Subcutaneous Administration of Bortezomib

Hello, I am Sandy Kurtin. We are going to talk about subcutaneous administration of bortezomib. Bortezomib, a reversible proteasome inhibitor, is a first-in-class proteasome inhibitor that originally received accelerated review by the FDA[1] based on the results of the Phase-II Summit Trial establishing safety and efficacy of single-agent bortezomib versus post-dexamethasone in patients with relapse multiple myeloma who had received one to three prior lines of therapy.[2] The initial findings showed a significant improvement in time to progression, with improvement in overall response rate and survival. Subsequent and final analysis at 22 months of followup showed a 6-month improvement in overall survival, 30 months versus 24 months, significant improvement in overall response rate, 43% versus 18%, and an improved depth of response, CR rates of 9% versus less than 1%.[3] In addition, a 2.7-month improvement in time to progression was noted. Based on these data, bortezomib was approved for IV administration using 1.3 mg/m² on days 1, 4, 8, and 11 every 21 days. The most common dose-limiting toxicities in this trial were myelosuppression and peripheral neuropathy. Nausea, vomiting, diarrhea, and hypotension were also reported requiring pre-medication with anti-emetics and administration of additional intravenous fluid. A subsequent non-inferiority trial conducted by Moreau and colleagues compared the efficacy of bortezomib as an intravenous push compared to subcutaneous injection administered using the same dose and schedule.[4] This was conducted in relapsed multiple myeloma patients that have received one to three prior therapies. There were no differences in overall response rate, depth of response, or time to response between the two study arms. However, the incidence of peripheral neuropathy was significantly reduced in the cohort treated with subcutaneous bortezomib, 38% versus 53% for all grades, and 6% versus 16% for grade 3 and higher. The incidence and severity of hypotension and GI toxicities were also reduced, eliminating the need for IV hydration or anti-emetic pre-medications in the majority of patients. The results of this trial have led to a change in a favored route administration from IV to subcutaneous and a change in the standard schedule of administration to twice-weekly dosing schedule for two cycles followed by weekly dosing.[5,6] Together, these changes offer similar efficacy and the opportunity to improve treatment outcomes with continued therapy and improved quality of life by lessening toxicity, specifically neuropathy. Additionally, patients reported 54 minutes less chair time on average and 46 minutes less clinic time on average, reducing the time away from family, friends, work, or other daily activities. The incidence of herpes zoster reported with bortezomib is variable. It was notably decreased when anti-viral prophylaxis was mandated in the VISTA trial.[7] It is important to remember that antiviral medication requires dose modification for renal impairment and should be dosed based upon creatine clearance [Note: refer to the antiviral agent’s prescribing sheet]. Subcutaneous administration does require some specific considerations and techniques.[8] The thickness of the skin in adults is between 1.9 and 2.4 mm with little variation in different body locations or among individuals of varying race, sex, or body mass index. There are however differences in the thickness of subcutaneous tissue by site and sex, with women having greater subcutaneous thickness than men; subcutaneous thickness being greatest in the abdomen, and subcutaneous thickness reduced in the individual. Injection site reactions were reported in approximately 6% of patients receiving subcutaneous bortezomib, with the majority of reactions being mild mostly hyperpigmentation and resolving in approximately 6 days. To reduce the incidence of injection site reactions, selecting the proper site for injection, using the proper skin fold technique, proper needle size, and angle of injection can reduce the incidence and severity of injection site reaction. Given the thickness of the skin, needles that are between 4 to 6 mm have been proven to be effective in delivering
subcutaneous medication. Injections using these needles should be administered at a 90-degree angle. Use of the air-sandwich technique, applying a fresh non-primed needle to the syringe with bortezomib, then drawing in an additional 0.5 to 1 mm of air, inverting the needle, and injecting using this standard subcutaneous technique will in effect lock the drug into the subcutaneous fat, avoiding sheering of drugs through the subcutaneous fat on injection and would drop the needle. You can find more information about subcutaneous administration of bortezomib at the Managing Myeloma website.

References:


