ORIGINAL ARTICLE

The Proteasome Inhibitor Bortezomib (Velcade) in the Treatment of Relapsed/Refractory Multiple Myeloma. The First Experience in the Czech Republic

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ABSTRACT

Background. Multiple myeloma is the second most prevalent and, in most cases, fatal hematological cancer. Research into the biological nature of the disease has focused on the identification of mechanisms that could become the targets of new therapeutic procedures. Currently this means intervention into the interaction of myeloma cells and the micro-environment of the bone marrow and influencing the intracellular metabolic processes in tumor cells. One group of substances intervening into the intracellular mechanism (the principle of targeted therapy) is inhibitors of proteasomee and bortezomib (Velcade), the first agents from this group applied in clinical practice.

Methods and Results. In 2004, 29 patients, 18 men and 11 women, aged 42 to 80 years, with refractory/relapsed myeloma were treated with bortezomib (Velcade, Millennium Pharmaceuticals) in six hematological centers in the Czech Republic. The initial dose of Velcade was 1.3 mg/m^2, though in one case the dose was adjusted to 1 mg/m^2 due to pre-existing renal failure. Response was achieved in 17 patients (59%), of these 4 achieved complete remission, 11 partial remission and 2 a minor response. 5 patients were stabilized, in 6 cases there was progression of the disease during therapy. One patient died of sepsis soon after the start of treatment. The average response time was 55 days (2.6 cycles).

Conclusions. The most common adverse effects were thrombocytopenia, anaemia, neuropathy, gastrointestinal complication, renal failure and fatigue. The risk of grade 4 toxicity was 44.8% (5x thrombocytopenia, 2x gastrointestinal and 2x renal failure, 1x sepsis, leucopoenia, hepatopathy or anaemia). Grade 3 peripheral neuropathic pain was reported in 4 cases; in one patient therapy had to be interrupted. Our data confirm the encouraging results of phase II trials.

Key words: multiple myeloma, proteasomee, bortezomib, pre-existing renal failure.

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Following non-Hodgkin's lymphomas, multiple myeloma (MM) is the second most common hematological malignancy; it accounts for 1–2% of all tumors and leads to 20% of deaths of patients with hematological cancers (1). In spite of the indisputable benefit of high-dose therapy, it remains in most cases an incurable disease. However, new findings on the biological nature of the disease have led to the identification of the molecular mechanisms participating in the pathogenesis of the disease, in the malignant proliferation, survival and drug resistance of the myeloma population (2).

An important role in these processes is played by the interaction of clonal MM cells with the proteins of the extracellular matrix and with supporting cells (stromal cells of the bone marrow, osteoclasts, osteoblasts) (3). The known mechanisms include, for instance, the integrin bond to fibronectin with the following inhibition of Fas-mediated apoptosis (4), the intercellular interaction mediated by adhesive molecules, inducing cytokine secretion (5), the effect of the main growth factor IL-6, the TNFalpha effect mediated by transcription nuclear factor kappaB (NFκB) (6), the secretion of angiogenesis factors (VEGF – vascular endothelial growth factor, FGF – fibroblast growth factor) (7), the effect of the insulin-like growth factor 1 (IGF1) and of the stroma-derived factor 1 (SDF1) (8) or the interaction between the myeloma population and osteoclasts (osteoprotegerin/RANK, RANKL system) (9).

Intercellular interaction and the dynamic cytokine network, as well as certain recently identified intercellular processes, are the current target of new drugs that could overcome resistance to conventional chemotherapy. The preliminary results of studies concerning the preparations affecting these mechanisms, administered in advanced and, recently, also in initial forms of myeloma, are very promising.

