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Erythropoetin in Urologic Oncology

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Key Words

Erythropoetin · Anemia · Urological tumors

Abstract

Objectives: The use of erythropoietin (EPO) for the treatment of anemia associated with urological malignancies is not well defined. The rate of anemia is dependent on the type of cancer and on the different types of treatment. Only with a substantial risk for blood transfusion is substitution treatment by EPO justified. Additionally, the long-term risks of blood transfusions have to be balanced against the costs of EPO treatment.

Methods: Different experts have reviewed the literature on anemia and EPO regarding the four main tumor entities.

Results/Conclusions: In prostate cancer, EPO treatment may be justified before radical prostatectomy and in patients with advanced, hormone-refractory disease. In bladder cancer, significant treatment-related anemia mainly occurs in patients who have to undergo radical cystectomy and in patients who will be treated with polychemotherapy for metastatic disease. Patients with renal cell carcinoma rarely suffer from anemia and thus are usually not candidates for EPO treatment. Testis cancer patients only have a substantial risk for blood transfusions if they belong to the intermediate or poor prognosis group according to IGCCCG or if they need salvage chemotherapy or salvage surgery. However, in testis cancer patients EPO treatment should generally be preferred to blood transfusions since cure rates are excellent and thus the potential risks of transfusion-related infections are significant.

Introduction

Biotechnologically derived human erythropoietin (EPO, rHuEPO) has been available for the treatment of anemia for the last 10 years. EPO is a renal glycoprotein that stimulates the bone marrow in the production and differentiation of primordial red blood stem cells. In patients with renal insufficiency, EPO is the treatment of choice since the necessity of transfusions is significantly reduced and the quality of life is enhanced without the risks of infections by blood transfusion. The role of EPO treatment in oncology, however, has not been well defined. In Germany, EPO is approved

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for the treatment of cisplatin-related anemia in adults and since May 2000 EPO has been approved for the treatment of chemotherapy-related anemia in adult patients with solid and non-solid neoplasms if they are at risk of needing blood transfusions during chemotherapy. Hence, it is important to define the role of EPO in urologic oncology to avoid blood transfusions in patients that could be treated with EPO instead and to avoid the unnecessary costs of EPO treatment in patients who are not at risk of needing transfusions. The German Association of Urologic Oncology as part of the German Cancer Society has initiated a workshop on the indications for EPO in urologic oncology, and experts regarding the four main tumor entities (prostate, bladder, kidney, and testis) have reviewed the current literature in order to define the role of EPO in urologic oncology.

Anemia in Patients with Cancer of the Prostate

J.M. Wolff

Cancer of the prostate (CaP) has become the first neoplasm in men and the second leading cause of cancer death [1]. Therapy is dependent on the degree of tumor progression at the time of diagnosis. While the therapeutic aim for most cases of localized prostate cancer is radical prostatectomy, the therapy of choice for metastasized CaP is androgen ablation. Anemia in CaP may be tumor-related as well as treatment-related, and the necessity of EPO treatment needs to be defined.

Tumor-Related Anemia

Geenen et al. [2] performed an investigation of the red, white and platelet blood count in 49 patients with benign prostatic hyperplasia (BPH), in 24 hormonally treated patients with metastatic CaP, in 17 patients with untreated CaP without metastases and 14 patients with untreated metastatic CaP. Significantly lower red blood cell counts, hemoglobin levels and hematocrit values were found in the hormonally treated CaP group in comparison with the other 3 groups. The development of anemia was not influenced by palliative hormonal therapy. Hence, metastatic tumors as such were responsible for tumor-related anemia.

Treatment-Related Anemia – Surgery

An important side effect of radical prostatectomy is intraoperative blood loss. According to a compilation by Breul et al. [3], patients require an average of 2.9 units of blood intraoperatively as well as 2.8 additional units postoperatively. The preoperative use of EPO would be, within this context, feasible. Chun et al. [4] examined 104 patients who had undergone a radical prostatectomy. In 52 cases, patients had donated blood for their own use 3 weeks before surgery. The other 52 patients were given an injection of recombinant human EPO (rHuEPO; 600 IU/kg body weight 14 days and, if necessary, 7 days before surgery). The need of transfusions from blood donors was the same in both the EPO group and the autotransfusion group (9.6%). Additionally, there was no difference in the amount of transfusions used per patient in both groups (0.19 vs. 0.23). The authors carried out an additional time and cost analysis and were able to show that, although the costs per patient are higher with EPO than with autotransfusions, this is made up by the time saved in the following ways: (1) less time spent by the medical staff on the patient; (2) less work time lost by the patient, and (3) only a slight protraction of surgery. They concluded that the application of EPO in patients before a radical prostatectomy is indeed an alternative to autotransfusions. Recently Rosenblum et al. [5] reported the results of a prospective study, in which they investigated the effect of rHuEPO in 305 patients with clinically localized CaP undergoing radical prostatectomy. The authors observed a significant increase in hemotacrit levels and noted that only 7% of these patients required an allogenic blood transfusion.

