Reply to Letter to the editor, by Ishiguro et al. (Ann Oncol)

Referring to our recent publication, Ishiguro and colleagues raise concerns about the use of pegfilgrastim 6 mg per cycle to support dose-dense (dd) chemotherapy. While we welcome debate, we would like to correct an inaccuracy in the interpretation of our study. The suggestion that hematological
toxicity led to more discontinuations in the pegfilgrastim-supported dd epirubicin-cyclophosphamide-docetaxel (dTECT) and ddTEC arms compared with patients receiving conventional TEC (also with pegfilgrastim support) is incorrect. Neutropenia was the most common adverse event, with grade 4 neutropenia occurring more frequently in patients receiving dTECT than in the other two arms. Adverse events leading to discontinuation were also most frequent with dTECT, but no withdrawals in either dd arm resulted from hematological toxicity.

We are unable to comment extensively on the patient reported by your correspondents. This 48-kg Japanese breast cancer patient is described as having a ‘prolonged neutropenia’ after receiving dose dense doxorubicin plus cyclophosphamide supported by pegfilgrastim, yet severe neutropenia was not actually observed until day 26. The hypothesis that this delayed event was linked to prolonged presence of pegfilgrastim seems unlikely. There is some evidence of increased myelosuppression when colony-stimulating factors are given concurrently with chemotherapy [1], but this was not the case here. Dr Ishiguro indicates that some patients receiving pegfilgrastim 6 mg in the study by Green et al. [2] (weight range: 46–125 kg) had elevated levels of the drug at day 14. Yang et al. [3] defined the lowest pegfilgrastim serum concentration to elicit a meaningful clinical effect as 2 ng/ml. They analyzed data from patients (N = 187) in six breast cancer and lymphoma studies, including Green. Over 50% of these patients received pegfilgrastim 6 mg. Serum pegfilgrastim levels dropped sharply from day 7 and, assuming a log-normal distribution of serum concentrations in the population, the proportion of patients with pegfilgrastim levels >2 ng/ml at day 12 was 0.2%. Moreover, in their study of elderly lymphoma patients receiving dd chemotherapy with pegfilgrastim support, Mey et al. [4] reported no accumulation of pegfilgrastim.

Although no large-scale clinical trials of pegfilgrastim with dd chemotherapy have been conducted by the manufacturer, there are increasing reports of its use in this setting (e.g. by Burstein et al. [5]). Consequently, the recommendation that the European Society of Medical Oncology warns against pegfilgrastim use with dd chemotherapy is not supported by the weight of current evidence. Undoubtedly, the patient described was at the lower end of the weight range for which pegfilgrastim 6 mg has been studied (246 kg). Furthermore, pegfilgrastim has not been specifically studied in Japanese patients. The use of pegfilgrastim in dd regimens is supported by pharmacokinetic/pharmacodynamic data. Nevertheless, physicians must use their clinical judgement in individual cases.

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references


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