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Review

Hematopoietic growth factors: Personalization of risks and benefits

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ABSTRACT

A common side effect of cancer treatment is bone marrow suppression. The resulting myelosuppression and anemia can cause significant morbidity and mortality for patients. Agents such as granulocyte colony stimulating factors (GCSF) and erythropoietin stimulating agents (ESAs) may be helpful to ameliorate this depression of blood counts; however these agents have risks which also need to be carefully weighed.

Among the most common side effects for many cytotoxic antineoplastics is bone marrow suppression with resulting neutropenia, anemia, and thrombocytopenia. Enhanced understan ding of the pathways for development of blood cells has led to the development of specific growth factors, especially to support red and white blood cell production. In recent years, there have been specific recommendations for growth factor use, particularly in light of adverse outcomes associated with erythropoietin analogs. As selection of cancer treatment overall is personalized to the individual, the treatment and prevention of side effects related to bone marrow suppression is personalized as well, with a careful assessment of risks and benefits of growth factor treatment to guide use.

1. Granulocyte colony growth factors (GCSF)

The use of myeloid growth factor has significant impacted oncology care, not only by reducing infectious complications related to febrile neutropenia, but by maintaining chemotherapy dose intensity and dose density, as well (Pettengell et al., 1992; Fossa et al., 1998; Citron et al., 2003). Febrile neutropenia (FN) is defined as an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L , or an ANC that is expected to decrease to <500 cells/μL with the next 48 h with fever or clinical signs of sepsis (Freifeld et al., 2011; Aapro et al., 2011). FN is a major complication of chemotherapy treatment and may lead to treatment delays or chemotherapy dose reductions,

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which may impact overall survival as described above. Khan et al. (2008) found that dose delay was the most common neutropenic event and occurred in 30% of patients. In addition, dose reduction due to neutropenia was noted in 20% of patients.

Primary prophylaxis refers to the prevention of neutropenic complications by use of GCSFs during the first cycle of chemotherapy. The use of prophylactic growth factors requires an assessment of each patient's inherent risk of developing FN. According to the 2006 ASCO Guidelines and the 2010 Guidelines from the Infectious Diseases Society of America, primary GCSF prophylaxis is recommended if the risk of FN is greater than 20% (Smith et al., 2006; Freifeld et al., 2011). A patients' risk for FN depends upon age, co-morbid medical conditions, disease characteristics, and myelotoxicity of the specific chemotherapy regimen to be administered (see Figure 1). Also, for regimens with shortened duration between cycles, "dose-dense regimens," the use of GCSFs is required. Patients with certain risk factors (Figure 1) are at increased risk of FN although the specific regimen being used may not have a high risk in patients without such risk factors. For those patients the use of prophylactic treatment is recommended as well. Trials have demonstrated that it is more cost effective to use primary prophylaxis in these patients as the hospitalization of neutropenic patients is quite costly (Vogel et al., 2005; Timmer-Bonte et al., 2006). In a meta-analysis that included 3493 patients from 17 randomized controlled trials, there was a 46% decrease in risk of febrile neutropenia (RR of 0.54, 95% CI 0.43–0.67), a 45% decrease in infection-related mortality (RR of 0.55, 95% CI 0.33–0.90), and a 40% decrease in all-cause mortality (RR 0.6, 95% CI 0.43–0.87) during the time of chemotherapy with the use of GCSF prophylaxis (Kuderer et al., 2007).

The recommended dose for filgrastim or GCSF is 5 μg/kg per day and for sargramostim (GM-CSF) is 250 μg/m^2 per day. Usually, therapy begins 1–3 days after chemotherapy and occurs daily until neutrophil recovery has been achieved (Ozer et al., 2000). Pegfilgastrim is the pegylated form of GCSF and has a longer half-life, thus allowing for a single dose. The usual dose of Pegfilgastrim is 6 mg given one day after chemotherapy. It has been demonstrated that Pegfilgastrim is as effective as filgastrim, and is more convenient for patients (Holmes et al., 2002).

It is important to note that the use of myeloid growth factors as either primary or secondary prevention of neutropenia is not without side effects or risks. One of the most commonly reported side effects is bone pain. A retrospective study examined the rates of bone pain on pegfilgrastim, filgrastim, and without either agent (Gregory et al., 2010). The rate of any grade bone pain with pegfilgrastim was 62.3% for pegfilgrastim and 66.1% for filgrastim, with incidence of grade 3/4 bone pain being 6.6% with pegfilgrastim and 7.9% with filgrastim. The underlying malignancy appeared to influence the incidence of severe bone pain (Non-small cell lung cancer (19.6%) vs. breast cancer (6.2%)). The contribution of regimen given (taxane or not), age, and gender was mixed depending on severity of bone pain. Of note, while studies with pegfilgrastim as compared to no growth factor use, the rate of any grade bone pain was higher with pegfilgrastim (32.7% vs. 23%), however, the rates of severe pain were similar (3.4% vs. 2.0%).

