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Hematopoietic Growth Factors: Current Recommendations

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Abstract: Anemia and neutropenia are common problems associated with cancer. Neutropenia is a major dose-limiting toxicity of systemic chemotherapy, experienced by almost 40 to 60% of patients and can be associated with substantial morbidity, mortality, and costs apart from an adverse psychological impact. Febrile neutropenia (FN) often necessitates hospitalization, use of broad-spectrum antibiotics and can lead to dose reductions or treatment delays compromising the clinical outcome of cancer. Prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of neutropenia. Despite these benefits, CSFs are not administered to all patients receiving myelosuppressive chemotherapy because of the costs. Various guidelines earlier recommended prophylactic use if the risk of FN was more than 40% but now based on emerging evidence, use is recommended if the risk is over 20%. New guidelines include special situations such as elderly patients, pediatric patients and use during radiotherapy or accidental exposure to radiation. Anemia in cancer is a common multi-factorial problem occurring in over 60% of patients and has an adverse impact on quality of life as well as treatment outcome. Management consists of assessment of the cause, correction of nutritional factors and either transfusion of packed cell transfusion or use of erythropoietin or both. Packed cell transfusion has its associated transfusion related problems of reactions, infections, while use of erythropoietin has a favorable outcome on quality of life, despite addition to cost of treatment. Guidelines about use of erythropoietin are available and discussed.

INTRODUCTION

Chemotherapy, as a part of multimodal treatment, over the last few decades has changed the results in cancer patients in terms of responses and survival. Apart from being curative in some of the malignancies, they are effective for palliation and prolongation of survival. In addition, some of the agents are being used as radiosensitisers in carcinoma cervix, head and neck cancers with significant survival benefit. Better results are being observed with discovery of effective newer agents, newer combinations, dose intense and dose dense schedules. In the present era of targeted therapy with monoclonal antibodies, small molecules, medical management of cancer is undergoing a radical change with very exciting results. Amongst the side effects of chemotherapy, neutropenia is the most dreaded complication commonly occurring during the initial cycles and predisposes patients to serious and often life-threatening infections with an adverse impact on the outcome. About 20-40% of treatment-naïve patients develop febrile neutropenia (FN) with common chemotherapy regimens and it remains a serious challenge. The effects of FN on the patient and treatment are multifarious; it can lead to mortality,

morbidity and cost escalation. Overall risk of death is about 10% and the risk varies according to cancer, patient, and treatment related factors. FN often results in treatment delays and dose reductions, compromising the cancer outcome. *Use of empirical antibiotics has changed the scenario of FN and lessened the mortality and morbidity. An episode of uncomplicated febrile neutropenia in American hospitals may cost about \$20,000, while in India it is around Rs 25000. Administration of CSFs results in a 50% risk reduction of developing FN and hence prevention of FN with prophylactic CSF is a clinical priority.*

CURRENT RECOMMENDATIONS

Guidelines from American Society of Clinical Oncology (ASCO),¹ National Comprehensive Cancer Network (NCCN)² and European Organization for Regional Cooperation and Training (EORTC)³ have been published recently. Amongst these, ASCO 2006 guidelines are most exhaustive, covering most of the clinical situations and include newer situations. A major change in these guidelines is the recommendation to use prophylactic CSF when the risk of FN is 20% or more, a deviation from earlier risk of 40%. As understanding the risk of FN during chemotherapy is the basis for the decision of prophylactic use of CSF, all guidelines have published lists of regimen with the possible risk of neutropenia. Table 14.1 enumerates one such list.

ASCO GUIDELINES¹

ASCO published its first evidence-based clinical practice guidelines in 1994 on the use of CSF and were updated in 1996, 1997, 2000 and 2005. ASCO recommendations 2006 are summarized in the following paragraphs.

Primary prophylactic CSF administration (first and subsequent-cycle use) is recommended:

(a) when the risk of FN \geq 20%, (b) for “dose dense” regimens, and (c) when risk of FN is $<$ 20% with presence of clinical factors predispose to increased complications from prolonged neutropenia.

These circumstances include patient age $>$ 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; combined chemoradiotherapy; bone marrow involvement by tumor; poor nutritional status; the presence of open wounds or active infections; advanced cancer, as well as other serious co-morbidities.

Secondary prophylactic CSF administration is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy without CSF, in which a reduced dose may compromise disease-free or overall survival or treatment outcome.

