CONFERENCE ARTICLE
UDC: 616-006:616.15:615-085

Management of hematological complications of malignancy and chemotherapy: The role of hematopoietic growth factors

Svetislav Jelić

ABSTRACT

lInstitute of Oncology and Radiology of Serbia, Belgrade, Serbia & Montenegro; Address correspondence to: Svetislav Jelić, Institute of Oncology and Radiology of Serbia, Department of Medical Oncology, Pasterova 14, 11000 Belgrade, Serbia & Montenegro, The manuscript was received: 15.08.2004, Accepted for publication: 15.09.2004

KEY WORDS: *Neoplasms; Antineoplastic Agents; Hematologic Diseases; Anemia; Thrombocytopenia; Neutropenia; Hematopoietic Cell Growth Factors*

Cancer related syndromes involving haematopoesis and the process of hemostasis are not exceptional.

The hematopoietic disturbances related to cancer include erythrocytosis, cancer related anemia, and either thrombocytosis or thrombocytopenia.

Pancytopenia with erythroblastosis in peripheral blood is usually the consequence of bone marrow invasion and might be a terminal phenomenon. Treatment is supportive and includes transfusions of packed red blood cells, eventually platelets when needed. It is sometimes associated with disseminated intravascular coagulation when appropriate measures are required. Nevertheless this syndrome is usually a sign of generalized malignancy, not any more candidates for cytotoxic treatment.

Erithrocytosis has been traditionally associated with erythropoietin producing tumors such as renal cell carcinoma, hepatocelular carcinoma and cerebelar hemangioblastoma. In the clinical practice this syndrome is extremely rare. Erytrocytosis secondary to tumors is usually not high enough to require treatment.

Thrombocytosis is quite common in cancer patients and is usually associated with advanced disease. Thrombosis and hemorrhage are rarely associated with cancer thrombocytosis and if not associated with hypercoagulability syndrome does not require treatment. Anemia in cancer patients most commonly affects the form of the normocytic and normochromic anemia of chronic disease. It is supposedly caused by a number of factors including iron metabolism and storage disturbance and deficient erythropoietin production. Recombinant erythropoietin has been avocated in low-grade cancer anemia but the issue remains controversial.

The most important hematological disturbances in cancer patients are migrating thrombophlebitis and disseminated intravascular coagulation.

Migrating thrombophlebitis is most often seen in patients with adenocarcinoma, especially in mucin producing adenocarcinomas of the gastrointestinal tract. It can also occur in breast, ovarian, prostate, and especially pancreatic cancer. The treatment of this disorder includes treatment of the underlying malignancy as the most effective measure when possible. Treatment should also include heparin application but it is frequently ineffective; better results are obtained with low molecular weight heparins, enoxaparin sodium being possibly the most effective drug at the moment available.

Disseminated intravascular coagulation in cancer patients may occur in several prognostically different settings:

- As a terminal event in disseminated malignant disease; in this situation the specific treatment is usually ineffective and very often only symptomatic treatment is required.
- As a component of the tumor lysis syndrome; in this situation we are dealing with a chemotherapy responsive tumor and every effort of treatment with antithrombin III preparations, platelets transfusions and low molecular weight heparins is required.
- As a potentially transitory event during febrile neutropenia caused by gram-negative bacteria; this potentially fatal complication should be dealt with most seriously in order to save the patient. Treatment includes all measures as in the disseminated intravascular coagulation related to tumor lysis syndrome.

The synthesis of recombinant hematopoietic growth factors has opened a new era in treating cytopenic complications of both malignancy and chemotherapy.

The thrombopoietins for treatment of cytotoxic drug induced thrombocytopenia are still in very early investigational clinical phases. Thrombocytopenia related to cancer or to cytotoxic chemotherapy is best treated by platelet transfusions.

Treatment of cancer or chemotherapy related anemia by different recombinant erythropoietins has been and still remains a topic of controversy. Erythropoietins have been claimed to have beneficial effects in low-grade cancer and chemotherapy related anemia especially the anemia during chemotherapy with platinum derivatives.

The beneficial effects claimed for erythropoietins include better chemotherapy efficacy, relief of the so-called fatigue syndrome and improvement of quality of life. Several trials have assessed the impact of erythropoietin administration in low-grade anemia patients receiving chemotherapy. The results were not equivocal. There are data suggesting that erythropoietin administration positively affects quality of life; these data apparently need more

detailed evaluation. It has been stated that although some of the results indicate that epoetin has positive effects on quality of life, methological limitations inherent in most of the studies hamper interpretation of data. More robust designs are required to show any significant quality of life and fatigue relieving benefits for cancer patients undergoing erythropoietin treatment.