Proteasomee is a multi-catalytic enzyme complex, present in cytoplasm and in the nuclei of eukaryotic cells, which plays a key role in the management of proteins controlling the development of the cellular cycle and of the process of apoptosis (10, 11). Proteins

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"marked" by ubiquitin enter this complex and are degraded by it (12, 13). Bortezomib, originally PS-341, is currently the only proteasome inhibitor used in clinical practice. It has a high affinity and specificity for the catalytic sites of 26S proteasome and can thus block the degradation process in this complex. One of the main mechanisms of the effect is the impact on the function of transcription factor NFκB (13). However, other possible mechanism have been identified, too – inhibition of signaling processes controlled by IL-6 by "down regulating" GP130 (IL-6 receptor) in the cytoplasm, weakening of the MM cells bond to the stromal cells, overcoming the protective effect of IL-6 against apoptosis induced by dexamethasone, and some others (4).

The results of preclinical studies, of phase 1 and especially phase 2 studies, led in May 2003 to the approval of bortezomib for the treatment of the relapsing and refractory forms of myelomas in the U.S., applying the exceptional, so-called accelerated procedure. Soon after that the drug was approved for clinical use in the European Union. We present the summary of the first results attained from 29 patients in the Czech Republic.

PATIENTS AND METHODS

From April to December 2004, 29 patients, 18 men and 11 women, age 42-80 years (median 61), with the relapsing/refractory form of myeloma were treated at six hemato-oncological centers in the Czech Republic; all had previously undergone at least 2 lines of treatment. Bortezomib (Velcade, Millennium Pharmaceuticals) was administered as part of the VIP (Velcade Initiation Program) program, provided for and sponsored by Janssen-Cilag (supply of free drug). Five patients included into our analysis were treated under the same conditions and following the same procedure as prescribed by the multicentric clinical trial phase 3b. In the past, the patients had received 2 (10x), 3 (12x), 4 (4x), 5 (2x), or 6 (1x) lines of treatment. In a large majority of the cases (16x) the patients had received high-dose chemotherapy supported by stem cells (ATKD) (5x after single, 8x after double, 3x after triple ATKD); in 11 cases thalidomide had been administered at an earlier period. Besides tandem ATKD one of the patients underwent combined autologous and mini-allogennous transplantation. The basic data are summarized in Table 1.

The basic inclusion criteria for start of treatment were: age over 18 years, general state scored according to Karnofsky at 60 or more per cent, thrombocytes exceeding $29x10^9$/l, Hb>69 g/l, minimum number of neutrophils $0.5x10^9$/l, absence of severe hypercalcemia, liver lesions, peripheral neuropathy >1st degree according to the WHO, and creatinin clearance values 30 ml/min and more. All patients signed an informed consent form before being included into the program/trial.

Velcade was administered in initial doses of 1.3 mg/m^2 as an i. v. bolus, the 1st, 4th, 8th and 11th day as a part of a 21-day cycle. In one case the dose was initially reduced to 1.0 mg/m^2 due to pre-existing renal insufficiency. When the disease progressed after the 2nd cycle, or if the response (stabilization) was inadequate after the 4th cycle, dexamethasone was administered simultaneously in doses of 20 mg/day, on days 1+2, 4+5, 8+9 and 11+12. The anticipated number of cycles was 6; in case of complete remission, the treatment was terminated after a further 2 cycles. However, treatment could be prolonged to 8 or more cycles if it was evident that such continuation would be beneficial in the given case. Doses were reduced (to 1 mg/m^2 or 0.7 mg/m^2) in cases with non-haematological toxicity 3 according to the WHO or hematological toxicity 4 according to the WHO.

Therapeutic response was assessed according to EBMT criteria (14). The start of treatment/trial was preceded by the approval of the State Institute for Drug Control (SÚKL), of the multicentric Ethical Committee (ET) and of local ETs.