Therapeutic use of CSF: CSFs should not be routinely used for patients with afebrile neutropenia or as adjunctive treatment with antibiotic therapy for patients with FN. However, CSFs should be considered in patients with complicated FN or with poor prognostic factors such as prolonged (\geq 10 days) neutropenia, severe ($\leq 0.1 \cdot 10^9/L$) neutropenia, age $>$ 65 years, uncontrolled primary disease, pneumonia, hypotension, multi-organ dysfunction, invasive fungal infection, or requirement of hospitalization at the time of the development of fever.

Dose-intense and dose-dense regimen: Use of CSFs allows a modest to moderate increase in dose density and dose-intensity of chemotherapy regimens. Available updated data suggests a survival benefit from the use of dose dense with CSF support in a few specific settings: node-positive breast cancer; NHL in young with CHOP-14 regime, and old patients with CHOP-14 regime.

Stem-cell transplantation (SCT): After high dose chemotherapy is a standard of care in many cancers such as Hodgkin's and non-Hodgkin's lymphoma, and germ cell tumors. Role of CSFs in transplantation is well established in the following settings: (a) to mobilize peripheral-blood progenitor cell (PBPC); (b) to shorten the period of neutropenia after conditioning regime. Severe thrombocytopenia and splenic rupture have been documented.

Acute myelogenous leukemia (AML)

- a. *Induction* CSF administration soon after initial induction chemotherapy can produce modest decreases in the duration of neutropenia hence is considered reasonable. Patients older than 55 years of age are likely to benefit.
- b. *Consolidation therapy* Use after consolidation therapy in AML in CR is justified. The expected benefits are decrease in the duration of severe neutropenia, reduction of incidence of severe neutropenia, a decreased rate of infection and antibiotic requirement. However, there is no effect on complete response duration or overall patient survival.
- c. *Priming* Use of CSFs for priming effects is not recommended due to lack of evidence.

Myelodysplastic syndrome (MDS): CSFs can increase the absolute neutrophil count in MDS. Data supporting the routine long-term continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

Acute lymphocytic leukemia (ALL): CSFs are recommended after the completion of the induction, as they can shorten the duration of neutropenia. Effects on the incidence, duration of hospitalization, occurrence of serious infections, prolongation of disease-free or overall survival are uncertain, though improved CR rates has been reported. G-CSF can be administered concomitantly with the continued corticosteroid or antimetabolite therapy.

Relapsed leukemia: CSFs should be used judiciously, if at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia. Remote possibility of stimulatory effect of CSF on leukemia exists.

Radiation therapy: CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In patients receiving radiation therapy alone therapeutic use of CSFs may be considered if prolonged delays in treatment are expected due to neutropenia.

Age groups: In patients over 65 years, on curative chemotherapy, prophylactic CSF should be administered to reduce the incidence of FN and infections. In other clinical situations, guidelines as outlined above apply. In pediatric patients, use of G-CSF is considered reasonable for the primary and secondary prophylaxis or for therapy in high-risk patients. A potential risk exists for secondary myeloid leukemia or MDS associated with G-CSF in patients with ALL.

Radiation injury: In patients exposed to lethal doses of total body radiotherapy (3-10 Grays), prompt administration of CSF is recommended, as benefits of better survival have been observed in radiation accident victims and animal models.

OTHER GUIDELINES

NCCN guidelines² emphasize assessment based on risk stratification and intent of treatment as summarised in Table 14.2. Various risk factors useful in this stratification are listed in Table 14.3. In addition, they emphasize the importance of evaluation of each cycle administered with or without CSF to the patient. An episode of FN during treatment without CSF is to be considered as high risk, and prophylactic CSF is recommended from next cycle. If the patient experiences such an episode despite CSF, dose reduction, or change in treatment regimen, is recommended. EORTC guidelines 2006³ also reflect a similar change in strategy and patient, treatment and disease related risk factors are considered important in decision-making.

