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CLINICAL PRACTICE OF RECOMBINANT HUMAN ERYTHROPOETIN IN CANCER RELATED ANEMIA

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ABSTRACT

Anemia is a complication commonly encountered in malignancy, especially of hematological origin, either at presentation or during the course of treatment. Anemia of chronic disease, a condition characterized by disordered iron metabolism, shortened RBC half-life and inefficient erythropoiesis, is the major contributor to cancer anemia. Anemia effects up to 90% of Cancer patients with more than 60% requiring blood transfusion during or after treatment with the advent of recombinant human Erythropoietin (rHuEPO), an alternative to red blood cell transfusion has become available rHuEPO is now widely used in Cancer patients, as it improves hematocrit, lowers blood transfusion requirements and improves quality of life. So far, three drugs have been approved for the treatment of anemia in patients with malignancies (epoetin Alfa epoetin Beta and darbopoetin Alfa). New concepts for the cure of erythropoietin in cancer patients include 3 and 4 weekly dosing, as well as loading dose concepts. Although three rHuEPOs act on the same erythropoietin receptors, there are some variations on the degree of glycolylation, which lead to the differences in the pharmacokinetics and pharmacodynamics among the RhuEPOs. The cost effectiveness and medical justification of the administration of RHuEPO in tumor patients with respect to its positive effects on tumor oxygenation, tumor growth inhibition and support of chemo and radiotherapy is still a matter of debate. The largest systematic review on the use of erythropoietin in cancer patients undergoing treatment indicates a suggestive but not significant survival advantage of erythropoietin treated patients. Besides highlighting both the historical and functional aspects of RHuEPO, this review discusses the applications of RHUEPO in oncology.

INTRODUCTION: Anemia defined, as an inadequate number of hemoglobin containing red blood cells, is a widely prevalent complication among cancer patients and varies by type of neoplasia and cytotatic treatment [1-3]. Apart from the physical symptoms and diminished quality of life [4] patients with anemia experience, there is some evidence that anemia; with the consequence of increased tumor hypoxia might result in a poorer response to radiotherapy [5-9] or chemotherapy. Besides the overall quality of life, low Hb levels may negatively influence the patient's physical performance. Although blood transfusion in the fastest means to alleviate symptoms associated with anemia, there are short and long-term risks associated with this treatment such as

transmission of infections agents, transfusion reactions, alloimmunization, and overtransfusion [10]. The development of increasingly more aggressive antineoplastic treatments that may lead to anemia has increased the need for blood transfusions and has promoted oncologists to weigh advantages and disadvantages of transfusion [11, 12].

With the introduction of human erythropoietin rHuEPO in oncology about 10 years ago, an alternative to RBC transfusion becomes available. Two forms of rHuEPO, epoeitin α and epoetin β both with similar clinical efficiency are available to treat anemia and have been tested in randomized controlled trials. Recently, a novel long acting erythropoietin variant (novel erythropoeitics stimulating protein – NESP) or (darbopoetin-a) has been introduced into clinical practice.

In order to give a frame work for EPO therapy, the American Society of Clinical oncology CASCO) and American Society of Hematology (ASM) and more necessarily, the European Organization for Research and Treatment of Cancer (EORTC), developed evidence – based guidelines on the use of epoetin in cancer patients [13, 14]. To increase treatment efficiency and to improve patient compliance, a number of different administration regimes for rHuEPO are currently under evaluation, including less frequent dosing and loading dose concepts. In addition with longer half-life has become available owing mainly to economical considerations; the [15] general use of recombinant erythropoietin has not become common practice in oncological setting.

Anaemia in Cancer Patients: Many Cancer patients suffer from anemia, which has a major detrimental effect on their quality of life. Tumor associated factors can be acute or chronical tumor bleeding, hemolytic, deficiency in folic acid and vit B12, as well as infiltration of the bone marrow Immune cell activation triggers the release of several cytokines, affecting the proliferation of progenitor cells or the production of Erythropoietin. Tumor necrosis factor – (a) recreated by monocytes & macrophages in inhibits the proliferation of the erythroid precursors BFU-e and EFV-e. In addition, activation of MQs can lead to a shorter erythrocyte half-life & to a decrease in iron utilization.

Released cytokines also inhibit the production of erythropoietin in the Kidney, resulting in relatively low levels of the hormone, compared with the grade of anemia observed. Depending on the drug & schedule used, cytostatic therapy has a major impact on the incidence of anemia in cancer [16, 17] patients contributing factors include the inhibition of EPO production by nephrotoxin platinum compounds & the myelo suppressive effects on the erythroid precursor cells. Dose-intensified treatment negimusor shortened treatment intervals; as well as multimode therapies are associated with a higher degree of anemia. In addition some vinonelbine are strongly myelo suppressive & cause high degrees of anemia [17].

