Supportive care - Present use of biologicals in supportive care

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Dose and schedule are important factors in the therapy of cancer. Animal model and clinical data show that there is a significant correlation between dose-intensity and survival; moreover, the shortening of interval between chemotherapy cycles prevents from tumor regrowth and maximize the effect of chemotherapy on cancer cells (Gregory SA, Trumper L, 2005). Most of anti-cancer drugs are non-selective and act indiscriminately on dividing cells. Hematological toxicity is one of the most important limiting factor for the protocols that are based on the dose-escalation or the dose-density of chemotherapy. This result in peripheral blood cytopenia (neutropenia, anemia and thrombocytopenia), higher transfusion requirement, severe infectious complications, prolonged hospitalization and higher health care expenses. The use of hematopoietic growth factors such as the granulocyte colony-stimulating factors (G-CSF) filgrastim or lenograstim and erithropoietin represented a step forward to reduce the hematological toxicity of high-dose chemotherapy and to manage the frequent infectious complications.

G-CSF

G-CSF is a natural cytokine that acts on committed myeloid progenitor cells. Its secretion is stimulated by infections or by the reduction of mature myeloid cells, as a result of bacterial lipopolysaccharides and chemotherapy, respectively (Lieschke GJ, Burgess AW, 1992); so the serum G-CSF concentration increase from approximately 25 pg/ml of healthy people to 1,000 pg/ml of patients with severe infections or after stem-cell transplantation (Kawakami et al, 1990).

Several studies showed a clear benefit of the use of G-CSF in terms of reduction of length of severe neutropenia, incidence of infections, use of intravenous antibiotic and duration of hospitalizations. Overall, G-CSF facilitates the delivery on time of chemotherapy planned dose but the high costs of acquisition raised the issue of its appropriate use. The guidelines of The American Society of Clinical Oncology (ASCO), updated in 2000, indicated the settings where the use G-CSF is recommended on the basis of the available clinical data. In particular, G-CSF is recommended as primary prophylaxis of febrile neutropenia in patients with an expected incidence of chemotherapy-induced neutropenia greater than or equal to 40%; in the treatment febrile neutropenia in patients at high risk of severe infections (sepsis, pneumonia, fungal infections); after high-dose chemotherapy with autologous progenitor stem-cell rescue; in the mobilization of peripheral blood progenitor cells (PBPCs); in patients with acute myeloid leukemia to reduce the neutropenia of the post-induction chemotherapy; and in patients with acute lymphoblastic leukemia to reduce the neutropenia that follows the induction chemotherapy. The adult indications of the use of G-CSF are generally extended to paediatric patients, though less data are available (Ozer et al, 2000).

Recently, new interest in G-CSF therapy has been obtained with the introduction of pegfilgrastim, the pegylated form of filgrastim (Waladkhani AR, 2004). Filgrastim, the recombinant human G-CSF, is a relatively small protein that is rapidly eliminated from the body via the kidneys. The short half-life, about 3.5 hours, requires its daily administration by intravenous or subcutaneous injection until the recovery to normal values of the absolute neutrophil count. Pegfilgrastim consists of a 20-kDa polyethylene glycol molecule covalently
bound to the N-terminal amino group of filgrastim molecule. Polyethylene glycol molecule are pH-neutral, non-toxic, water soluble polymers that confers to pegfilgrastim a larger volume and a slower renal clearance; as a result the half-life of pegfilgrastim is 35 hours. The most important route of elimination of pegfilgrastim is the so-called neutrophil-mediated clearance: after binding with the G-CSF receptor on surface of neutrophils, the molecule is removed from circulation and the resulting molecule-receptor complex is internalized and metabolized. The neutrophil-mediated clearance is a process slower than renal clearance and in healthy volunteers this molecule produced a sustained neutrophil count for 9-10 days (Molineux et al, 1999). The study performed on neutropenic cancer patients showed that pegfilgrastim reached a peak approximately 24 hours after injection, remained high for all the neutropenic period without daily fluctuation and declined as the patient recovered the baseline count of neutrophils. This favourable kinetic provides a patient’s tailored protection from severe neutropenia and a smooth recovery of neutrophil levels.