Rare, but notable toxicities with myeloid growth factors include increased bleomycin-related pulmonary toxicity, splenic rupture, and acute leukemia. Bleomycin pulmonary toxicity was seen in 26% of bleomycin-treated patients with Hodgkin's lymphoma who received GCSF and in 9% of patients

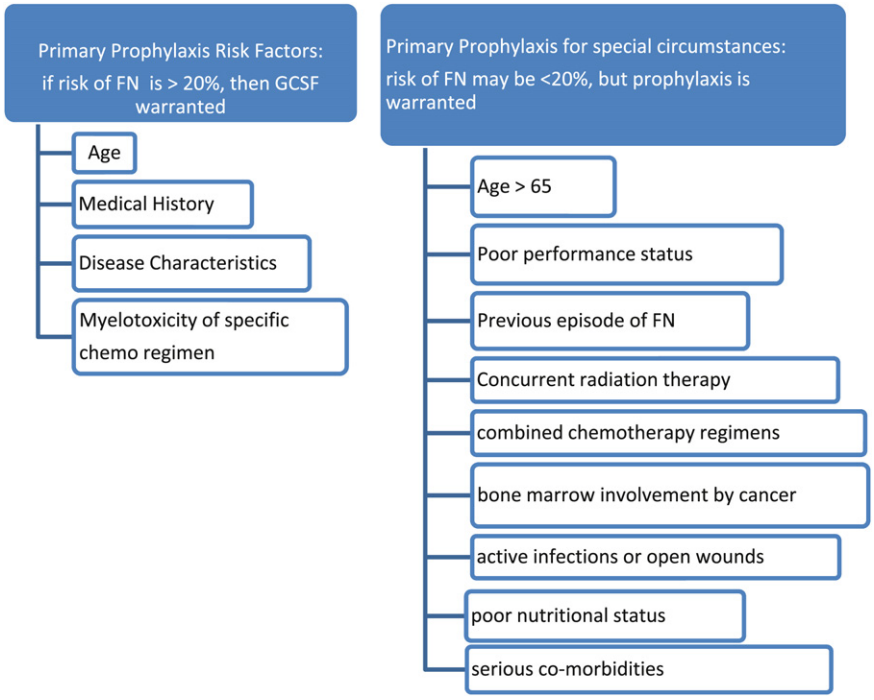

Figure 1 – Febrile neutropenia risk factors.

who did not receive GCSF (Martin et al., 2005). However the enhancement of pulmonary toxicity with GCSF has not been seen in other bleomycin-treated malignancies, such as non-Hodgkin's lymphoma and testicular cancer (Bastion et al., 1994; Saxman et al., 1997). Currently, this association is not a contraindication for treatment, however it is important for clinicians to be aware and inform their patients. Splenic rupture has been reported in otherwise healthy bone marrow transplant donors as well as recipients of hematopoietic stem cell transplants (Tique et al., 2007), and appears to be more rare in patients receiving prophylactic GCSF in the setting of chemotherapy for solid tumors (Watring et al., 2007; Masood et al., 2008). The later risk of developing treatment-related myeloid dyscrasia or leukemia has been examined in patients treated with GCSF. A review in over 12,000 patients treated with these agents did reveal infrequent development of later AML/MDS which was higher in those who received GCSF (RR 1.92, $P = 0.007$); however all-cause mortality was lower in those who received GCSF (Lyman et al., 2010). At this time, growth factors are not contraindicated in any specific population.

