

# SUMMARY OF THE ASCO GUIDELINES FOR THE USE OF COLONY-STIMULATING FACTORS (CSFs) – 2006

## GUIDELINES FOR PRIMARY PROPHYLACTIC CSF ADMINISTRATION

### *General Circumstances*

Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose dense” regimens, CSFs are required and recommended. New clinical trial data support the use of CSF when the risk of FN is in the range of approximately 20% or higher. The use of regimens, if available, that do not require CSFs because of equal efficacy and lower risk of FN remain standard medical practice. In the absence of special circumstances, most commonly used regimens have risks of FN of less than 20%. In making the decision to use prophylactic CSF or not, oncologists should consider not only the optimal chemotherapy regimen, but also the individual patient risk factors and the intention of treatment; that is, curative, prolongation of life, or symptom control and palliation.

### *Special Circumstances*

Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive.

Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age greater than 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate even with regimens with FN rates less than 20% (consensus of the expert committee).

## GUIDELINES FOR SECONDARY PROPHYLACTIC CSF ADMINISTRATION

Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.

## GUIDELINES FOR THERAPEUTIC USE OF CSF THERAPY

- A. *Afebrile Patients*: CSFs should not be routinely used for patients with neutropenia who are afebrile.
- B. *Febrile Patients*: CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. CSFs should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features included expected prolonged (> 10 days) and profound (< 0. x 10<sup>9</sup>/L) neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension, and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

## RECOMMENDATIONS FOR USE OF CSFs TO INCREASE CHEMOTHERAPY DOSE-INTENSITY AND DOSE-DENSITY

Use of CSFs allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. Available data would suggest a survival benefit from the use of dose-dense (but not dose-intense) regimens with CSF support in a few specific settings (e.g., node-positive breast cancer; and possibly NHL pending confirmation of results of individual trials). However, additional data in these settings are needed and these results cannot be generalized to other disease settings and regimens. Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.

## GUIDELINES FOR USE OF CSFs AS ADJUNCTS TO PROGENITOR-CELL TRANSPLANTATION

CSFs are recommended to help mobilize PBPCs and after PBPC infusion. Mobilized PBPCs have largely replaced bone marrow-derived cells for use in autologous transplantation. Side effects associated with mobilization and subsequent apheresis is usually limited and includes constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combinations of chemotherapeutic agents and a CSF. The optimal dose of CSFs and chemotherapeutic agents is the subject of ongoing investigations, but a higher (10 micrograms/kg/day) dose of G-CSF in the setting of mobilization may yield greater content of CD34+ progenitor cells in the PBPC product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis. Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of G-CSF, either alone or in combination with GM-CSF, or after the use of chemotherapeutic agents, generates PBPCs, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs. Further investigations are necessary to assess the potential risks especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and CSFs. Administration of CSFs following allogeneic HSCT is not a currently recommended.

## GUIDELINES FOR USE OF CSFs IN PATIENTS WITH ACUTE LEUKEMIA AND MDS

### *Acute Myeloid Leukemia:*

*Induction Therapy:* Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial induction chemotherapy. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest. CSF use following initial induction therapy is reasonable, although there has been no favorable impact on remission rate, remission duration or survival. Patients older than 55 years of age may be most likely to benefit from CSF use.

*CSF Priming:* There is no evidence that CSFs given either before or concurrently with chemotherapy for *priming effects* are of benefit, and their use in this fashion cannot be recommended outside the setting of the clinical trial.

*Consolidation Therapy:* CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after *consolidation chemotherapy* for patients with AML in remission than for patients receiving initial induction therapy. There is not effect on the duration of complete response duration or overall survival. There is, as yet, no information about the effect of longer acting, pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical trials.

*Myelodysplastic Syndromes (MDS):* CSFs can increase the ANC in neutropenic patients with MDS. Data supporting the routine, long-term, continuous use of CSFs in these patients is lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

*Acute Lymphoblastic Leukemia (ALL):* CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of less than  $1 \times 10^9/L$  by approximately 1 week. There are less consistent effects on the incidence and duration of hospitalization and the acquisition of serious infections. Although there was a trend for improved complete response rates in one large study, particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelo-suppressive effects of the chemotherapy. As in AML, it is not known from the published data whether the CSFs significantly accelerate recovery to ANC of  $0.1 - 0.2 \times 10^9/L$ . In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the CSFs were taken into consideration. Cost estimates of CSFs for adults with ALL have not been reported.