RESULTS

Complete remission (CR); absence of the M-component confirmed by immunofixation, negative bone marrow finding, was confirmed in 4 patients (14%) in our group, partial remission (PR) in 11 (38%) and minimum response (MR) in 2 patients (7%). In another 5 cases the disease was stabilized (SD). On the whole, a good or very good response (CR or PR) was achieved in 52%, sat-

Tab. 1. Group of patients

Age	**median**	**61 (42–80)**
Sex	M	18
	F	11
Clinical stage		
(Durie-Salmon)	I. A	1
	II. A	9
	III. A	16
	III. B	3
M-component	IgG	18
	IgA	7
	LC	4
Preceding lines		
of therapy (number)	2	10
	3	12
	4	4
	5	2
	6	1
Type of preceding therapy		
ATDK 1x		5
ATDK 2x		8
ATDK 3x		3
alo-TDK		1
thalidomide		11

Tab. 2. Dependence of type of response on the number of preceding lines of treatment

Number of preceding lines of therapy	Number of patients	CR	PR	MR	Stabilization	Progression
2	10	2	4	1	2	1
3	12	1	5	1	1	4
4	4	1	1	0	1	1
5	2	0	1	0	1	0
6	1*	0	0	0	0	0

*The patient died of sepsis in the first week of treatment.

isfactory response (KR+PR+MR) in 59%, and at least a partial response (CR+PR+MR+SD) in 76% of the patients. The probability of achieving any kind of therapeutic response (if it is at all possible to evaluate such a small number of cases in the individual groups) did not depend on the number of earlier lines of therapy (90% after 2, 75% after 3, 75% after 4, 100% after 5 lines) (Tab. 2).

In 9 patients in whom the effect was inadequate we combined administration of bortezomib with high doses of dexamethasone. In 2 cases there was an improved therapeutic response, in 4 cases the procedure had no effect and in 3 patients the diseases progressed in spite of this combination.

The mean response time was 2.6 cycles (activity was evaluated on the 1st day of each cycle); in 5 patients the response was observed as early as after the 1st cycle, and in 4 cases after the 2nd and in 4 cases after the 3rd cycle.

The most common adverse effects of the therapy were thrombocytopenia (55.2%), anemia (34.7%), sensomotoric neuropathy (31%), gastrointestinal (GIT) complications (31%), leucopenia (24.1%), renal failure/insufficiency (17.2%), fatigue/weakness/somnolence (10.3%) and hepatopathy (10.3%) (Fig.1). The risk of 4th degree toxicity, according to WHO, was 44.8% – 5x thrombocytopenia, 2x GIT complications, 2x renal complications, 1x hepatopathy or anemia or leucopenia. One patient (after 6 lines of treatment, tandem ATKD and combined ATKD+mini-alo TKD) died of sepsis during the first week. Most of all other complications were reversible. Treatment was terminated prematurely in 8 patients – in 6 cases due to progression of the disease and only twice due to toxicity (1x renal failure, 1x neuropathy grade 3 according to WHO).

Fig. 1. Incidence of most common adverse effects of treatment. RI/RS – renal insufficiency, renal failure

DISCUSSION

Compounds which penetrate intercellular relations, the cytokine network and/or intracellular metabolic processes of tumor cells present a new option in the treatment of cancer. "Historically" the oldest drug of this type is thalidomide (15). Other preparations have been included into clinical trials in phases 1 and 2, or even 3 – functional analogues of thalidomide (immunomodulating drugs and selective cytokines – inhibiting substances), arsenic trioxide, inhibitory farnresyltransferase inhibitors, VEGF receptor inhibitors, new bisphosphonates, and others (16). A phase III trial comparing the effect of one of the immunomodulating drugs – Revlimid – with dexamethasone was recently terminated preliminarily due to an unequivocally evident effect (*private information received by the authors*). Currently however the greatest attention is being paid to the effect of bortezomib, the first proteasomee inhibitor used in clinical practice.

Proteasomee inhibition leads to the induction of apoptosis by entering the balance between anti- and proapoptotic signaling processes (12). Moreover, it has been repeatedly demonstrated that by influencing the proteasome function it may be possible to overcome some of the chemoresistance mechanisms that reduce the effect of commonly administered drugs – adnate resistance by translocation of the Bcl-2 antiapoptotic regulator, acquired resistance by elevated expression of the P-glycoprotein efflux pump, or resistance induced by $NF_{\kappa}B$ activation (17).

