

The chemotherapy regime of bortezomib valcade



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I will critically discuss the use of this regime and its mode of action in relation to the cell cycle. I will identify the short and long term side effects of this regime and explore on particular side effect analysing the impact of this side effect on patients and their families. The management of the chosen side effect will be explored using available evidence based research alongside the professional and ethical dimensions of practise.

Bortezomib is a proteasome inhibitor approved for use in Multiple Myeloma patients and is the first proteasome inhibitor licenced to use (Rajkumar, 2005). Dexamethasone is a steroid taken in tablet form on the same day as the Bortezomib and on the day after.

According to Armand et al (2007) a proteasome is a large multi protein particle present in all eukaryotic cells and is the primary element of the cells protein degradation pathway. The proteasome is vital to cell cycle processes such as regulation and apoptosis. Adams (2004) informs us that the blockade of proteasome activity results in cell death and that tumour cells appear to be noticeably more sensitive to proteasome inhibition than regular cells. Unlike in previous standard chemotherapy, which Morgan (2003) states “ has an ability to inhibit the process of cell division and an inability to distinguish between normal and malignant cells”.

Ling et al (2002) explains that Bortezomib acts in the G2-M section of the cell cycle (Image 1) causing cell cycle arrest and apoptosis, at the final check point before mitosis occurs. Bortezomib is a molecule that explicitly and reversibly hinders the 26S proteasome which is the enzyme that plays a key role in a cell by regulating protein degradation.

This process maintains the balance of proteins in the cell cycle, therefore inhibition of the 26S proteasome results in a loss of control of this process, leading to a build-up of cell cycle and regulatory proteins, thus causing apoptosis (Adams 2004). According to Landowski et al (2005) recent reports suggest that Bortezomib also deregulates intra cellular calcium metabolism, which also causes apoptosis.

Field-Smith (2006) informs that Bortezomib is usually given as an intravenous infusion in the outpatient setting, with a 72 hour gap between infusions to allow recovery of the proteasome inhibition in the normal cells. So as to prevent excessive side effects and allow cell recovery there is a 10 day treatment-free period and total of up to 8 cycles may be given subject to response and toxicities.

The rationale for using Bortezomib alongside dexamethasone as a chemotherapy treatment for relapsed myeloma was developed and supported by the evidence gained from its phase II and phase III clinical trials.

Hideshema et al (2001) informs us that the combination of Bortezomib with dexamethasone results in an increased Myeloma cell kill compared to Bortezomib alone. The phase II SUMMIT trial which included 202 patients with relapsed myeloma showed an overall response rate of 35%, this response rate increased to 50% when dexamethasone was added. (Richardson et al, 2005b).

The phase II CREST trial which included 54 patients, showed a response rate of 33% increasing to 50% when a higher dose of Bortezomib was used. Once
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again response rates increased when dexamethasone was added from 44%-62%.

The phase III APEX trial, compared the use of Bortezomib as a sole agent with high dose dexamethasone, as a second line treatment in relapsed multiple myeloma patients. The trial included 669 people and the results showed such a substantial benefit in the Bortezomib group, the trial was terminated early. (Richardson et al, 2005a).

Richardson et al (2005a) concluded that “ Bortezomib is far superior to high dose Dexamethasone” as a second line treatment as the overall survival at one year was 80% compared to 67% in the Dexamethasone group. The trial also showed the Bortezomib group to have a survival advantage of around 6 months.

Richardson et al (2004) explain that although the treatment advantages of Bortezomib & Dexamethasone are well researched and documented, there are also a great number of adverse side effects (Table 1) which were up to 20% higher in patients receiving the higher dose of chemotherapy (Jagannath et al, 2004). However we can see from the results that good response rates will still be achieved in the event of dose reduction due to a need to reduce toxicity related side effects.

Curran & McKeage (2009) conclude that although Bortezomib offers significant benefit for patients, its effectiveness is limited by its side effects. The most frequent side effects associated with Bortezomib include gastrointestinal events (diarrhoea, constipation), peripheral neuropathy and asthenic conditions (such as general weakness). The less common side

effects of Bortezomib according to Richardson et al (2005) include low white blood cell count, insomnia, joint pain and headache.

O'Connor et al (2005) explain that even though Bortezomib is highly effective in the treatment of multiple myeloma, only about 35% of multiple myeloma patients are sensitive to Bortezomib, indicating more than half of patients possess resistance to proteasome inhibition, this is a critical limitation of Bortezomib therapy. The clinical usage of Bortezomib is also hampered by acquired resistance to this drug, which appears to be associated with overexpression (Fisher et al, 2006).

Kim et al (2009) concur that some natural compounds also interfere with the anticancer effect of Bortezomib, reporting that the proteasome-inhibitory activity of Bortezomib can be blocked by chemicals found within green tea. Likewise, it has been found by Perrone et al (2009) that Vitamin C and dietary flavonoids also inhibit the anticancer effects of Bortezomib.