On the other hand several recent data point to extreme caution in prescribing erythropoietin. It has been shown that several pediatric tumors express a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. Also erythropoietin receptor appears frequently expressed in papillary thyroid carcinoma. Experimental data suggest that erythropoietin/erythropoietin receptor system is a significant angiogenic factor in chemically induced murine hepatic tumors. More data are needed in a variety of other human tumors in order to determine or eliminate the possibility that erythropoietin might as tumor facilitating agent.

The recombinant factors that induce granulocytopoiesis i.e., GC-SF and GM-CSF have been synthesized and subject to extensive studies. ESMO has provided (11) minimal clinical recommendations for the applications of these factors outside controlled clinical trials.

It that been stated that rates of febrile neutropenia and related mortality rates are relatively low for most standard chemotherapies. These low rates do not justify routine use of G-CSF or GM-CSF in primary prevention of febrile neutropenia in routine chemotherapy regimens. Indications for primary prophylaxis of febrile neutropenia include the probability of febrile neutropenia over 40% for a given chemotherapy regimen or situations where dose reduction is deemed to be detrimental to outcome.

The special situations for use of G-CSF or GM-CSF during chemotherapy include special situations for primary prophylaxis, secondary prophylaxis, and therapy of high-risk febrile neutropenia.

Primary prophylaxis is indicated when bone marrow reserve is a reduced due to:

- Prior extensive chemotherapy resulting in a stable neutrophil count below 1.5x109/L.
- Prior radiotherapy involving over 20% of hematopoietic bone marrow.
- Patients affected with human immunodeficiency virus, especially if under retroviral chemotherapy.

Secondary prophylaxis is indicated in the following situations:

- Further infections in the next treatment cycle considered life threatening.
- Need for chemotherapy dose reduction below threshold of efficacy.
- Need for delay of next treatment cycles if considered detrimental for response achievement and/or compromising cure rate or disease free and overall survival.

The granulocyte colonies promoting factors are indicated in the treatment of febrile neutropenia only in the category of high-risk febrile neutropenia i.e. febrile neutropenia lasting for more than 7 days, or associated with hypotension or sepsis, or associated with pneumonia or fungal infection.

The application of these factors is not indicated in the general therapy of febrile neutropenia and even less in the therapy of afebrile neutropenia. Their use is contraindicated during radiotherapy to the chest due to increased rate of complications and death. If they are given immediately prior or simultaneously with chemotherapy there is a risk for severe thrombocytopenia. They should not be applied in patients with chemotherapy induced bone marrow aplasia and severe thrombocytopenia. The use of hematopoietic growth factors in autologous or allogenic stem cell transplantation or for mobilization of peripheral blood stem cells is outside the scope of this presentation.

SUGGESTED LITERATURE

1. Bettomley A, Thomas R, van Steen K, Flechtner H, Djulbegovic B. Human recombinant erythropoietin and quality of life: wonder drug or something to wonder about? Lancet Oncol 2002;3(3):145-53.
2. Yasud Y, Fujita Y, Matsuo T, Koinuma S, Hara S, Tazaki A et al. Erythropoietin regulates tumour growth of human malignancies. Carcinogenesis 2003;24(6):1021-9.
3. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. Blood 2002;100(7):2303-20.
4. Nakamatsu K, Nishimura Y, Suzuki M, Kanamori S, Maenishi O, Yasuda Y. Erythropoietin/erythropoietin-receptor system as an angiogenic factor in chemically induced murine hepatic tumors. Int J Clin Oncol 2004;9(3):184-8.
5. Eccles TG, Patel A, Verma A, Nicholson D, Lukes Y, Tuttle RM et al. Erythropoietin and the erythropoietin receptor are expressed by papillary thyroid carcinoma from children and adolescents. Expression of erythropoietin receptor might be a favorable prognostic indicator. Ann Clin Lab Sci 2003;33(4):411-22.
6. Batra S, Perelman N, Luck LR, Shimada H, Malik P. Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. Lab Invest 2003;83(10):1477-87.
7. Zhou M, Liao QK, Li FY, Gao J, Fu RY, Luo CH et al Erythropoietin increases transferrin receptor expression and the impact of erythropoietin on K562 leukemic cell cycle. Zhonghua Er Ke Za Zhi 2003;41(7):528-30.
8. ESMO Minimum Clinical Recommendations for the application of hematopoietic growth factors (hGFs), European Society for Medical Oncology, Lugano, 2004
9. John V, Foon KA, Patchell RA. Paraneoplastic syndromes. In: De Vita V, Hellman S, Rosenberg S, editors. Cancer-Priciples and Practice of Oncology, 5th ed. Philadelphia: Lippincot-Raven; 1997. p. 2397-422.
10. Griffin JD. Haematopoietic growth factors. In: De Vita V, Hellman S, Rosenberg S, editors. Cancer-Priciples and Practice of Oncology, 5th ed. Philadelphia: Lippincot-Raven; 1997. p. 2639-57.
11. Available from www.esmo.org