*Leukemia in Relapse:* CSFs should be used judiciously, or not at all in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia. Because of the relatively low response rates in AML patients with relapsed or refractory disease, clinicians may be faced with the difficult dilemma of whether the persistence of leukemia after chemotherapy is a consequence drug resistance or a stimulatory effect of the CSF. Although drug resistance is the most likely cause of treatment failure, it is sometimes necessary to stop the CSF and observe the patient for a few days to be certain.

## **GUIDELINES FOR USE OF CSFS IN PATIENTS RECEIVING RADIOTHERAPY WITH OR WITHOUT CONCURRENT CHEMOTHERAPY**

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

## **GUIDELINES FOR USE OF CSFS IN OLDER PATIENTS**

Prophylactic CSF for patients with diffuse aggressive lymphomas aged 65 years and older treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.

## **GUIDELINES FOR USE OF CSFS IN THE PEDIATRIC POPULATION**

The use of CSFs in pediatric patient will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential for secondary myeloid leukemia or MDS associated with CSFs represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSFs in children with ALL should be considered with caution.

## **GUIDELINES FOR CSF DOSING AND ROUTE OF ADMINISTRATION**

In adults, the recommended CSF doses are 5 micrograms/kg/dose for G-CSF (filgrastim) and 250 micrograms/m<sup>2</sup>/dose for GM-CSF (sargramostim) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 micrograms/kg/dose is preferable. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of CSF administration is subcutaneous.

Pegylated filgrastim (pegfilgrastim) should be given once, 24 hours after completion of chemotherapy. Pegfilgrastim is not currently indicated for stem cell mobilization. The safety and efficacy of pegylated filgrastim has not been fully established in the setting of dose-dense chemotherapy. The 6 mg formulation should not be used in infants, children, or small adolescents weighing less than 45 kg.

## **GUIDELINES FOR INITIATION AND DURATION OF CSF ADMINISTRATION**

CSFs should be given 24 to 72 hours after the administration of myelotoxic chemotherapy. In the setting of high-dose therapy and autologous HSCT, CSF can be given between 24 and 120 hours after the administration of high-dose chemotherapy. CSF should be continued until reaching an ANC of at least  $3 \times 10^9/L$ . For PBPC mobilization, CSF should be started at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis.

## **SPECIAL COMMENTARY ON COMPARATIVE CLINICAL ACTIVITY OF G-CSF AND GM-CSF**

Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative CSF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for CSF administration, eg, support after BMT or use with nontransplantation chemotherapy regimens. The panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

## **SPECIAL COMMENTS ON GROWTH FACTORS AS A TREATMENT FOR RADIATION INJURY**

Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs includes the prompt administration of CSF or pegylated G-CSF. Accidental or intentional (eg resulting from a terrorist attack or war) total body irradiation leads to probable or certain death from bone marrow failure at doses of 3 to 10 Gy without supportive care, CSFs and/or bone marrow transplant. Doses below that level are almost always survivable with excellent nursing care, and higher doses are lethal because of injury to other organs such as the gastrointestinal tract. The chance for mortality from any radiation dose rises with combined injuries to the skin, lungs, and so on. Hematopoietic growth factors can increase the survival, proliferation, amplification, and differentiation of granulocyte progenitors to produce neutrophils. Although no prospective, randomized trials have been carried out to determine the benefit of hematopoietic growth factors in humans exposed to accidental or intentional radiation injury, they have been used in radiation accident victims, and neutrophil recovery appears to have been hastened in 25 of 28 cases. In animal models, prompt administration of HGFs after otherwise lethal TBI dramatically increases survival.

### References:

[Smith TJ, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. \*J Clin Oncol\* 2006;24:3187 - 205.](#)

[Ozer H, et al. 2000 Update of recommendations for the use of Hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. \*J Clin Oncol\* 2000;18:3558 - 85.](#)

## SUMMARY OF THE ASCO AND THE ASH GUIDELINES FOR THE USE OF EPOETIN IN PATIENTS WITH CANCER

**NOTE:** SEE [FDA BLACK BOX WARNING](#) FOR EPOETIN-INDUCED POLYCYTHEMIA

### GENERAL RECOMMENDATION:

As in any medical situation, it is essential to give consideration to other correctable causes of anemia before proceeding to therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B<sub>12</sub> deficiency where indicated, and assess for occult blood loss. Coomb's testing may be appropriate for patients with chronic lymphocytic leukemia; endogenous erythropoietin levels may predict response in patients with myelodysplasia.

