Epoetin treatment of anemia associated with multiple myeloma and non-Hodgkin’s lymphoma

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Introduction

Anemia is observed in most patients with multiple myeloma (MM), non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL) and may already be manifested at the time of diagnosis. In patients with MM, hemoglobin values < 10.0 g/dL were found in 49% and severe anemia (hemoglobin < 7.5 g/dL) in 19% of the patients already at the time of diagnosis (MRC working party 1980). Patients with NHL have been reported to have an anemia rate of approximately 40% (Coiffier et al. 1999). In a recent European survey, anemia (Hb < 12 g/dL) was found in 52% of patients with MM or NHL at enrollment and observed in 73% of those patients who were followed for up to 6 months (Ludwig et al. 2004). Anemia usually (but not always, especially in MM) normalizes in patients who achieve complete remission after chemotherapy. However, it persists in patients who are unresponsive to treatment, and recurs in those with relapsing disease. Anemia is a general finding in later phases of the disease, when toxicity of long-term treatment, impairment of renal function, and heavy tumor load contribute to its induction and aggravation.

The cause of anemia in MM, NHL and CLL is multifactorial. Among them, anemia of chronic disease (ACD) is a major cause. It is characterized by blunted production of endogenous erythropoietin (EPO), reduced erythrocyte life-span, poor iron re-utilization and suppressed erythropoiesis due to secretion of inflammatory cytokines such as interleukin-1, TNF-α and interleukin-6 (Denz et al. 1990; Means 1995; Maccio et al. 2005) (see also chapter 5 in this book). The inhibitory effect of these cytokines on erythropoiesis has been shown in vitro to be partially overcome by recombinant human erythropoietin (rhEPO, epoetin) (Means and Crantz 1991). In vivo, inflammatory cytokines were reported to correlate with rhEPO hyporesponsiveness in hemodialysis patients (Kalantar-Zadeh et al. 2003). IL-1 and TNF also suppress the endogenous EPO synthesis (Faquinet et al. 1992). Inade-
quate EPO production seems to be of pathogenic importance, especially in patients with MM (Musto 1998) where it is found also in many patients with normal creatinine levels (Beguin et al. 1992). Another contributing factor to the patients’ blunted EPO response may be the increased plasma viscosity due to a high level of M-component in the plasma of some patients with MM (Singh et al. 1993). The impact of displacement of erythropoiesis in the bone marrow by tumor cell infiltration has probably been overestimated in the past because normal blood counts may sometimes be seen even in patients with heavy myeloma and lymphoma cell infiltration of the bone marrow. Anemia may also be induced by chemotherapy and radiotherapy. A variety of cytostatic drugs as well as irradiation directly impair erythropoietic precursor cells in the bone marrow and, thus, inhibit their proliferation. Notably, also low-intensive regimens such as oral melphalan and chlorambucil may induce anemia, probably because of their potent stem cell killing capacity.

**Treatment of anemia: blood transfusions**

For decades, only markedly decreased hemoglobin levels (below 8.0–8.5 g/dL) were the indication for treatment of anemia. The immediate effect of blood transfusions is crucial when a patient is suffering from severe anemia. However, the resulting increase in hemoglobin levels is transient, i.e. returning to baseline within a short time. Even if the risk of infection due to allogeneic red blood cell (RBC) transfusions has been reduced, there are other negative aspects of transfusions that need to be taken into account in patients with advanced malignancies. Allogeneic RBC transfusions may induce or worsen immunosuppression, which was associated with a significant risk of infectious complications (George and Morella 1986; Heiss et al. 1993). RBC transfusions may also possibly inhibit endogenous erythropoietin production resulting in further impairment of erythropoiesis and, as a consequence, an even higher dependence on allogeneic transfusions (Stockman 1996). Repeated RBC transfusions are associated with a highly variable, unstable hemoglobin concentration which often includes periods of overt anemic symptoms. The fluctuating hematocrit may negatively influence the physiological compensatory mechanisms, such as increase in cardiac output and red cell 2,3-diphosphoglycerate.

**Treatment of anemia: epoetin**

The introduction of epoetin represents a therapeutic alternative to blood transfusions by stabilization of the hemoglobin concentration at a level not usually reached by the current transfusion policy. In addition, maintaining an optimal quality of life (QOL) has become as important as intensive attempts