During the Phase II & III trials, many of the side effects previously mentioned were reported with 51% of patients reported diarrhoea, which is why I have chosen to look further into this side effect and its management. According to Stein (2010) the pathophysiology of chemotherapy induced diarrhoea is multifaceted, complex and still under investigation.

The absorptive and secretory capacity within the gut is altered during chemotherapy, due to the toxicity damaging the intestinal epithelium (Robinson & Dobish, 2007), superficial necrosis and inflammation of the bowel wall, causing an imbalance between absorption and secretion in the small bowel resulting in diarrhoea (Stringer, 2009).

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Sharma (2005) informs us that if chemotherapy induced diarrhoea is uncontrolled the consequences can be devastating both physically and psychologically. According to Cherny (2008) Diarrhoea can lead to, dehydration, electrolyte imbalance, renal issues and death.

Viele (2003) confirms that at the psychological effects of diarrhoea include depression, social isolation and anxiety. Patients suffering from chemotherapy induced diarrhoea will often require additional healthcare resources which raises costs for the healthcare system (Dranitsaris et al 2005). Arnold (2007) explains that chemotherapy induced diarrhoea can interfere with cancer treatments affecting schedule, dose reductions ultimately leading to a worse outcome.

In a retrospective study of 378 cancer patients with chemotherapy induced diarrhoea. Arnold et al (2005) discovered that nearly 65% of patients experienced a reduction in dose intensity, 45% required a dose reduction, 71% experienced a delay in treatment and 3% had their therapy discontinued completely. Maroun et al (2007) conclude that treatment delays, discontinuation of therapy and dose reductions have a direct adverse effect on patient mortality and morbidity.

Therefore clear objectives must be in place in order to manage chemotherapy induced diarrhoea effectively. According to Skelley (2005) healthcare professionals must promptly diagnose and treat patients with chemotherapy induced diarrhoea, minimise treatment delays, maximise chemo intensity and therefore maximise the patients' quality of life whilst undertaking treatment.

Patient education is the keystone, to the management of chemotherapy induced diarrhoea. Before commencing chemotherapy, patients must be informed of the potential risks and what actions to take, if they develop diarrhoea.

Patients will require nutritional advice such as to drink plenty of fluids to prevent dehydration, also be advised to eat small but regular amounts of low fibre foods and to avoid greasy fried foods (Benson, 2004). There are many more aspects to dietary advice therefore input from a dietician would be beneficial.

It is important for healthcare professionals to actively encourage patients to report their bowel movements, because patients fear that reporting diarrhoea will delay their treatment (Maroun, 2007). As a healthcare professional we should aim to reassure patients that prompt diagnosis and early treatment can prevent delays to their chemotherapy.

According to Cherny (2008) patients with chemotherapy induced diarrhoea should have a full assessment including medical history, dietary history and medication review, and before treating for chemotherapy induced diarrhoea other common causes of diarrhoea should be considered and excluded such as medications, infections and co-morbid conditions.

To manage and treat diarrhoea in an acute setting effectively healthcare staff should grade diarrhoea using the National Cancer Institute Common Toxicity Criteria for Diarrhoea (Image 2) (Skelley, 2005) also an accurate stool chart must be maintained. Completing these measures enable medical staff to prescribe the correct treatment and it helps to monitor the

effectiveness of the treatment. Benson et al (2004) show that in grades I – II diarrhoea Loperamide is the recommended medication.

If diarrhoea still persists, high dose Loperamide should be used and Codeine Phosphate can be added. If diarrhoea continues after 48hours or becomes grade III – IV, Octreotide is the recommended treatment, as a sub-cutaneous injection three times per day. Octreotide according to Barbounis et al (2001) has a 60% – 90% success rate in resolving persistent diarrhoea. Zidane (2001) explains that although Octreotide has proven to be more successful than Loperamide, it still remains as a second line treatment due to its high cost.

Chemotherapy induced diarrhoea has tremendous effects on patients' safety and quality of life, the management of cancer patients necessitates increased attention to this side effect from nurses, appropriate management of diarrhoea is crucial for improving quality of life, enhancing adherence to medication regimens and enhancing overall efficacy of therapy.

It is also imperative to remember the beneficial effect that diet may play in alleviating diarrhoea symptoms. Further investigation of treatment options is essential for the management of this debilitating side effect.

Bortezomib has proven a potent therapeutic strategy in the treatment of relapsed multiple myeloma and acts by reversibly impeding the proteasomal activity in cancer cells and results show an improved survival rate in relapsed patients when compared with patients treated with dexamethasone alone.

The effectiveness of Bortezomib has been thoroughly investigated in Phase I, II and III clinical trials. However, many disadvantages of Bortezomib do exist due to its severe side effects, interactions and the acquisition of drug-resistance. Nevertheless Bortezomib in general, is well tolerated with most side effects only being mild to moderate.

The introduction of Bortezomib in the treatment of myeloma has been a major innovation in the relapsed setting. New research into the use of Bortezomib alongside other chemotherapy agents looks very favourable as a front line treatment for myeloma and due to the novel mechanism of action of proteasome inhibition it will inevitably be used in alongside other agents as a first line treatment in newly diagnosed patients.