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Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma? *

-Bortezomib (Velcade®) shows survival benefit over standard therapy for multiple myeloma patients in relapse

A recent study, published in the prestigious New England Journal of Medicine* entitled "Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma?" showed that bortezomib (VELCADE®) provides a survival advantage and a greater delay in disease progression for people whose multiple myeloma has relapsed. In addition, more people respond to bortezomib therapy than to high-dose dexamethasone (a corticosteroid), a commonly-used treatment for relapsed multiple myeloma.

Of note, bortezomib showed such a significant prolongation of time before another reoccurrence of the disease and such an improved overall survival that researchers halted the study one year earlier than scheduled. Also, of note, the survival benefit was maintained in patients who switched to bortezomib therapy after experiencing disease progression on dexamethasone.

Treatment of multiple myeloma

New cases of multiple myeloma are typically treated with high-dose chemotherapy followed by bone marrow (stem-cell) transplant. However, treatment for patients who relapse is not well established, although high-dose dexamethasone is often used. Since there is no cure, the goal of treatment is to slow the progression of the disease and to control its symptoms.

By the time multiple myeloma has recurred after two lines of therapy, this cancer becomes one of the most difficult to treat. So this study offers new hope to multiple myeloma patients.

Bortezomib or High-Dose Dexamethasone?

The goal of the study was to compare the effectiveness and safety of bortezomib injection with high-dose, oral dexamethasone in patients who had experienced relapse after receiving between one and three previous therapies for multiple myeloma. The study also compared the time to disease progression in the two groups of patients, as well as one-year survival, response rate (complete or partial response) and duration of the response. The time to infection and time to fracture or other bone deterioration were also studied.

The trial was conducted in 93 centres in the U.S., Canada, Europe and Israel, and study findings were validated by an independent European Blood and Marrow Transplantation review committee.

The results of 627 patients who had undergone one to three prior courses of therapy and who had then experienced relapse were evaluated: 315 received bortezomib and 312 were treated with dexamethasone. Each had been assigned on a random basis to receive either bortezomib intravenously or dexamethasone orally
As is the case in such clinical trials, an interim analysis was conducted as soon as a set number of patients had experienced disease progression, in order to ensure that patients received the best-available therapy. The analysis showed that patients taking bortezomib benefited for a significantly longer period of the time before the disease began to progress again and had a longer overall survival, compared with patients receiving dexamethasone. Consequently, all of the patients in the dexamethasone group were offered bortezomib.

Side effects
Fewer patients receiving bortezomib discontinued treatment due to adverse evens or disease progression than patients receiving dexamethasone. However, over the course of the trial, 37 percent (121) of the patients in the bortezomib group had adverse events necessitating early discontinuation of treatment. These events included peripheral neuropathy (lack of sensation in hands and feet, for example), thrombocytopenia, various gastrointestinal disorders, fatigue, hypercalcemia, and spinal cord compression. In the dexamethasone group, 29 percent (96) of the patients discontinued treatment, because of adverse events including: psychotic disorder, hyperglycemia, and thrombocytopenia.

Response rates and survival benefits
Patients treated with bortezomib versus dexamethasone experienced statistically improved survival, with 14 per cent fewer deaths at the end of one year on bortezomib versus dexamethasone. Forty-five per cent of patients achieved a complete or partial response with bortezomib, compared with 26 per cent on dexamethasone. Time to progression of the disease also was significantly improved.

Early-phase treatment
Analysis conducted on patients who had received only one prior therapy (38 per cent of the overall patients in the study) demonstrated that they also had significantly improved outcomes. The observation that outcomes improve when bortezomib is given to patients in earlier lines of therapy led the investigators in this study to conclude that this medication should be investigated in the initial phase of multiple myeloma therapy.

The study results highlight the survival benefit of bortezomib for relapsed multiple myeloma patients. It also showed that the drug has the potential to improve the quality of responses when received earlier in treatment. These findings have resulted in approximately 80 clinical trials (in Europe, the U.S., and Canada) investigating the use of bortezomib in all stages of multiple myeloma getting under way.