Some groups of cancer patients show particularly high incidences of anemia during/after cytotoxin therapy. This is the case for 70% of myeloma patients & 50% of lung & ovarian cancer patients [18]. Anemia is also observed frequently in patients with head & neck tumors, breast cancer genito urinary tumors & lymphomas [17].

Erythropoietin – Mechanism of Action: The human body generates 2.5 million new red blood cells (RBCs) per second from the bone marrow to replenish the continuous removal of effect RBCs. The production of RBCs (Erythropoiesis) is controlled by an intricate interaction between various human factors and cytokines. A specific cytokine, a siaglycoprotein known as erythropoietin, which acts directly on certain RBC progenitors and precursors in the bone marrow, controls the proliferation, differentiation and maturation of RBCs. The expression of erythropoietin is markedly increased in kidneys during hypoxic state, a condition mediated by the transcription factor HIF-I [19]. (The ultimate effect is to increase erythropoiesis in an attempt to maintain O_2 delivery to vital organs).

Synthesized in the kidney and to a minor degree in the liver, EPO, the native glycoprotein hormone has a molwt of 34 KDa & consists of 165 aa. About 40% of the molecular mass is composed of carbohydrates [20]. Glycosylation itself does not influence the biological activity, but delays the clearance of the hormone from the plasma [21] particularly important in this aspect are the sialic acid residues bound to four of the carbohydrate hydrate side chains, leading to a biological half-life of the molecules ~ 8.5 h [22].

The response to a decrease in tissue oxygenation, EPO is released into the plasma & binds to EPO receptors on the surface of red blood cell precursors (BFU – e, CFU – e, erythroblasts) located in the bone marrow. As well as prolonging their survival, EPO inhibits apoptosis of the precursor cells, there by inducing their proliferation and differentiation [23].

Recombibnant Human Epos: Three Epos have been approved for the treatment of anemia in cancer patients: epoetin α, epoeitin β and darbopoetin. Epoetin and darbopoetin are approved for patients with solid tumors and non-myeloid malignancies under chemotherapy in general. The indication for epoetin is restricted to patients with solid tumors undergoing platinum containing chemotherapy [24, 25, 26].

Modifications of RHuEPO: As the N-glycosylation confers the biological activity of RHuEPO, an increase in the number of glycosylation site may enhance its activity. A hyper glycosylated RHuEPO, known as NESP (Novel Erythropoiesis stimulating protein; Darbopoetin) has recently been introduced [27] by using a process called "Site Mutagenesis", the polypeptide backbone of the RHuEPO is modified, leading to the creation of 5 N – glycosylation sites (compared with other RHUEPO). 7 compared with the RHuEPOs, NESP has a higher negative charge and 3 fold longer half-life. It requires a less frequent dosing schedule and produces a similar clinical outcome and safety profile as RHuEPOs in treating anemia of malignancy [28,29,30].

Another strategy to enhance the biological activity of RHuEPO is to provide a "protective vehicle" so as to decrease the rate of elimination, thus prolonging the half-life RHuEPO. Methods such as micro encapsulation and pegylation to RHuEPO are currently being assessed.

Treatment of Cancer related Anaemia with EPO: More than half of cancer patients have a low serum level of EPO [31]. RHuEPO has been employed in connecting the anemia, either as supportive or preventive treatment, with an excellent safety profile. Interestingly, RHuEPO has recently been shown capable to induce apotopsis in myeloma cell culture, suggesting it's anti tumor activity [32]. In general, anemia could be correlated in about 50% of patients when RHUEPO is given after chemotherapy.

A higher proportion of anemia correction could be achieved in patients who received platinum based chemotherapy [33, 34].

When RHUEPO is applied before chemotherapy, it prevents the decline in hemoglobin and decreased the requirement of blood transfusion during the course of chemotherapy [35, 36]. Nowrosian has suggested that when given substaneously at a dose of 150 µl/kg three times a week in selected patients, rHuEPO can produce a response rate of up to 80%. In a large prospective community study, the use of rHuEPO increased the functional capacity and the quality of life of patients. It also improved the level of Hemoglobin and minimized blood transfusion requirements [38].

The positive outcomes correlated with the hemoglobin level but independent of the tumor response. Recent clinical studies have demonstrated that a normal or near normal level of hemoglobin before radiotherapy with/without chemotherapy could improve the treatment outcome [39].