Treatment-Related Anemia – Androgen Deprivation

Palliation is an important tissue in patients with advanced CaP. Most disabling among symptoms associated with disease progression are bone fractures, urinary tract obstruction and spinal cord compression as well as anemia, coagulation disorders and edema [6]. At the time of the diagnosis, 30% of the CaP patients with skeletal metastases already have anemia with <12 g/dl hemoglobin. A result of the standard modern therapy of androgen ablation is the exacerbation of this anemic state, as testosterone and EPO work synergistically. In a study by Strum et al. [7] it was shown that during maximal androgen blockade (MAB) the level of hemoglobin decreases significantly. Already after 1 month of therapy the hemoglobin decreased 1 g/dl and, after 5 months of therapy it fell from an average of 14.9 to 12.3 g/ dl. It is evident that some patients are more strongly affected by normocytic hypochromic anemia during therapy. In these patients there is a decrease in the hemoglobin level of an average of 4.3 g/dl. If the MAB is interrupted, hemoglobin begins to rise again and reaches its original level, usually after 6 months, without further therapeutic measures. The speed and extent of this increase in hemoglobin is, however, dependent on the patient's age and the length of

the MAB. The older the patient is and the longer he has received antiandrogen therapy, the more slowly his hemoglobin level recovers. Here the drop in the level of hemoglobin is a result of the androgen withdrawal and not primarily due to the prostate cancer with skeletal metastases. A similar effect has been reported in patients with BPH, who were treated with an LHRH agonist. Those patients exhibited a temporary drop of 7% on average in their hemoglobin levels [8, 9].

In the treatment of anemia in patients with metastatic CaP, the application of EPO presents itself as a possible alternative to blood transfusions. In this context, Beshara et al. [10] studied 9 patients with hormone-refractory prostate cancer who received 150 units/kg body weight of EPO 3 times a week over 12 weeks. In 4 patients there was a median increase in the hemoglobin level of approximately 2 g/dl; in 3 patients, an increase of approximately 1.7 g/dl. The latter group required additional blood transfusions. In only in 2 patients, there was no rise in hemoglobin level observed; in these cases, an inadequate response to EPO due to defective bone marrow was discussed. The authors concluded from their observations that the anemia is caused by the suppression of erythropoiesis due to androgen ablation as well as to a modified hemorrheology. Possibly this can be positively influenced by applying EPO. While both single as well as complete androgen blockade result in an anemic state, the degree of anemia during single androgen blockade is less extreme. On the other hand monotherapy with a nonsteroidal antiandrogen did not result in an anemic state. Decensi et al. [11] studied 24 patients with metastatic CaP, who were treated with nilutamide as a monotherapy.

In summary, it has been determined that the application of EPO in patients with CaP appears to be sensible in the following instances. (1) Patients with localized CaP, before a radical prostatectomy. Here the necessity of a blood transfusion can be reduced through a preoperative application of EPO. (2) Patients with anemia and advanced hormone-refractory prostate cancer. In at least some of these patients, the application of EPO appears to be a feasible way of reducing the amount of donor blood required for transfusions.

Anemia in Patients with Bladder Cancer

H. Schwaibold

Bladder cancer is the second most common cancer in the genitourinary tract, with an annual incidence of about 19 cases per 100,000 in Germany. Approximately 70–80% of bladder cancers are superficial, and of 20–30% of bladder tumors that are diagnosed as invasive at the initial presentation, more than half of the patients will die from progression of the disease [12]. Spontaneous anemia associated with bladder cancer is relatively rare and will be found in patients with either recurrent hematuria or due to advanced disease. In most cases, however, anemia is due to bladder cancer therapy.

Treatment-Related Anemia – Surgery

Transurethral resection and intravesical immunotherapy or chemotherapy are currently used to treat superficial disease (Ta, T1, cis). Bleeding is one of the most common problems associated with transurethral resection of bladder tumors but hemorrhage requiring blood transfusion is relatively rare [13], the highest rates reported are about 13% [14].

In contrast to transurethral resection, 80% of patients undergoing cystectomy require transfusion [15].