2. Erythropoietin analogs

In cancer patients, anemia can have multiple and overlapping etiologies including toxicity of chemotherapy, direct bone marrow involvement, chronic blood loss with bleeding from tumors (such as in gastrointestinal cancers), and anemia of chronic disease/inflammation. Erythropoietin (EPO) is secreted primarily by the kidney and is required for the formation of red blood cells. Erythropoietin Stimulating Agents (ESAs) are generally used in patients with hemoglobin of less than 10 and include agents such as epoetin and darbepoetin. ESAs have been shown in clinical trials to decrease the transfusion requirements and increase the hemoglobin in patients with chemotherapy induced anemia (Rizzo et al., 2010). However, these trials have not shown that ESAs prolong survival, or improve quality of life in these patients (Pronzato et al., 2010). A meta-analysis performed by Bohlius et al. (2006) compared 57 studies including 9353 patients assigned to ESAs and blood transfusions vs. only blood transfusions found that in patients with a hemoglobin of less than 12, ESAs significantly increased the likelihood of obtaining an increase in HGB of at least 2 g/dL from baseline (RR of a HGB response 3.4, 95% CI 3.1–3.8). ESAs were also found to reduce the use of RBC transfusions (relative risk [RR] 0.64, 95% CI 0.60–0.68) and patients treated with an ESA received on average one unit less of red blood cells than those in the control group (Bohlius et al., 2006). ESAs are an option for patients who are averse to blood transfusions for personal or religious reasons. Transfusions are not without other risks including transfusion reactions, iron overload, viral infections, and the risk of alloantibody development.

ESAs, however, have been associated with a number of undesirable outcomes in cancer patients including an increased risk of stroke and venous thromboembolism, worse cancer outcomes and overall increased mortality. The meta-analysis described above by Bohlius and colleagues reported a near doubling in the incidence of thromboembolic events, from 3.8% for patients not on ESA and 6.1% when ESAs were given. Similarly, an additional meta-analysis performed by Bennett et al. (2008) also showed that VTE risk was increased in patients receiving ESAs (7.5 vs. 4.9% in patients not receiving ESAs, relative risk 1.57 [95% CI 1.31–1.87]). Patients who were treated with ESAs had greater all-cause mortality (HR = 1.10, 95% CI 1.01–1.2) although this was not statistically significant ($P = 0.11$). A later meta-analysis also found detriment to mortality in a diverse group of cancer patients treated with ESAs to the overall population evaluated (HR 1.06, 95% CI 1.00–1.12) (Bohlius et al., 2009).

One of the major concerns with the use of ESAs sparked by the observation of worse mortality is that tumor cells of various histologies have erythropoietin receptors and may, in fact, be stimulated by the ESAs (Acs et al., 2001, 2004; Mohyeldin et al., 2005; Lai et al., 2005; Lai and Grandis, 2006; Kumar et al., 2005, 2006) With the findings of worse outcomes in patients treated with ESAs, both the US Food and Drug Administration (FDA) and the European Medicines Agency issued warnings against the use of ESAs particularly when treating patients with a goal of cure. The 2010 ASH/ASCO (American Society of Hematology/American Society of Clinical Oncology) Guidelines recommend a thorough workup for other causes of anemia before initiation of ESAs as well as discussion of the potential benefits and harms of ESAs. They also stressed that ESAs should only be used in anemia associated with chemotherapy when the hemoglobin is <10 g/dL and the patient is symptomatic and not in patients who are not currently receiving chemotherapy. Patients at an increased risk for thromboembolic events, such as those with a history of thromboses, surgery, prolonged periods of immobilization or limited activity, should consider the risks and benefits carefully before the initiation of ESA therapy (Rizzo et al., 2010).

In light of the aforementioned concerns with worsened outcomes associated with ESA therapy, the United States Food and Drug Administration (FDA) has mandated a risk evaluation and mitigation strategy (REMS) for hospitals and physicians that prescribe ESA therapy. The manufacturer of currently available ESA's was required to develop a program for prescribers, ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) with specific training on the adverse outcomes associated with these agents. There is also educational information for patients (US FDA, 2010). These materials outline specifically that the risks of ESAs include increased tumor progression and death from cancer, as well as increased risk of myocardial infarction, heart failure, stroke, and blood clots. Healthcare professionals must re-enroll in the program every three years.

3. Conclusions

Side effect profiles are often a major challenge in cancer treatment. Adverse hematopoietic response to treatment may ultimately deter a patient from receiving the appropriate treatment. Age, other co-morbid conditions, progression of disease and toxicity of chemotherapy are often factors that influence how a patient will react to a drug. Granulocyte colony growth factors (GCSF) can be lifesaving when the patients' overall risk for febrile neutropenia is considered to be greater

than 20%. In addition, chemotherapy related anemias that require blood transfusions may be associated with undesirable risks that may be curtailed by using ESAs. However, the individual risks of using such therapies must be weighed against the benefits. An individualized approach must be used to determine the likelihood of side effects for patients. When determined safe to use, growth factors may prolong the duration a patient may be able to undergo chemotherapy, and may ultimately lead to improved cancer outcomes.

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