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9

Does anything work for anaemia in myelofibrosis?

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Anaemia is a common finding at diagnosis in myelofibrosis, and becomes a symptomatic problem in most patients with time. There are several treatment options for specific anaemia treatment, none of which has been tested in large, randomized, controlled trials. However, as myelofibrosis is not a disease with spontaneous remissions, even non-randomized trials carry weight. In this survey, the existing evidence will be analysed, both for the commonly used treatments like erythropoiesis-stimulating agents, androgens and thalidomide and for the new drugs in the area, and conclusions will be drawn concerning standard clinical anaemia treatment in myelofibrosis, which according to evidence from studies has a 40–50% chance of response in patients with not too advanced disease.

Introduction

Primary myelofibrosis (PMF) is the most serious of the three Ph1-negative myeloproliferative neoplasms, and anaemia is the most common and often the most serious problem of the patients. Thirty % of PMF patients present with anaemia at diagnosis [1,2], and all patients with PMF will eventually develop anaemia. At diagnosis, the bone marrow shows hyperproliferation, but unlike in PV only of the white cell and megakaryocyte compartments.

Patients with MF secondary to essential thrombocytemia (ET) or polycythaemia vera (PV) show a similar development as PMF with regard to anaemia, and the management is also similar.

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The nature of the anaemia has long been presumed to be secondary to the fibrous infiltration of the bone marrow, with fibres reducing the erythropoietic tissue, a more or less mechanic mechanism. Due to recent progress in the mapping of pathophysiological mechanisms in MF, a more varied view of anaemia development has emerged with inflammation as a potential key mechanism. The fibrosis in itself is a phenomenon secondary to the clonal proliferation of a malignant stem cell [3].

As anaemia develops and worsens, there is often a continuous enlargement of the spleen, and extramedullary erythropoiesis develops in an attempt by the organism to compensate for the reduced bone marrow activity. With worsening spleen enlargement, however, destruction of red blood cells (RBC) in the spleen increases. Therefore, anaemia treatment based on stimulation of erythropoiesis has a smaller chance of effect in patients with advanced disease and large spleens.

There are several options for specific anaemia treatment in MF, which will be presented here. Although there is a lack of controlled, randomized studies of anaemia treatment, there is evidence enough for a recommendation that all anaemic patients with MF should be considered for specific anaemia treatment.

Erythropoiesis-stimulating agents (ESA)

Human recombinant erythropoietin (rHuEPO) was first used in the treatment of PMF anaemia in small pilot studies in the beginning of the 1990ies [4–8]. Although results were promising, no larger study was performed until 2004, when Cervantes collected 20 PMF patients with either transfusion dependency (13/20) or Hb level below 9 g/dl(9). 4/20 patients normalized their Hb level, and 9/20 (45%), had either a complete response (CR) or a partial response (PR). In the same paper, the authors added 31 cases from the literature to their own material and found a CR rate of 31%, PR 24%, total responses 55%. Positive factors for response were lack of transfusion dependency and an S-Epo level <125 U/L. In a later study with long-acting rHuEPO the same authors found a similar response rate in 20 patients [10]. The most positive responses published can be found in a prospective study with 20 transfusion-dependent PMF patients, in whom a 60% response rate was found (CR Hb > 12 g/dl or Transfusion independence (40%), PR increase by 2 g/dl or double transfusion interval (20%)) [11]. In contrast, a retrospective study from the Mayo clinic showed no responders among 16 transfusion-dependent patients and no responders among 9 patients with Hb levels >10 g/dl [12]. These results have not been supported by any other study.

The dose of rHuEPO used has been the standard dose given in other cancer anaemias, 30,000 U weekly, although usually given as 10,000 three times weekly subcutaneously which used to be the standard dosing in the early days of rHuEPO treatment. The efficacy of a dose increase has not been evaluated. No studies have been published with the use of biosimilars or other forms of erythropoiesis-stimulating agents (ESA) of more recent development.

Conclusion

The studies are small (no larger prospective study than $N = 20$), and the response criteria used are not uniform. However, a response rate of 40–50% within 6–8 weeks can be found in the studies with a minimal response criterion of Hb increase >2 g/dl or a 50% reduction of transfusions. Factors that are predictive of response include limited or no transfusion dependency and a non-severe anaemia. Response correlation to S-Epo levels is inconclusive. [9,12] ESAs were generally very well tolerated.

Androgens

Androgen therapy has been used for many years for various bone marrow failure syndromes, and early studies in MF showed promising results. In a small 1978 prospective study in 11 patients, 5 of whom were transfusion dependent, long-term oxymetholone treatment resulted in loss of transfusion dependency in all and > 3 g/dl Hb increase in 9 of the 15 courses given [13]. In a 1982 study including 23 PMF patients, a response rate of 57% was found (sustained increase in Hb level or cessation of transfusion need within 3 months), with a significantly better response among patients with normal karyotype (92% response) [14].