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Managing chemotherapy toxicity issues

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The side effects that are most commonly encountered due to the administration of cytotoxic chemotherapy include lethargy/fatigue, nausea and vomiting, stomatitis, diarrhoea, constipation, dyspnoea, thrombocytopenia, pain/arthralgia/myalgia, rash, infection, alopecia, peripheral neuropathy, mucositis and neutropenia. The results of the Breast Cancer International Research Group (BCIRG) 001 study demonstrate that the absolute increases in disease-free survival (DFS) and in overall survival (OS) associated with the TAC regimen (docetaxel; 75 mg/m^2/doxorubicin; 50 mg/m^2/cyclophosphamide; 500 mg/m^2) compared with the FAC regimen (5-FU; 500 mg/m^2/doxorubicin; 50 mg/m^2/cyclophosphamide; 500 mg/m^2) are among the most robust reported to date [1]. It is well known that the risk for the development of side effects is directly related to the intensity of chemotherapy. As such, being one of the most effective chemotherapeutic regimens to date, the TAC regimen has associated toxicities, namely myelosuppression and, in some cases, subsequent febrile neutropenia. The occurrence of febrile neutropenia and subsequent hospitalisation can be problematic for some patients; therefore, it is important to realise that there are effective strategies that can be employed to prevent or manage febrile neutropenia, thereby improving patients' access to the most efficacious regimens. The two main strategies are primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) for prevention, and dose reduction for minimising the risk for development of febrile neutropenia in cases where primary prophylaxis with G-CSF was not employed. The reduction of TAC-induced febrile neutropenia achieved by the use of prophylactic G-CSF was effectively demonstrated in the Spanish GEICAM 9805 study [2]. This trial had exactly the same design as BCIRG 001 but enrolled node-negative patients. Of the 1047 evaluable patients, 528 received the TAC regimen and 519 received the FAC regimen. In the BCIRG 001 trial, nearly 25% of patients in the TAC arm had an episode of febrile neutropenia, compared with 2.5% in patients who received FAC [1]. One year after initiation of the GEICAM 9805 study, a protocol amendment was included to permit G-CSF primary prophylaxis in all new patients enrolled in the TAC arm ($n = 414$). G-CSF primary prophylaxis resulted in a significant reduction in the per-patient incidence of febrile neutropenia from 24.6% to 6.5%. Similarly, there was a significant decrease in the per-patient incidence of infections, from 31.6% in the pre-amendment population to 21.7% in the post-amendment population (Fig. 1). A similar study that investigated the benefits of primary G-CSF prophylaxis in the metastatic setting demonstrated that, in addition to a highly significant reduction in the incidence of febrile neutropenia from 17% to 1% ($P < 0.001$), such practice also significantly reduced the use of anti-infectives from 10% to 2% ($P < 0.001$) [3]. The results of the GEICAM 9805 study also revealed that the benefits of primary G-CSF prophylaxis were not confined to improvement in haematological toxicity, but also reduced the incidence of asthenia, stomatitis and nail toxicities [2].

Whereas it is widely accepted that chemotherapy-induced neutropenia is the major dose-limiting toxicity of systemic cancer chemotherapy and that risk is related to intensity of chemotherapy, at present, colony-stimulating factors (CSFs) are not routinely administered to all patients receiving myelosuppressive chemotherapy because of the costs associated with their use. However, as detailed above, the selective use of CSFs in patients at increased

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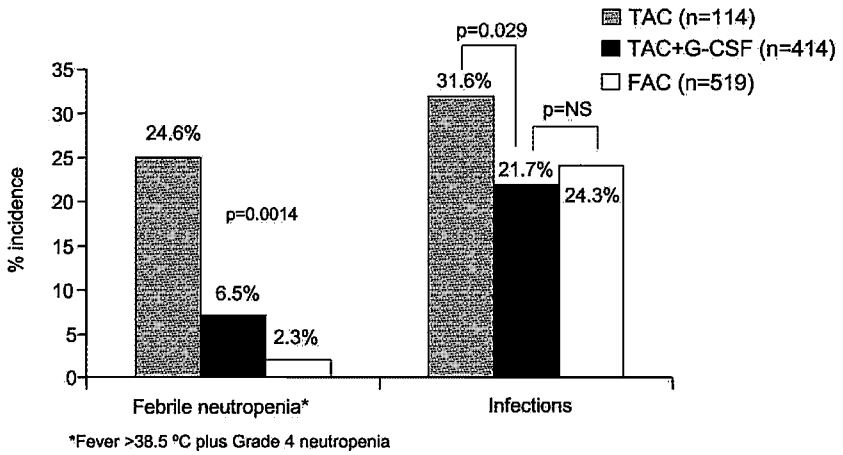

Fig. 1. Benefits of primary G-CSF prophylaxis in the adjuvant setting.

risk for neutropenic complications may in fact prove to be cost-effective, especially with regard to preventing hospital admissions.

Adherence to guidelines can enhance individual therapy by preventing under- or over-treatment and avoiding administration of inappropriate treatment. The updated 2005 National Comprehensive Cancer Network (NCCN) guidelines now recommend the use of prophylactic G-CSF support in patients who have a greater than 20% risk of developing febrile neutropenia or other neutropenic events compromising treatment. This recommendation is regardless of whether the purpose of therapy is curative, to prolong survival or quality of life, or to provide symptom management [4]. In addition, these guidelines suggest that prophylactic G-CSF support should be considered in patients who have an intermediate (10–20%) risk of developing febrile neutropenia. The NCCN classifies the TAC regimen as being in the high-risk category, and as such recommends the use of G-CSF prophylaxis with this regimen [4].