### CHEMOTHERAPY-INDUCED ANEMIA:

The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level  $\leq 10$  g/dL. RBC transfusion is also a treatment option depending on the severity of anemia or clinical circumstances.

### DOSE AND SCHEDULE FOR EPOETIN:

For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration of  $< 12$  g/dL, but who never have fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.

The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.

Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (e.g.,  $< 1$  to 2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in non-responders, 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.

Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.

### MYELODYSPLASIA, MULTIPLE MYELOMA, NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA (ANEMIA PRIMARILY RELATED TO HEMATOLOGIC MALIGNANCY)

There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined in the previous section.

Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.

Reference: [Rizzo JD, et al. \*J Clin Oncol\* 2002;20:4083 - 107.](#)

**COMPARISON OF ERYTHROPOETIC AGENTS  
FOR TREATMENT OF CANCER-INDUCED ANEMIA (CIA) IN ADULTS**

**FDA- APPROVED DOSING OF ERYTHROPOIETIN AGENTS FOR CIA:**

	<b>EPOETIN (PROCRIT)</b>	<b>DARBEPOETIN ALFA (ARANESP)</b>
Dosing	150 units/kg SC/IV 3 times per week, *if no response after 8 weeks of therapy, increase dose to 300 units/kg.	2.25 mcg/kg SC weekly; if no response after 6 weeks of therapy can increase up to 4.5 mcg/kg or 500 mcg SC every 3 weeks.
Shands Acquisition Costs	40,000 units/vial = \$ 256.03	200 mcg syringe = \$472.50 100 mcg syringe = \$236.25  NOTE: Shands costs, 2006

\*Defined as a patient failing to achieve at least a 1 g/dL increase from their baseline hemoglobin level.

**RECOMMENDED DOSE EQUIVALENCY BETWEEN EPOETIN ALFA AND  
DARBEPOETIN ALFA FOR TREATMENT OF CIA IN ADULTS**

<b>EPOETIN ALFA</b>	<b>DARBEPOETIN ALFA</b>	<b>REF</b>
40,000 units SC weekly equivalent to	<sup>a</sup> 200 mcg SC q 2 weeks	1, 2
	100-150 mcg SC weekly	3
	300 mcg SC q 3 weeks	2, 4
	500 mcg SC q 3 weeks	5
60,000 units SC weekly equivalent to	150 mcg SC weekly	3
	<sup>b</sup> 300 mcg SC q 2 weeks	1,2
<b>EPOETIN ALFA</b>	<b>EPOETIN ALFA</b>	
40,000 units SC weekly equivalent to	<sup>c</sup> 120,000 units SC q 3 weeks	6
<b>DARBEPOETIN ALFA</b>	<b>DARBEPOETIN ALFA</b>	
100 mcg SC weekly equivalent to	200 mcg SC q 2 weeks	2
	300 mcg SC q 3 weeks	3, 4
	500 mcg SC q 3 weeks	5