We hereby present the first results of treatment with bortezomib (Velcade) in patients diagnosed with MM in the Czech Republic. In 29 patients with refractory or repeatedly relapsing MM, therapeutic response (remission + stabilization of the disease) - in this group with a very unfavourable prognosis - was achieved in 76% of the cases; in almost 60% there was a remission of the disease, and in 52% a very good therapeutic response (CR+PR). Our results are slightly more favorable than those of the first phase II studies (SUMMIT – remission + SD 59%, remission 35%, CR+PR 27%, CREST – remission 30–50% depending on the doses of bortezomib and combination with dexamethasone) (18, 19), which is evidently the consequence of the smaller number of patients. We have included patients presenting a rather higher risk or having undergone a more intensive previous treatment – this is reflected in the higher incidence of severe adverse effects (WHO grade 4) in our group - 45%, compared to 14% in SUMMIT study and 9% in CREST. Unlike the mentioned studies, we have observed organ complications (ileus, hepatopathy, renal failure). Nonetheless, early termination of treatment because of severe adverse effects was necessary in 3 cases only (of this once due to early death and to sepsis during the first week of treatment).

In spite of hitherto limited experience it is evident that the main clinically severe complications of bortezomib treatment are thrombocytopenia and sensomotoric neuropathy. Thrombocytopenia is very frequent (55% in our group, 40% in SUMMIT, 30% in CREST); it is, however, transient and in most cases the number of blood platelets becomes adjusted - at least partially - by the time of the start of the next cycle. A more frequent incidence has been observed in patients who had a lower number of thrombocytes even before the start of treatment (20). The cause of this complication is not clear. Preclinical studies have shown that bortezomib has no toxic effect on hemopoiesis, including megakaryocytes and their precursors. Direct myelotoxic effect can be excluded also by the short duration of trombopenia and by frequent reversibility. Nor is a disorder of the main thrombopoiesis regulatory mechanism the cause, since adequately increased production of thrombopoetin has been found in patients included in the SUMMIT study (20).

Neurotoxicity in our group was observed in 31% of the patients (in phase II studies in 31%, and 41%). This in some cases may lead to early termination of treatment, also due to the fact that so far there is no known specific treatment. According to preliminary results, however, interruption of bortezomib therapy results in partial or complete adjustment in most patients (71%) within a relatively short time (median 47 days) (21).

In conclusion, it may be stated that our results of bortezomib treatment of relapsing/refractory forms of MM have confirmed the very favorable results of earlier clinical studies. The strong effect in the advanced stages has inspired the effort to include, in a broader and more precise manner, the drug into the spectrum of therapeutic options for myeloma: application at earlier phases of the disease or utilization of combinations with commonly applied drugs (bortezomib + dexamethasone, melfalan, liposomal doxorubicin, protocol PAD – PS 341/bortezomib + adriamycin + dexamethasone), which, according to first reports, provide a significantly higher number of therapeutic responses. The application of new drugs will probably lead to a change of therapeutic approach to MM (22) and to the transformation of what is currently usually a fatal disease into a "chronic" one.

Abbreviations

ATKD - high-dose chemotherapy with the support of stem cells
CR - complete remission
ET - ethical commission
FGF - fibroblast growth factor
GIT - gastrointestinal tract
IGF1 - insulin-like growth factor 1
IL-6 - interleukin 6, the main growth factor
MM - multiple myeloma
MR - minimal response
NFκB - nuclear factor kappa B
PR - partial remission
RANK - receptor activator of nuclear factor-kappaB
RANKL - RANK ligand
SD - stabilization of the disease
SDF1 - stroma-derived factor 1
SÚKL - State Institute for Drug Control (Prague)
VEGF - vascular endothelial growth factor
WHO - World Health Organization

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