In recent multicentre, randomized study in patients with pelvic malignancies the addition of rHuEPO to the treatment course of radiotherapy improved both treatment response rate and potential survival [40].

Furthermore, a recent analysis of 2 large scale studies involving 4382 patients, has revealed that patients with solid tumors received RHUEPO had a significant improvement in quality of life occurring b/w hemoglobin levels from 80 - 140g [41]. The most noticeable benefit, from an incremental increase in hemoglobin, occurred when there was a change in Hb from 110-120 g/l.

Hematological Malignancy/Pre-Lukaemic Stem Cell Disorder: Multiple myeloma, lympho proliferative diseases and chronic lymphocytic leukemia are those hematological disorders that benefit significantly from rHuEPO therapy, with an average response rate of 60% whether RHUEPO is given as supportive (post-chemotherapy), preventive (pre- treatment) or maintenance (optimization of hemoglobin while not on treatment) therapy, it increases the hemoglobin and minimizes the requirement for blood transfusions [42-45]. However, a delay in treatment response of up to 4 weeks may occur.

Darbepoetin: Data on the use of darbopoetin in the oncological setting are more scare than for the other Epos. This is due to the fact that so far most trials are dose – finding studies, investigating the efficiency and safety of different regimens uses a dose – finding study on the weekly administration of dar- in patients with solid tumors receiving chemotherapy indicated that the most efficient weekly dose is 4-5µ g/kg [47]. Compound with recommended dose of 2.25µ g/kg per week after 12 weeks of therapy, this dose resulted in an earlier on set of response (7 versus 10 weeks) as well as higher response rates (76% vs. 52%) & a more rapid increase of Hb levels (2.7 vs. 1.5 µg/dl). The same study showed that administration of 9µ g/kg per week.

In most phase III studies using darbepoetin, a starting dose of 2.25 µg/kg/week was used. One example is the applient trial for patients with solid tumor, enrolling 320 patients with lung cancer who had Hb levels < 11g/dl [47] patients received db-d or placebo for a period of 12 weeks during platinum containing chemotherapy. In addition to a significant reduction in the proportion of patients transfused during weeks 5-12 patients under db- had a higher haematopeitic response, achieving a Hb level of 12g/dl. Improvement in fatigue symptoms was better in the db - but did not quite reach statistical significance. This might in part be due to the delayed increase in the average H bevel after 4 & after 12 weeks, respectively [46]. A dose escalation to 4.5 µg/week was applied in 43% of patients.

A recent phase III swtudy by Hydenusetal [47] in patients with lymphoma & myeloma gave cleaner, better results. In a close finding study [47], db- was administered every 3 weeks. Doses of 4.5, 6.75, 9, 12, 13.5 & 15µ g/kg as well as placebo were given for 12 weeks. Patients with solid tumors & a base line Hb level of < 11µg/dl were included. The best results were observed in the group receiving 12µ g/kg, which showed a response rate of 71% & a final increase in Hb of 2.64 g/dl. Similar results were observed in another dose – finding study for the administration of db - every 4 weeks, comparing placebo & doses of 9, 12, 15 &18 g/kg in 145 patients. While the highest response rate & increase in Hb was achieved with a dose of 15 µg/kg, a dose of 18 µg/kg gave worse results.

CONCLUSIONS: Anemia caused by the tumor itself or by cytotoxic treatment, is frequently observed in cancer patients, negatively influencing their over all QoL and also worsening prognosis. This review analyzed the effectiveness of EPO in the treatment of cancer patients. With the development of rHuEPOs, well-tolerated alternative to RBC transfusions have now become available. Treatment with epoetins has been shown to be effective in reducing transfusion rates. There is strong and consistent evidence that treatment with rHuEPO may reduce the need for red blood cell transfusion and increase hemotologic response rates, there by improving the QOL & large systematic review analyzing date published before 2002 hints towards a possible influence of epoetins on survival.

In order to improve efficiency and convenience of EPO treatment, a number of different administration regimens are currently being tested, ranging from lies frequent application of higher doses to loading dose and early intervention concepts. Although initial promising results have been observed, the value of these concepts still has to be shown in larger randomized trials. Comparing the efficiency of the different epoetins is difficult due to lack of large randomized head to head studies. Clinical trials with EPO aimed at correction of Hb levels beyond anemia indicated a higher risk of thrombovascular events. Larger meta-analysis is needed to fully elucidate the impact of epoetin and Hb levels on outcome.

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