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Pegfilgrastim
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Neutropenia is the most significant life-threatening and dose-limiting problem associated with administration of chemotherapy. In an attempt to maintain dose intensity, filgrastim is administered to patients following treatment with chemotherapy to prevent the complication of neutropenia and sepsis. A number of clinical trials have demonstrated the effectiveness of this strategy in preventing febrile neutropenia and subsequent hospitalisations. In many countries, the use of filgrastim is approved for prevention of this complication in a number of malignancies. However, the major difficulty of this approach is the requirement for daily subcutaneous injections of filgrastim by the patient or by a visiting nurse. This adds both to the cost and the discomfort, and the likelihood that patients will not adhere to the treatment protocol.

In an effort to overcome the need for daily injections, a longer-acting form of filgrastim has been developed by the addition of polyethylene glycol to filgrastim, resulting in a new molecule called pegfilgrastim. This molecule has decreased renal clearance and an increased plasma half-life compared to the parent molecule filgrastim.

Phase II studies in patients with breast and thoracic malignancies demonstrated the efficacy of pegfilgrastim compared to filgrastim. Two pivotal phase III studies were subsequently designed to address the question of the relative efficacy of pegfilgrastim compared to filgrastim. These studies compared the duration of severe neutropenia as well as the incidence of febrile neutropenia in women receiving a standard dose schedule of chemotherapy. Both studies were identical in design, with one being conducted in the US and the other being conducted internationally. Both studies enrolled women with breast cancer who were treated with the standard dose of docetaxel and doxorubicin on day 1 of a 21-day cycle. Women were treated for a maximum of four cycles. The only difference between the two studies was that patients in the US were randomised to receive a single subcutaneous injection of pegfilgrastim with 100 μg/kg per chemotherapy cycle, whilst those patient in the international study were randomised to receive a fixed dose of pegfilgrastim 6mg per chemotherapy cycle. The control element in both studies was the daily injection of subcutaneous filgrastim at the standard dose of 5 μg/kg/day for up to 14 days. In both studies, pegfilgrastim was administered as a subcutaneous injection on day 1 after administration of the chemotherapy.

The rationale for evaluating a fixed dose of pegfilgrastim was based on current prescribing practice for filgrastim, where the entire contents of a 300 or 480μg syringe are commonly administered for reasons of convenience and ease of dosing compliance. The previously referred to phase II studies had demonstrated that a fixed dose of 6mg of pegfilgrastim should be adequate to cover the broad range of patients irrespective of their weight. The international study addressed the issue of weight by stratifying patients according to four weight groups and analysing those groups independently. Both studies demonstrated, in an identical noninferiority design, that one injection of pegfilgrastim per chemotherapy cycle was comparable to daily subcutaneous injections of filgrastim with regard to the efficacy endpoints of duration of severe neutropenia and the depth of absolute neutrophil count nadir in all cycles. In both studies, there was also a reduced incidence of febrile neutropenia across all cycles in recipients of pegfilgrastim compared with that in recipients of filgrastim.

The major toxicities identified in both studies were primarily due to the administration of the chemotherapy to these patients. However, the one toxicity which is attributable to filgrastim and pegfilgrastim, i.e. bone pain, was identical in frequency across both groups.

These two studies both met the endpoint of equivalence between pegfilgrastim and filgrastim and demonstrated that pegfilgrastim would be a viable alternative to the daily administration of filgrastim. The use of pegfilgrastim would have a

profound effect on patients, by reducing the number of injections, possibly the cost of administration (especially if nurses are required to administer injections at home), and almost certainly the reliability of administration. This increased reliability of administration may further improve the benefit profile of this cytokine. ▲