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Clinical application of haemopoietic growth factors - state of the art
D. CROWTHER

Haemopoietic stem cells have the ability to survive and self renew. Their progeny have multilineage potential and only a small number is responsible for the production of a prodigious number of mature blood cells on a daily basis ($>10^{11}$ cells). Production rates are highly regulated allowing flexibility in a multilineage response to stress and several growth factors and cytokines have been identified which influence haemopoiesis and are available for clinical use. The use of G-CSF or GM-CSF has been shown to reduce the incidence of neutropenic fever, infection and antibiotic usage following chemotherapy but the agents are of little value during conventional chemotherapy where infection rates are low. Their use allows a modest increase in cytotoxic dose intensity but the value of an relatively small increase in dose intensity in treating patients with cancer remains in doubt. Many haemopoietic growth factors (HGFs) have been shown to mobilise sufficient peripheral blood progenitor cells (PBPC) to allow full haemopoietic rescue following high dose chemotherapy using autotransfusion techniques. The HGFs have an important role in this regard because haemopoietic reconstitution is more rapid following PBPC than autologous bone marrow transplantation. For this reason PBPC transplants have largely replaced autologous bone marrow transplantation in this setting and allogeneic transplantation has also been shown to be safe and feasible using similar methodology. The recognition that high dose, myeloablative therapy can cure some patients with forms of high risk cancer with a low likelihood of long term survival using conventional dose chemotherapy means that HGFs have an important role in mobilising PBPC in this context. Newer techniques involving sequential autotransfusion of PBPC after each cycle of chemotherapy are allowing substantial increases in the dose intensity of multicyclic chemotherapy. Whether this increase in dose intensity results in any improvement in survival remains to be seen and HGFs should not be used outside the context of a clinical trial in this setting.

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THROMBOPOIETIN (TPO):BASIC BIOLOGY, CLINICAL PROMISE
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The regulation of platelet (plt) production is the least understood aspect of hematopoiesis. Recently, we and others obtained cDNA for a c-Mpl ligand (ML), an Epo-related polypeptide which supports Mk colony formation, increases Mk size, ploidy and expression of plt glycoproteins, and is a potent stimulus of thrombopoiesis. Although these findings establish that ML is identical to Tpo, it is not yet clear whether the hormone is absolutely essential for plt production. To test whether other cytokines which support Mk development require culture-derived Tpo for their action we utilized a soluble form of the c-Mpl receptor (MPLsol) to neutralize Tpo activity. Mk development in response to KL, IL-6 or IL-11, alone or in combination, was eliminated by MPLsol. In contrast, in the presence of MPLsol, IL-3 induced Mk formation was reduced but never eliminated. However, such Mks were underdeveloped, their ploidy was markedly reduced and they lacked demarcation membranes and platelet specific granules. Thus, full Mk maturation is absolutely dependent on Tpo.

In order to test its potential for alleviating the complications of cytotoxic therapies, we employed a murine model of combined radiation/ chemotherapy. Myelosuppressed mice treated with Tpo recovered both plt and red cell levels much more rapidly than control animals. The biological basis for the later finding was the capacity of Tpo to synergistically interact with Epo in the generation of erythroid progenitor cells. These results suggest that the therapeutic benefit of Tpo may be greater than initially anticipated.

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Erythropoietin for Chronic Anemia of Cancer: Treatment Results and Prediction of Responsiveness
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In the present study, the efficacy of erythropoietin treatment for chronic anemia of cancer was investigated in several types of malignancies. In addition, an intensive search for parameters which in individual patients may predict response or non-response to EPO treatment was conducted by stepwise multivariate discriminant analysis and Cox's logistic regression model.

In total, 165 patients with chronic anemia of cancer and different types of solid tumors of hematologic malignancies were studied for efficacy of erythropoietin treatment (150 U/kg sc, 3 x per week; dosis escalation up to 300 U/kg). Response, i.e., an increase of at least 2 g/dl hemoglobin, was observed in 78 of 150 evaluable patients (52%). The highest response rates were achieved in multiple myeloma (86%), esophageal cancer (76%), lung cancer (75%), and ovarian cancer (50%), the lowest in Hodgkin's disease (25%) and MDS (8%). None of the more than 30 clinical and laboratory parameters studied in 80 patients allowed to predict responsiveness accurately at baseline. After 2 weeks of treatment, however, lack of responsiveness was very likely (predicitive power 93%) if the serum EPO level was >100mU/ml and hemoglobin concentration had not increased by at least 0,5 g/dl. Serum EPO levels of <100 mU/ml and gains in hemoglobin of >0,5 g/dl predicted response with an accuracy of 95%. Alternatively, a serum ferritin level of >400 ng/ml after 2 weeks of EPO treatment strongly indicated unresponsiveness (predictive power 88%), while a level of <400 ng/ml suggested response correctly in three out of four patients.

In conclusion, EPO effectively corrects anemia in several types of cancer. Patients who most probably will not benefit from this treatment could be identified during the second week of treatment by the simple use of common laboratory parameters.