MYELOID GROWTH FACTORS

Filgrastim, Pegfilgrastim and Sargramostim are currently available myeloid growth factors. Filgrastim (G-CSF) should be administered in doses of 5 µg/kg/d, 24-72 hours after standard

chemotherapy or 24-120 hours after high dose therapy in SCT and should be continued until reaching an ANC of at least $2-3 \times 10^9/L$. For mobilization, G-CSF should be started at least 4 days before the first leukopheresis procedure and continued until the last one. Pegfilgrastim is not currently indicated for stem cell mobilization. Single dose of Pegfilgrastim 6 mg should be administered 24 hours after chemotherapy. The safety and efficacy of pegylated G-CSF has not yet been fully established in the setting of dose-dense chemotherapy. 6 mg formulation should not be used in infants, children, or small adolescents weighing < 45 kg. GM-CSF (sargramostim) has been licensed specifically for AML and post BMT. It should be initiated on the day of bone marrow infusion or 24 hours from the last chemotherapy and 12 hours after radiotherapy and continued until an ANC greater than $1.5 \times 10^9/L$ for 3 consecutive days is obtained. The drug should be discontinued early or the dose be reduced by 50% if the ANC increases to greater than $20 \times 10^9/L$. The dose is $250 \mu\text{g}/\text{m}^2/\text{d}$ for all clinical settings other than peripheral blood progenitor cell (PBPC) mobilization, where a dose of $10 \mu\text{g}/\text{kg}/\text{d}$ seems preferable. Subcutaneous route is preferred for all three agents. No recommendations are available regarding the equivalency of the G-CSF or GM-CSF.

USE OF ERYTHROPOIETIN IN CANCER

About 50% of patients with solid tumors and 60-70% of patients with hematological malignancies present with anemia at diagnosis. Anemia impacts the patient by impaired functioning of organs and systems and lowered quality of life (QOL) with fatigue. It may lead to decreased response to treatment and lower survival, as tumor hypoxia is known factor leading to resistance to radiotherapy. It is associated with a poor prognosis in several cancers, including lymphoma and cancers of cervix, head and neck, prostate, bladder and lung. Etiology can be multifactorial and may not be always due to the direct effects of cancer or its treatment. Patient should be assessed with a drug history, checked for occult blood loss, screened for nutritional deficiencies and hemolysis. Routine testing for EPO level is not recommended. Treatment options include RBC transfusion and use of erythropoietin (EPO). RBC transfusion is recommended if a quick escalation in hemoglobin in patients with limited life span or severe/life-threatening anemia with organ dysfunction. In all other cases, RBC transfusion is not optimal because of issues of cost, transmission of infections, and a possibility of reduced survival. Blood transfusion in cancer patients has been assessed as an independent risk factor for lower survival. Though reason is unknown, immune suppression could be a causative factor. Two recombinant variants of EPO are available in clinical practice, epoetin alpha and beta. A long acting derivative, darbepoetin (Aranesp), is also available (not yet in India). Epoetin alpha and darbepoetin alpha are licensed for patients with solid tumors and non-myeloid malignancies undergoing chemotherapy. There are no differences in the clinical outcome with these three agents as seen in various trials. Benefits of EPO administration include reduced risk of blood transfusion, improved hemoglobin and better quality of life. Adverse effects mainly includes thrombosis and caution is required while use in patients predisposed to thrombosis. Tumor growth due to EPO receptors on the cancer cells has been under investigation. Pure red cell aplasia (PRCA) has not been reported in cancer patients.

CURRENT GUIDELINES REGARDING USE OF EPO⁴

Comprehensive guidelines on the use of EPO have been laid down by various societies including the American Society of Hematology (ASH), ASCO, EORTC, and NCCN. Modified ASCO/ASH guidelines are given below:

1. EPO is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level < 10 gm%.

2. For patients with declining hemoglobin and levels between 10 to 12 gm%, the decision to use EPO should be determined by clinical circumstances.
3. The recommended starting dose is 150 U/kg given subcutaneously thrice weekly for a minimum of 4 weeks. An alternative weekly dosing regimen (40,000 U/wk) can be considered. In non-responders, dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks is recommended. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.
4. Continuing EPO treatment beyond 6 to 8 weeks in the absence of response (defined as 1gm rise in month) despite appropriate dose, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.
5. After hemoglobin levels reach 12 gm%, dosage of EPO should be titrated to maintain that level or restarted when the level falls to near 10 gm%.

CONCLUSION

Cancer treatment is undergoing a major change and its attendant problems of anemia and neutropenia need attention. Summary of guidelines mentioned in this article can enable a physician in treatment decisions. None of these guidelines can account for individual variations in patients and for special clinical situations, for which the treating physician must use his judgment and individualise the treatment.

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