The second strategy for management of docetaxel-induced febrile neutropenia is dose reduction. The effectiveness of reducing the dose of docetaxel, when used as single agent, from 100 mg/m^2 ($n = 185$) to 75 mg/m^2 ($n = 190$) or 60 mg/m^2 ($n = 149$) was demonstrated in the Mouridsen study [5]. With a reduction in dose from 100 mg/m^2 to 60 mg/m^2, the incidence of febrile neutropenia in patients receiving docetaxel was significantly reduced (from 14% to 5%), as was the incidence of docetaxel-related infection (from 7% to 2%). This reduction in dose did not generally affect the activity of docetaxel, in that there was no significant difference in either time to progression or OS in patients who received the 60 mg dose compared with those who received the 100 mg dose [5], however, due to the relatively small size of this study, further analysis is required to confirm this conclusion.

A number of other side effects are commonly reported after administration of chemotherapy, some of which, though not potentially life threatening, can be severely distressing for patients. Management of these side effects is crucial for the maintenance of quality of life and continuation of therapy. One such side effect is alopecia, and management should be initiated by informing the patient when they should expect to start losing their hair. It is also extremely important to emphasise to patients that hair loss is reversible. Reversible alopecia occurs 2–4 weeks after initiating docetaxel therapy and the median recovery time is 22 weeks from initial hair loss, although the exact time to recovery is also influenced by the age of the patient. Scalp cooling has been demonstrated to reduce the incidence and severity of alopecia and provides adequate protection (World Health Organisation [WHO] Grades 0–2) in 86–97% of patients [6,7]. Hypersensitivity reactions are usually mild to moderate, and occur within a few minutes of infusion. The occurrence of such reactions is routinely prevented by premedication with oral corticosteroids. However, such reactions can differ in severity, and the course of action should be modified accordingly. Mild reactions are generally managed by reducing the infusion rate of chemotherapy while the reaction subsides, after which point, the infusion rate can be gradually increased. Cutaneous reactions occurring as a result of docetaxel administration are usually mild to moderate and most docetaxel-related skin eruptions resolve within 21 days and do not require intervention. However, severe cases can be managed by premedication with oral corticosteroids. Fluid retention is usually mild to moderate and although it is cumulative, it is reversible and resolves after an average time of 16.4 weeks. Non-severe cases can be managed with diuretics, while premedication with oral corticosteroids reduces the risk in all patients. With regard to nausea and vomiting, patients should be advised as to when they will begin to feel nauseous. Although a constant feeling of nausea can be distressing for the patient, the use of prophylactic anti-emetics is not usually required, although low-dose anti-emetics may be useful if symptoms do occur. Patients should be advised to avoid spicy foods and to eat smaller portions; some patients have reported that ginger is helpful in alleviating these symptoms. Stomatitis is commonly reported as one

of the worst side effects associated with chemotherapy, but the discomfort caused by stomatitis can be reduced by a practical approach, involving avoiding spicy foods and citrus fruit, conducting regular inspections of the mouth and regular use of mouth wash, and cleaning the teeth or dentures and use of a soft toothbrush. Patients should be advised to check for fungal infections and be made aware of the appropriate use of analgesia and/or antifungals. Sucking ice chips during administration of chemotherapy may reduce the severity of this side effect in some patients. The widespread use of corticosteroid therapy as both pre- and post-chemotherapy medication means that patients often experience a long duration and dose intensity of such agents. This can result in corticosteroid withdrawal symptoms, including aching limbs and even flu-like symptoms. Such symptoms are common and are particularly prominent in older patients, but their occurrence can be ameliorated by a staged reduction in dose over a period of 2–3 days.

The knowledge and implementation of these management techniques ensures that patients continue their chemotherapy and that they consequently obtain the best possible outcomes from their cancer treatment. With this in mind, a national taskforce – the Nurse Advisory Group – was established to identify actions that were required to improve the management of patients receiving chemotherapy. Members from centres across the United Kingdom convened to discuss their experience with side-effect management protocols. Such items were deemed to be either difficult to find or incomplete, and in many hospitals they were found simply not to exist. As a consequence of these findings, the group determined that there was a requirement for baseline patient assessment pro-forma and chemotherapy side-effect algorithms/pro-forma. In March 2000, in our clinic at the Felindre Hospital in Cardiff, we initiated a phone-back service for patients who have received chemotherapy that has proved to be extremely helpful, especially in the first 48 hours following administration of chemotherapy. An audit of the service has demonstrated an increase in the levels of patient concordance with treatment since initiation of the service. There has also been an improvement in patient support and side-effect management, which has subsequently led to the establishment of a nurse/pharmacist-led chemotherapy clinic with reduced waiting times and high patient satisfaction.

To summarise, docetaxel has a predictable, manageable, and reversible side-effect profile, and the side effects associated with this agent are those that are commonly associated with most classes of chemotherapeutic agent. The potential development of febrile neutropenia is the most serious side effect associated with the use of docetaxel, but as are the majority of side effects, this is easily prevented or managed by using the appropriate interventions, including primary prophylaxis with G-CSF or dose reduction. Docetaxel is associated with a relatively low incidence of grade 3/4 non-neutropenic side effects. In conclusion, with effective management of side effects, there is no reason why patients should not, as they wish, receive the most powerful chemotherapeutic regimens to equip them with the best chance of beating their cancer.

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