Summary Table

	Bortezomib	Dexamethasone
Complete or partial response	38%	18%
Early discontinuation due to progression	29%	52%
Early discontinuation due to adverse events	37%	29%
Median time to disease progression		
First-time relapse	7 months	5.6 months
Second or third relapse	4.9 months	2.9 months

Multiple Myeloma

Multiple myeloma is a cancer of the plasma cells found in the bone marrow. The disease is characterized by a progressive overgrowth of these white blood cells, which normally form part of the immune system It is the second most common blood cancer, representing approximately one per cent of all cancers, and is responsible for two per cent of all cancer deaths.

The proliferation of plasma cells often causes the deterioration of bones, and may result in fractures and low blood counts. The plasma cells often produce abnormal antibody protein levels, which may lead to kidney disorders and increased susceptibility to infection. In 2004, there were 1,850 new cases of multiple myeloma; an estimated 6,200 Canadians live with multiple myeloma.

Bortezomib

Bortezomib (VELCADE®) has a generally predictable side-effect profile. In most cases side effects are manageable with appropriate monitoring and, if necessary, dose modification. The drug is not indicated in patients with hypersensitivity to bortezomib, boron, or mannitol. In clinical trials, the most commonly reported adverse events include fatigue, malaise and weakness, nausea, diarrhea, thrombocytopenia (decrease in blood clotting cells) and peripheral neuropathy (numbness of the hands, arms, feet or legs).

Bortezomib is the only approved treatment for patients with multiple myeloma who have relapsed after first-line therapy, and who are unresponsive to their most recent therapy. The drug offers a novel approach to treating multiple myeloma by acting on the proteasome, a unique target in cells.

In Canada, bortezomib is indicated for the treatment of multiple myeloma patients who have relapsed following front-line therapy and who are refractory (unresponsive) to their most recent therapy.

Government funding for bortezomib is currently available on a patient-by-patient basis across Canada, except in Ontario. The Ontario Drug Benefit Programme has yet to make the drug broadly available for patients with multiple myeloma who have failed first-line therapy and who are unresponsive to their most recent therapy.

While a myeloma diagnosis can be overwhelming, it is important to remember that there are several promising new therapies that are helping patients live longer, healthier lives.

DATA NOTES

The overall rate of response (complete or partial) to bortezomib was 38per cent compared with 18per cent in the case of patients receiving dexamethasone. Among patients who had only one previous treatment (i.e. first-time relapsed), the median time to disease progression was 7 months in the bortezomib group and 5.6 months in the dexamethasone group. Among patients who had 2 or 3 previous treatments, the median time was 4.9 and 2.9 months, respectively.

As mentioned above, disease progression led to early discontinuation in 29 percent (98) of the patients receiving bortezomib, and in 52 percent (174) of the patients receiving dexamethasone. Over the course of the trial, 37 percent (121) of the patients in the bortezomib group had adverse events necessitating early discontinuation of treatment. These events included peripheral neuropathy (lack of sensation in hands and feet, for example), thrombocytopenia, various gastrointestinal disorders, fatigue, hypercalcemia, and spinal cord compression. In the dexamethasone group, 29 percent (96) of the patients discontinued treatment, because of adverse events including: psychotic disorder, hyperglycemia, and thrombocytopenia.

After a median 8.3 months follow-up, the study showed a statistically significant survival advantage in patients treated with bortezomib. This survival advantage was maintained even when 44 per cent of patients began bortezomib therapy after experiencing progressive disease on dexamethasone. Bortezomib induced a 38 percent complete or partial response, compared with 18 per cent with dexamethasone. Statistically significant higher complete and near complete responses (13 percent versus 2 per cent) also were found with bortezomib, compared with dexamethasone, and the median time to progression increased by 78 per cent (6.2 months on bortezomib versus 3.5 months for dexamethasone)

*Richardson PG, Barlogie B, Berenson J, Singhal S et al. A phase two study of bortezomib in relapsed, refractory myeloma. The *New England Journal of Medicine* 2003; 348:2609-2617.