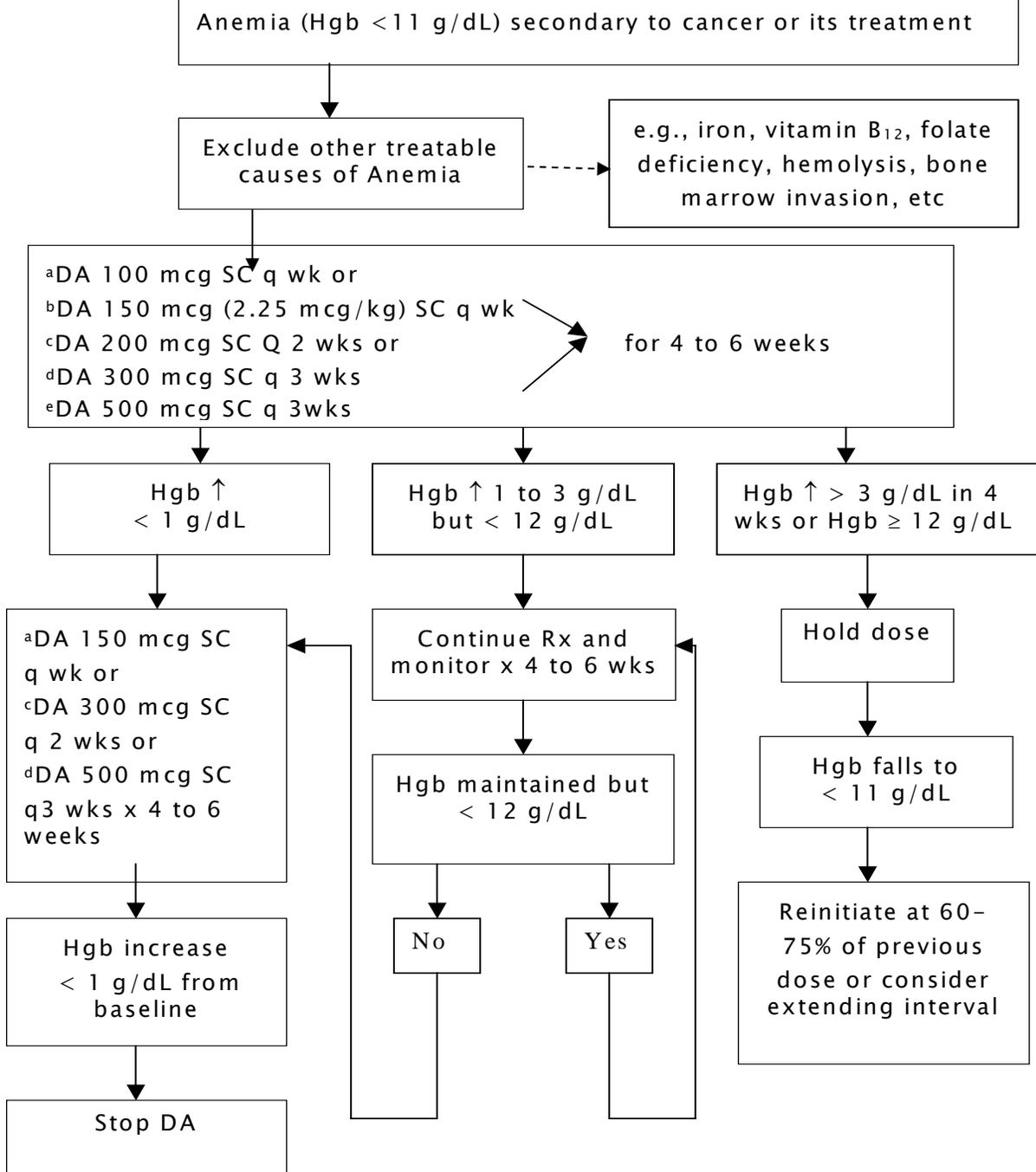
<sup>a, b, c</sup> based on prospective head-to-head trials comparing weekly dosing of epoetin (40,000 units) with various dosing intervals of darbepoetin alfa or epoetin alfa.

**NOTE:**

- In order to reduce the expenditures of these high cost drugs in an inpatient setting, it is recommended that all the inpatient orders should be written as WEEKLY DOSING.

