

Is it time for erythropoietin use in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients?

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Submitted Oct 26, 2012. Accepted for publication Nov 26, 2012.

DOI: 10.3978/j.issn.2304-3865.2012.11.13

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Anemia remains a frequent feature of hematologic malignancies. It was demonstrated that a significant proportion of multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) patients developed anemia at diagnosis, during chemotherapy or disease progression (1,2). Anemia itself has a detrimental effect on quality of life (QOL) and overall survival (OS) hence erythropoiesis-stimulating agents (ESAs) have been widely used across the globe. However, one should keep in mind the high cost of ESAs therapy and its safety concerns especially the increased risk of thrombotic complications. Other safety aspects of ESAs treatment have been focused on disease progression and/or mortality (3). The latter issue is of special interest for all physicians treating cancer patients with ESAs. Recently, Aapro discussed in details the results of several studies on this topic. Based on six meta-analyses, he concluded, there is no unequivocal evidence supporting the thesis that ESAs use negatively influences cancer progression. On the other hand, there are single reports suggesting that ESAs may affect disease progression in certain cancer subpopulation e.g., in patients with head and neck cancer receiving radiotherapy only. The possible mechanism of disease progression after ESAs has been postulated. Shortly, it was based on the concept that ESAs activate erythropoietin receptor (EPOR) that is expressed on tumor cells and thus cause neoplastic growth. However, several experimental studies on molecular level did not confirm the abovementioned hypothesis (4). The benefits and harms of ESAs use in cancer-related anemia have been summarized in a large meta-analysis that included 52 trials and more than 12,000 patients. It was demonstrated that ESAs treatment significantly increased the all-cause mortality if compared to no treatment arm: relative risk [RR] 1.15; 95% CI 1.03-

1.29. Moreover, the similar results were obtained when the patients were stratified according to the type of cancer (solid *vs.* hematologic) and agent used in the study (epoetin *vs.* darbepoetin). Other harms of ESAs administration included the increased risk of serious adverse events with RR of 1.16; 95% CI 1.08-1.24. Thrombotic episodes were observed more frequently in the treatment arm if compared to control group: RR 1.69; 95% CI 1.27-2.24. In contrary, it was also found that ESAs use led to an improvement in QOL and reduced the transfusion need. The frequency of cardiovascular events as well as tumor responses were similar between studied groups. In conclusions, the authors argued against routine use of ESAs in blood transfusion-dependent patients with cancer-related anemia. They also suggest that introduction of ESAs should always be based on benefit/risk evaluation (3).

Is it the same true when study population would be restricted to the patients with hematologic malignancies? As it was mentioned previously, anemia is frequently seen in patients with lymphoproliferative disorders (LPD) and the treatment with ESAs is common in this patient population (1,2). The pioneer study involving myeloma patients came from 1990. Thirteen patients with myeloma-related anemia received erythropoietin (EPO) three times a week for six months and 85% of them corrected anemia and improved their QOL. Tumor load measured as M protein level remained stable throughout the study duration (5). Two other randomized studies have demonstrated the high efficacy of EPO in anemic patients with MM and NHL and relatively low endogenous EPO production (6,7). However, one should realize that all these studies lack reproducible tools for QOL assessment. To investigate the benefits of EPO treatment on QOL, Österborg *et al.* performed a

randomized, double-blind, placebo-controlled trial of EPO in hematologic malignancies using a comprehensive and internationally recognized QOL instrument- the Functional Assessment of Cancer Therapy (FACT) scale. After 12 and 16 weeks of treatment the significant improvement in QOL was found in EPO arm if compared to placebo ($P=0.05$) and this amelioration was associated with a close-to-normal hemoglobin concentration (8).

Recently, a large meta-analysis examined the effect of ESAs treatment on disease progression and overall survival in patients with LPD receiving chemotherapy. This study has demonstrated that ESAs use did not have a negative impact on mortality and disease progression, however one should be aware of some limitations associated with studies design and patients characteristics (2). Moreover, the LNH03-6B study of elderly patients treated with R-CHOP-14 or 21 (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) regimen and EPO or conventional treatment has found that EPO group had an improved progression-free and disease-free survivals if compared to conventional treatment. There was no difference in OS between groups (9). Two other studies examined the effect of EPO in Hodgkin lymphoma and lymphoblastic leukemia/lymphoma patients. Both studies did not demonstrate the adverse impact of EPO use on remission duration and OS. Interestingly, no improvement in QOL was observed (10,11).

As it has been previously mentioned, ESAs administration is common in LPD. Conversely, their use in acute myeloid leukemia (AML) and allogeneic hematopoietic stem cell transplantation (alloHSCT) patients has not been evaluated so far. However, it should be noted that ESAs are licensed to treat anemia only in patients with non-myeloid malignancies. In the article that accompanies this editorial, Michallet *et al.* (12) presented the results of prospective study of EPO effect on patient's QOL, hemoglobin recovery, red blood cells (RBCs) transfusion need, overall and event-free survivals in AML and alloHSCT patients. The total costs of ESAs use and RBCs transfusions were also calculated. The study included two groups of adult patients with hemoglobin concentration <11 g/dL. The group 1 consisted of 52 AML patients after consolidation chemotherapy and group 2 encompasses 59 patients after AlloHSCT for different hematologic malignancies (18 patients transplanted for AML). Patients in both groups were matched with historical controls of not receiving ESAs. ESAs were injected once weekly for a maximum of 6 months and stopped at target hemoglobin concentration of 12 g/dL.

The patient's QOL results showed a significant and stable improvement in terms of FACT-anemia and FACT-fatigue scales during the 6-months follow-up. Patients in ESAs groups had higher hemoglobin concentration at hospital discharge and at the 6-month follow-up visit if compared to control groups. Moreover, the analysis has demonstrated that patients in treatment groups had significant reduction in RBCs transfusions. Noteworthy, there was no difference in safety concerns, overall and event-free survivals between study cohorts. The treatment with ESAs appeared to be also more cost effective. To our best knowledge it is the first prospective study regarding the ESAs use in myeloid malignancies. The results of Michallet study (12) regarding QOL, transfusion requirements and safety concerns were in line with those obtained for LPD patients (6,7,8). Data on the use of EPO after AlloHSCT are also sparse. Up-to-date studies suggest that early use of EPO after AlloHSCT may accelerate hemoglobin recovery and reduce transfusion need. This is true especially for patients who received reduced-conditioned transplants (13,14).

In conclusion, Michallet study (12) remains a key step towards the more common implementation of EPO to daily clinical practice in AML/AlloHSCT patients. It seems reasonable to undertake further prospective randomized placebo-controlled studies in order to confirm the efficacy and safety of EPO treatment in this patient population. My concerns regarding EPO use in myeloid malignancies are related to the risk of disease relapse/progression. It was found that EPOR was expressed on blast cells of AML patients and *in vitro* EPO use led to leukemic proliferation. This was true for all AML subtypes. Moreover, it was concluded that patients with both EPOR expression and EPO response *in vitro* were found to have shorter survival if compared to patients lacking the abovementioned receptor (15). These observations were additionally confirmed by reports including patients with myelodysplastic syndromes (MDS) where EPO-dependent leukemic transformation was demonstrated (16). For today, we must be aware that the recent guidelines of ASH/ASCO did not recommend EPO use for AML/AlloHSCT patients (17).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Helbig G, Kyrzcz-Krzemień S. Is it time for erythropoietin use in acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation patients? *Chin Clin Oncol* 2012;1(2):22. DOI: 10.3978/j.issn.2304-3865.2012.11.13