Several phase II-III studies with pegfilgrastim has been performed in lung cancer, breast cancer, and lymphoma (Waladkhani AR, 2004; Biganzoli et al, 2004; Holmes et al, 2002; Green et al, 2003; Siena et al, 2003) and the results are summarized as follows: a) the fixed dose of 6 mg (or 100 mg/kg) of pegfilgrastim, administered once per chemotherapy cycle, is equivalent to the 5 mg/kg-daily-dose of filgrastim, administered for 10-11 days, with respect to the incidence and duration of severe neutropenia, and the median time to absolute neutrophil count recovery; b) no dose-limiting toxicities were observed with pegfilgrastim, and the safety profile or the incidence of adverse events was similar to that of filgrastim, including bone pain; c) no effect of body weight was found on duration of severe neutropenia; d) a lower risk of febrile neutropenia was observed in patients who received pegfilgrastim than those given daily filgrastim: 11% vs 19% (relative risk 0.56, C.I. 0.35-0.89, p< 0.005); f) a trend towards a lower risk of hospitalization and use intravenous antibiotics was observed in patients treated with pegfilgrastim. A recent randomized study in breast cancer patients who underwent moderately myelosuppressive chemotherapy regimen showed that the use of pegfilgrastim compared to placebo was associated to a lower incidence of febrile neutropenia (1% vs 17%), febrile-neutropenia-related hospitalization (1% vs 14%) and intravenous antibiotic use (2% vs 10%). These findings demonstrated that the use of pegfilgrastim reduced significantly the incidence of infectious complications also in the patients with a moderate risk of febrile neutropenia (10-20%) and raised the issue of its use as primary prophylaxis out of the current guidelines of ASCO (Vogel et al, 2005). Phase II studies recently reported that pegfilgrastim was effective both in mobilizing a sufficient number of CD34+ peripheral stem cell in patients with myeloma and lymphoma (Isidori et al, 2005; Steidl et al, 2004) and in decreasing the duration severe neutropenia and febrile neutropenia after autologous peripheral blood stem cell transplantation (Staber et al, 2005). These data deserve a further validation by prospective randomized study. In conclusion, pegfilgrastim offers a simplified dosing regimen that is more convenient for nurses and patients but its potentiality warrants further investigation especially in setting where no data are still not available or conclusive (children, stem cell mobilization, autologous stem cell transplantation).

Erythropoietin (EPO)

Anemia is a common complication in patients treated with chemotherapy for cancer. Its occurrence may delay the chemotherapy schedule, affect negatively the quality of life (QoL) and compromise the anti-tumour activity of radiotherapy and chemotherapy (Ludwig H, Fritz E, 1998; Crawford et al, 2002). Prior to 1980s, the treatment of cancer-related anemia was based only on red blood cell (RBC) transfusion when the hemoglobin levels fell below 8-9 g/dl. The introduction of recombinant human erythropoietin in the ‘80s gave the opportunity to reduce the need for RBC transfusions and to improve overall QoL and possibly prognosis of patients. EPO is a protein synthesised in the kidney and, to a lesser extent, in the liver that binds erythropoietin receptors on surface of bone marrow red cell precursors (BFU-e, CFU-e, erythroblasts) and promotes
erythropoiesis. This glycoprotein hormone has a molecular weight of 34 kDa and consists of 165 aminoacids; carbohydrates represent around the 40% of the molecule. Three recombinant human EPO has been approved for anemia in cancer: epoetin alfa, epoetin beta and darbepoetin alfa (Engert A, 2005). Evidence-based guidelines have been published by ASCO and EORTC about the use of the recombinant human erythropoietin in patients with cancer. The major goals of the erythropoietin therapy is the correction of chemotherapy-related anemia (defined as Hb level < 9-11g/dl), prevent transfusions and possibly improve the QoL. The recommended dose of epoetin alfa and beta is 150 IU/kg three times a week for a minimum of 4 weeks that can escalated to 300 IU/kg three times a week for other 4-8 weeks in those patients who do not respond to the initial regimen. An alternative schedule is the administration of 30-40,000 IU once a week in order to improve patient compliance (Rizzo et al, 2002; Bokemeyer et al, 2004). Darbepoetin alfa is a biochemically distinct erythropoietin characterized by an increased carbohydrate content, a major number of sialic acid molecules and a higher molecular weight; these properties determine a longer hal-life (about 49 hours) and an increased biological activity compared to epoetin alfa or beta. The recommended dose of darbepoetin is 2.25 ug/kg per week but a dose finding study in patients with solid tumours showed that the most effective weekly dose is 4.5ug/kg (Glasy et al, 2002). In the same study, the administration of 9 ug/kg every 2 weeks had a comparable efficacy to the weekly dose of 4.5ug/kg. Other authors found that the doses of 12 ug/kg and 15 ug/kg of darbepoetin alfa allow to maintain the efficacy of darbepoetin despite a longer interval of administration, 3 and 4 weeks, respectively (Kotasek et al, 2002; Glasy et al, 2003). A recent meta-analyses including 27 prospective randomized trials published between 1985 and 2002 demonstrated that the use of recombinant human erythropoietin reduced significantly the risk of RBC transfusion, mainly in patients with solid tumours and gives some evidence for improving QoL and survival (Bohlius et al, 2005). Despite these favourable data, recombinant human erythropoietin is not routinely used in cancer patients for several reasons: limited data (children), best dosing schedule not defined yet, slow onset of response, costs, no clear impact on survival and risk of thrombovascular events when used to correct Hb levels beyond anemia.

In conclusion, the development of long-acting darbepoetin gives the opportunity to simplify the management of chemotherapy-related anemia but more data are needed to assess the real cost/benefit ratio and impact on outcome. -

References
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