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Update on the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia of multiple myeloma and lymphoma

Eirini Katodritou [a,c], Meletios A. Dimopoulos [b,c], Konstantinos Zervas [a,c], Evangelos Terpos [b,c,*]

[a] Department of Hematology, Theagenion Cancer Center, Thessaloniki, Greece
[b] Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece
[c] Greek Myeloma Study Group, Greek Society of Hematology, Greece

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SUMMARY

Anemia is a common side-effect of patients with multiple myeloma (MM) and lymphoma. The etiology is complex, but the main cause is the underlying mechanism of anemia of chronic disease, which is characterized among others, by impairment of iron metabolism and consequently iron restricted erythropoiesis (IRE), resulting from the up-regulation of the iron distributing regulator, hepcidin. Erythropoiesis-stimulating agents (ESAs) have been the standard of care since early 90's offering high response rates and improving the quality of life of the patients. However, the role of ESAs in the treatment of cancer-related anemia has been questioned recently, due to the growing evidence which support that ESAs may be associated with increased risk for thrombosis and may have a detrimental impact on patients' survival. Under the light of the recent considerations, the place of ESAs in the management of cancer-related anemia has been reassigned. Regarding the management of anemia in MM or lymphoma, the updated American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) 2007 clinical practice guidelines on the use of ESAs in cancer-related anemia, recommended that ESAs should be preferably omitted in patients planned to receive chemotherapy and applied in case that anemia does not improve over treatment. The quest for reliable predictors for response to ESAs and for indicators of IRE which plays a major etiological role for the development of anemia of cancer still remains an open issue. In the current review we present an update on ESAs use in anemia of MM and lymphoma.

Introduction

Anemia is a common complication of multiple myeloma (MM) and lymphoma that has a major impact on patients' quality of life and survival.[1,2] Kyle et al. reported that 73% of MM patients present with hemoglobin <12 g/dL at diagnosis (8% with severe anemia)[1] and virtually all patients with progressing disease become anaemic. Regarding lymphoma, 32% of patients are anaemic at diagnosis and an estimated 37–100% treated with the combination of cyclophosphamide, vincristine, anthracyclin and prednisone (CHOP) develop anemia during treatment course.[3,4] In the recent European Cancer Anemia Survey (ECAS) study, where 2360 myeloma and lymphoma patients were enrolled, 52.5% of patients were anemic at enrolment and 73% became anemic over a 6-month follow-up.[5]

The etiology of anemia in MM and lymphomas is complex and includes bone marrow infiltration, hypersplenism, autoimmune hemolysis, myelodysplasia, pure red-cell aplasia, blood loss, nutritional deficiencies and chronic renal failure.[6,7] However, the most common form of anemia in MM and lymphoma is anemia of chronic disease (ACD), which is characterized by inadequate production and blunted response to erythropoietin, inhibition of red cell progenitors, reduced red cell survival and impairment in iron metabolism and consequently, iron-restricted erythropoiesis (IRE), that is induced by the key iron distribution regulator, hepcidin.[8,9] Most recently, the role of hepcidin in MM-related anemia was highlighted by Sharma and colleagues who demonstrated that hepcidin m-RNA is up-regulated in MM by both interleukin-6-dependent and independent mechanisms, and thus, it may play an etiological role in the development of anemia.[10] In addition, MM and lymphoma treatments are cytoreductive and contribute to development of anemia; overall, 45–90% of myeloma and lymphoma patients receiving chemotherapy will require red blood cell (RBC)-transfusions during the course of their treatment.[11,12]

The management of anemia in MM and lymphomas includes the control of the primary disease, the administration of erythropoiesis-stimulating agents (ESAs) and the RBC-transfusions.

* Corresponding author. Addresses: Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece; 5 Marathonomahon street, 14572, Athens, Greece. Tel.: +30 210 7463803; fax: +30 210 7464676.
E-mail addresses: ikatodritou@otenet.gr (E. Katodritou), mdimop@med.uoa.gr (M.A. Dimopoulos), kzervas@mailbox.gr (K. Zervas), eterpos@imperial.ac.uk, eterpos@hotmail.com (E. Terpos).

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According to the ECAS study, about half of MM and lymphoma patients received anemia treatment if ever anemic during the course of the study.[5] The majority of the patients in the ECAS study were treated with ESAs (17.5%) whereas 14.9% received RBC-transfusions and 6.5% iron alone.[5] Erythropoiesis-stimulating agents has been an established option for the management of anemia in MM and lymphoma, for almost 20 years providing 60–70% response rates and releasing the patients from RBC-transfusions and their consequent side-effects.[11–13] However about 1/3 of patients do not respond mainly due to the impaired iron utility and the development of IRE that occurs either at diagnosis, or over treatment with ESAs.[8] The use of ESAs in cancer-related anemia has been intrigued recently, because of the growing evidence that supports their possible potential to compromise cancer patients' outcomes and to increase the risk for thromboembolic events, in both non-myeloid hematological malignancies and solid tumors.[14–19] Given the possible detrimental long-term side-effects of ESAs, their impact on quality of life and their cost-effectiveness has been also debated. Therefore, the need for reassigning the use of ESAs in oncology is mandatory. Under the light of the aforementioned concerns, we here discuss the most important aspects on the use of ESAs in MM and lymphomas in the new era.