# RECOMMENDED PRACTICE GUIDELINES FOR TREATMENT OF CIA

## DARBEPOETIN ALFA (ARANESP)

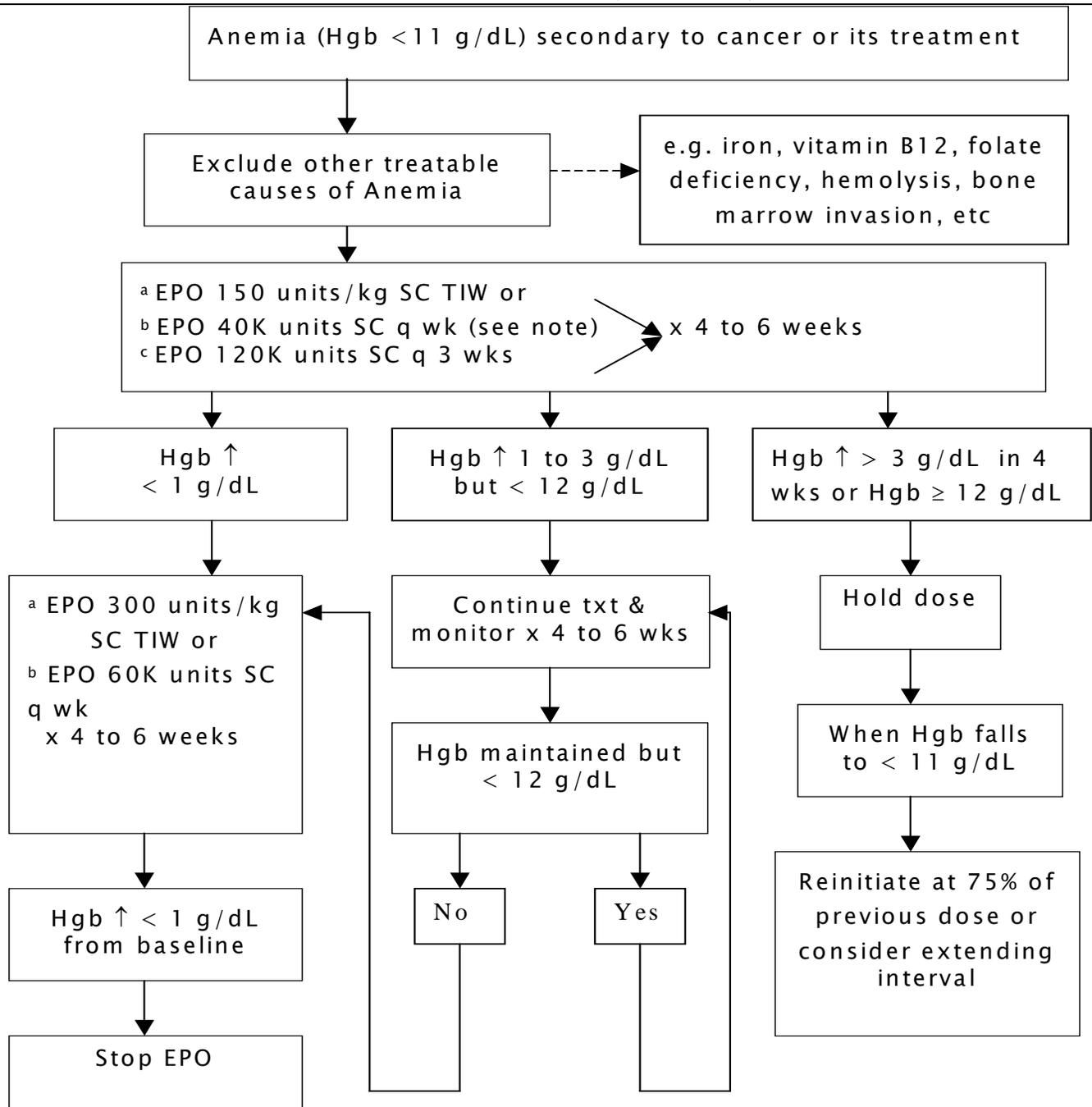


DA= DARBEPOETIN

Note: <sup>d</sup> The clinical trial showed that 60–70% of patients in both groups (500 mcg q 3wks and 2.25 mcg/kg q wk) had their dose reduced to 60% after 6 weeks of treatment due to rapid rate of rise in Hb concentration ≥ 13 g/dL.

Reference: [Canon JL, et al. J Natl Cancer Inst. 2006;98:273 – 84.](#)

## EPOETIN ALFA (PROCRIT)



EPO = EPOETIN ALFA

Note: <sup>c</sup> The clinical trial showed that ~60% of patients who were randomized to 120K units q 3weeks had their dose reduced by ~25% after 4 weeks of initial treatment due to rapid rate of rise in Hb concentration of  $\geq 13$  g/dL.

Reference: [Steensma DP, et al. J Clin Oncol. 2006;24:1079-89.](#)

## REFERENCES

- 1) [20030125 Study Group Trial](#). Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 Study Group Trial. *J Clin Oncol* 2006;24:2290 – 7.
- 2) [Glaspy J, Henry D, Canon J, et al](#). Darbepoetin alfa administered at varying intervals compared with weekly epoetin alfa for treating chemotherapy-induced anemia: a pooled analysis of 20 clinical trials. *Proc Am Soc Clin Oncol* 2006;24,18S;abstract 18508.
- 3) [Patton J, Reeves T, Wallace J](#). Effectiveness of darbepoetin alfa versus epoetin alfa in patients with chemotherapy-induced anemia treated in clinical practice. *Oncologist* 2004;9:451 – 8.
- 4) [Kotasek D, Steger G, Faught W, et al. Aranesp 980291 Study Group](#). Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double blind, placebo-controlled, randomised study. *Eur J Cancer* 2003;39:2026 – 34.
- 5) [Canon JL, Vansteenkiste J, Bodoky G, et al](#). Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. *J Natl Cancer Inst* 2006;98:273 – 84.
- 6) [Steensma DP, Molina R, Sloan JA, et al](#). Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;24:1079 – 89.

Prepared by Masha Lam, Pharm.D., BCOP; May 2006.