Prolonged neutropenia after dose-dense chemotherapy with pegfilgrastim

In the dose-dense (DD) chemotherapy trial result reported by Piedbois et al. [1], they found more hematological toxicity leading to treatment discontinuation in the pegfilgrastim supported DD chemotherapy arm. The manufacturer's product information for pegfilgrastim indicates that it should be used once per chemotherapy cycle and should not be used in the period between 14 days before and 24 h after administration of cytotoxic chemotherapy, which is not practically possible in DD chemotherapy. Although pegfilgrastim has not been approved in Japan, we observed an episode of prolonged neutropenia in a Japanese patient who had undergone DD doxorubicin plus cyclophosphamide (AC) neo-adjuvant chemotherapy in the United States before being referred to us to continue chemotherapy then perform resection.

She was a 48-kg female in her mid-30s who presented at the Ithaca Medical Group clinic (New York) with locally advanced breast cancer. She underwent four cycles of DD AC, with pegfilgrastim 6 mg s.c. on day 2 of each cycle. Her absolute neutrophil count (ANC) was 2350/mm³, 3650/mm³, 4150/mm³, and 7300/mm³ at the start of each cycle. After the fourth AC cycle, she was referred to us for further chemotherapy. ANC at day 20 of the fourth AC cycle was 3300/mm³ but decreased to 500/mm³ on day 26. Therefore, we had to postpone chemotherapy. Two weeks later (1 week after the last dose of filgrastim), the patient’s ANC recovered to 1500/mm³ and she received the first cycle of docetaxel (100 mg/m²). She had received a total of 14 administrations of filgrastim starting from day 3 of the first cycle of docetaxel and had been severely neutropenic from day 7 (300/mm³) to day 22 (300/mm³). Her ANC on days 29 and 36 were 600/mm³ and 1100/mm³, respectively. Due to prolonged neutropenia, we decided to proceed to surgery. The patient has completed weekly paclitaxel as adjuvant chemotherapy, begun 3 months after the last docetaxel, with no major hematological toxicity. Serum pegfilgrastim remained elevated in some patients even 14 days after the administration [2] and this seems dependent on weight-adjusted dose [3]. Chemotherapy administration during this period may very well cause more bone marrow suppression. It is possible that a 6-mg dose of pegfilgrastim is too large for Japanese patients in general. In our patient, the elevated ANC (3300/mm³) on day 20 and grade 4 neutropenia on day 26 suggests that the effect of pegfilgrastim lasted at least 3 weeks. We therefore caution against the routine use of pegfilgrastim in DD chemotherapy until an optimal dose in this setting is ascertained, especially for low-weight patients. We strongly recommend that the European Society of Medical Oncology warns oncologists against the routine use of pegfilgrastim in DD chemotherapy, which is not an indication approved, and in which situation the drug has never been formally tested for optimal dosage. Such a recommendation would be particularly effective if made through the Annals of Oncology, given that this journal is well known and influential publication for clinical oncologists worldwide.

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