ESAs and survival

During the last years, important concerns have emerged regarding the impact of ESAs on cancer patients' survival as well as their potential to increase the risk for thromboembolic events.[14,19] In March 2007, the United States Food and Drug Administration (FDA), based on four published studies in solid tumors, as well as on two unpublished studies on lymphoid malignancies,[14–19] instituted the addition of a black-box warning about the possible association of ESAs with tumor promotion and thromboembolic events. The updated American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) 2007 clinical practice guidelines on the use of ESAs in cancer-related anemia,[20] following the FDA instructions, suggested that hemoglobin levels should not exceed 12 g/dL and that ESAs could be used only when hemoglobin levels are $\leqslant$10 g/dL. These guidelines underscore the fact that physicians following patients with non-myeloid hematological malignancies should consider starting with chemotherapy and follow the hematological outcomes achieved through tumor reduction before deciding on ESAs administration; this latter recommendation is particularly important in chronic lymphocytic leukemia (CLL), in which bone marrow infiltration is one of the major causes of anemia. The updated ASCO/ASH also suggested that, transfusion could still be considered as an acceptable therapeutic option.[20]

Most recently, Bohlius and co-workers confirmed the previous concerns in a meta-analysis of 14,000 cancer patients demonstrating that, ESAs worsened survival by 6%, and that, this adverse impact was not influenced by known disease parameters, or therapy parameters; interestingly enough, the increase of deaths was less prominent in patients under chemotherapy.[21] Five studies, assessed survival in patients with non-myeloid hematological malignancies treated with either erythropoietins or darbepoetin alpha.[22–26] Littlewood et al. demonstrated in a double-blind, randomized, placebo-controlled trial including patients with solid tumors and non-myeloid hematological malignancies that, overall survival (OS) did not differ between the epoetin and the placebo group.[22] Likewise, in an updated analysis of a previous randomized study,[27] Osterborg and co-workers showed that the administration of epoetin beta did not increase the number of deaths and did not negatively influence OS in patients with lymphoproliferative disorders.[23] The French Lymphoma Study Group (GELA) also examined the impact of ESAs on survival, in the context of the LNH03-6B randomized study[24] that included patients with diffuse large B-cell lymphoma treated with R-CHOP14 or R-CHOP21; this study demonstrated that, survival was not inferior in patients who were randomized to receive darbepoetin alpha. In agreement with the previous studies, Hedenus et al. showed that, the median survival did not differ between patients who were randomized to receive darbepoetin alpha or placebo, in a pooled analysis of four randomized double-blind, placebo-controlled studies of a mixed population of patients with both solid tumors and lymphoproliferative disorders.[25] However, a subsequent follow-up of 344 patients with lymphoproliferative disorders included in one of the four aforementioned studies, showed that the use of darbepoetin alfa was associated with inferior survival (Hazard ratio: 1.37 95%, $p = 0.04$).[19,28] In a large randomized controlled, double-blind, placebo-controlled trial including 989 patients with solid tumors and non-myeloid hematological malignancies who were not receiving chemotherapy or radiotherapy Smith et al. demonstrated that survival was inferior in patients receiving darbepoietin alfa (Hazard Ratio: 1.33, $p = 0.022$);[26] of note, subset analyses suggested that the inferior survival differences were observed, mainly for MM (Hazard Ratio; 2.98) and non-Hodgkin lymphoma patients (Hazard Ratio: 2.25). Finally, most recently, the German Hodgkin's Study Group (GHSG) analysed the final results of the HD15-EPO trial which was the larger randomized study, planned to assess the impact of epoetin alpha on fatigue, anemia response and survival, in patients with advanced-stage Hodgkin's disease, receiving chemotherapy.[29] This study did not show any difference in the studied end-points including survival rates, between the epoetin alpha arm and the placebo arm. A recently published systematic review of the use of ESAs in patients with non-myeloid hematological malignancies summarized the results of the majority of the above mentioned studies suggesting that the data regarding the impact of ESAs on survival are still controversial and therefore, no safe conclusions could be drawn on this important issue.[30] We should address that the studies that investigated the possible impact of ESAs on patients survival had certain limitations: they included different diseases at different settings and none of them was well-balanced in terms of comparing two groups of patients with the same characteristics and the same treatment. In addition, one might argue that, ESAs may not worsen the clinical outcome, because of the current use of more effective treatments, however, "no inferior survival" could not be considered as a sufficient endpoint when studying the benefits and risks of a given compound, such as ESAs.

In the MM setting, 2 published studies and one abstract investigated retrospectively the possible impact of ESAs on survival. Richardson et al., examined the impact of ESAs on survival indicators within the context of the VISTA trial,[31] which was a randomized trial that compared the bortezomib-melphalan-prednisone (VMP) regimen with the standard melphalan-prednisone (MP) regimen in newly diagnosed MM patients. The above mentioned subgroup analysis suggested that, ESAs have no adverse effect on the time to progression and the 2-year OS.[32] The authors conclude that ESAs can be safely administered with VMP/MP for the treatment of anemia in MM patients who receive first line therapy with the afore-mentioned regimens. This study was well-balanced regarding the baseline characteristics; however, the relatively short median follow-up could hardly allow us drawing safe conclusions about the impact of ESAs on the long-term outcomes. In a study of 257 MM patients, Baz et al. reported a positive impact of ESAs on OS.[33] In particular, ESAs administration favored survival in patients with Southwest Oncology Group (SWOG) stage II, III and IV, when adjusted for other covariates such as age, time from diagnosis to enrollment, baseline hemoglobin concentration, platelet count, serum creatinine level and β2-microglobulin; however, the unadjusted survival was not statistically different ($p = 0.4$). In a study including 323 MM patients,[34] Katodritou et al. showed that