (60)
IgG/IgA/IgD/IgM, %	60/23/2/<1	59/24/1/0
Median yrs from diagnosis	3.5	3.1
Karnofsky performance scale ≥70% no. (%)	304 (94)	312 (96)
Median serum β2-microglobulin, mg/L	3.7	3.6
Median C-reactive protein mg/L	4.0	4.0
Median Hb, g/L	108	109
Median PLT, cells/mmc	193	188
Creatinine clearance ≤20 mL/min, no./total no. (%)	8/330 (2)	5/323 (2)
Median no. of previous therapies	2.0	2.0
Previous thalidomide/stem cell transplant %	48/67	50/68

Table 2. Summary of results of the APEX updated analysis.

	BORTEZOMIB		*HD-DEX*
	Update Dec 05	*Final Jan 04*	*Final Dec 04*
Response rate %	43%	38%	18%
CR	9%	6%	<1%
PR	34%	32%	17%
nCR	7%	7%	<1%
Median TTP	6.2	6.2	3.5
Median DoR	7.8	8.0	5.6
CR	9.9	9.9	NE
PR	7.6	7.8	5.6
nCR	11.5	-	-
1-year survival %	80	80	67

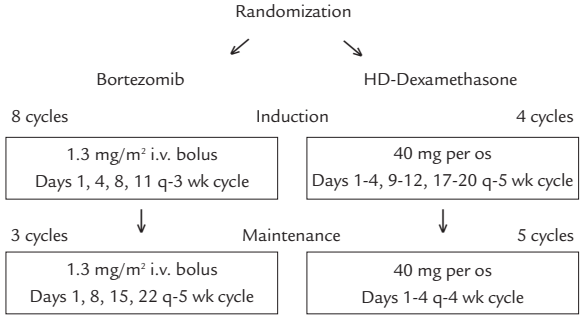

Figure 1. APEX scheme.

trial, 97% of responding patients (defined as CR+PR+MR) achieved the first response within the first 4 cycles.

In this updated analysis, although response is confirmed to be rapid, continued therapy is associated with improvement of quality of response. As shown in Table 3, in fact, 56% of patients improve response after cycle 6, 74% from MR to PR and 26% from MR or PR to CR. Furthermore, 28 of 135 responders (21%) achieved first response (CR/PR) after cycle 4, including 18 pts (13%) on or after cycle 6, and 10 pts (7%) on or after cycle 8.

Table 3. Time to maximal serum M-protein reduction in responding patients.

No of responding patients	135/315 (43%)
Median time to response, mo (range)	1.4 (0.5-6.0)
CR	0.8 (0.5-4.0)
PR	1.4 (0.5-6.0)
nCR	0.8 (0.6-2.4)
Improved response after cycle 6	
Total No	76/135 (56%)
from MR or PR to CR	20/76 (26%)
from MR to PR	56/76 (74%)
No patients achieving response (CR/PR): 10/135 (8%)	
≤cycle 4	107/135 (79%)
>cycle 4 and ≤cycle 6	18/135 (13%)
> cycle 6	10/135 (8%)

Conclusions

The updated analysis of APEX trial provides further evidence of the superior efficacy of Bortezomib (Velcade®) with respect to high-dose dexamethasone in patients with relapsed or refractory myeloma. This advantage is in terms of time to progression, response rates, time to response, duration of response, and survival. Although response to Bortezomib (Velcade®) remains rapid, response rate improves with longer treatment, supporting the indication to prolong the

treatment particularly in less responding patients.

The clinical benefits of Bortezomib (Velcade®) used as single agent after extended follow-up confirm its efficacy in multiple myeloma and suggest its early use in relapsed patients and the need of further studies in newly diagnosed patients.

References

1. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352: 2487-98.
2. Richardson PG, Sonneveld P, Schuster MW, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed myeloma. J Clin Oncol 2005; 23 (suppl): 568s.
3. Richardson P, Sonneveld P, Schuster M, et al. Bortezomib Continues Demonstrates Superior Efficacy Compared with High-Dose Dexamethasone in Relapsed Multiple Myeloma: Updated Results of the APEX Trail. Blood (ASH Annual Meeting Abstracts), Nov 2005; 106: 2547.