Treatment-Related Anemia – Chemotherapy/Radiation

Due to the minimal systemic absorption, anemia after intravesical instillation with chemotherapeutic substances is rarely reported. After systemic polychemotherapy for muscle invasive disease, anemia will be found more often in patients with metastatic disease than during adjuvant chemotherapy (table 1). Radiation therapy with or without concomitant chemotherapy rarely leads to anemia. In a big Canadian study 13% of the patients developed anemia not requiring transfusion. Interestingly, Gospodarowicz et al. [16] found a negative statistical correlation between anemia (Hb $<$ 12 g%) and tumor specific survival.

Due to the mostly unsuccessful attempts to improve current cisplatin-based chemotherapy, new agents with high single agent activity are included more and more in polychemotherapy regimens. Some of these agents show high rates of anemia, which might be due to the fact that studies evaluating new drugs restricted entry to those patients with prior exposure to systemic chemotherapy. Gallium nitrate, the metal salt of a group IIa metal which interferes with cellular iron metabolism as well as RNA synthesis, was tested in a phase I/II trial at the Memorial Sloan-Kettering Cancer Center. Anemia developed in almost all patients [17]. Also the three-drug regimen of vinblastine plus ifosfamide plus gallium nitrate caused significant hematologic toxicities including grade 3–4 anemia in 38% [18]. Anemia requiring transfusion is relatively rare after paclitaxel application, as well in monotherapy [19] as in paclitaxel-based combination regimens [20]. Combining paclitaxel with cisplatin and ifosfamide, Bajorin et al. [21] found grade 3 anemia in 30% of 30 patients. Paclitaxel/carboplatin combination resulted

Table 1. Chemotherapy-related anemia in bladder cancer patients

Polychemotherapy regimen	Type of chemotherapy	n	Percentage of patients with anemia (WHO grade)	Reference
Cisplatin	met	120	1 (grade 3–4)	Loehrer et al. [26], 1992
M-VAC	met	126	1 (grade 3–4)	Loehrer et al. [26], 1991
CMV	adj	25	4 (n.g.)	Freiha et al. [27], 1996
CISCA	adj	91	negligible	Skinner et al. [28], 1991
CMV	met	43	14 (grade 3)	Jeffery and Mead [29], 1992
CMV	neo	60	20 (grade 2–3)	Scattoni et al. [30], 1995
CMV + ifosfamide	met	32	31 (grade 3–4)	Kyriakakis et al. [31], 1997
Gemcitabine	met	15	53 (n.g)	Pollera et al. [23], 1994
Gallium nitrate	met	39	100 (n.g)	Seidman et al. [17], 1995
VIG	met	40	38 (grade 3–4)	Dreicer et al. [18], 1996
Paclitaxel, ifosfamide, cisplatin	met	30	30 (grade 3)	Bajorin et al. [21], 1998
Paclitaxel, carboplatin	met	47	12 (grade 3–4)	Droz et al. [22], 1998

n.g. = Not given; adj = adjuvant chemotherapy; neo = neoadjuvant chemotherapy; met = chemotherapy for metastatic disease; VIG = vinblastine, ifosfamide, gallium nitrate.

in grade 3/4 anemia in 12% of 47 patients [22]. High rates of anemia have been reported after gemcitabine therapy of advanced bladder cancer [23], especially in combination schedules, with grade III/IV anemia in up to >60% of patients [24, 25].

Taken together, there are two types of patients with bladder cancer who may develop anemia in higher percentages, and in whom the use of EPO is justified: (1) patients who undergo radical cystectomy, and (2) patients who will be treated with polychemotherapy, mainly for metastatic disease.

Anemia in Patients with Renal Cell Carcinoma

R. Heicappell

Anemia – either paraneoplastic or therapy-induced – is a rare symptom in renal cell carcinoma (RCC). Evaluation of published reports is difficult because different thresholds for anemia are used. While some authors consider a hemoglobin concentration of 12.9 g/100 ml or 11.9 g/100 ml as anemic, the definition used by the WHO defines grade 1 anemia as a hemoglobin concentration between 9.5 and 10.9 g/100 ml [32].

Tumor-Related Anemia

A remarkable feature of RCC is that paraneoplastic anemia may be observed as well as paraneoplastic erythrocytosis.

Polycythemia is found in 1–5% of all patients with RCC [33]. Since elevated EPO levels are found in the serum of patients with RCC [34–36], it was hypothesized that polycythemia in patients with RCC was induced by EPO. This hypothesis is supported by the fact that EPO may be detected by immunohistochemistry in histologic specimens of RCC [37]. Moreover, EPO has been demonstrated in the DNA [38] and RNA [39] of RCC. The role of EPO in RCC is, however, not completely understood at present.

Preoperative tumor-induced anemia was found in 20–30% of all patients with RCC in series published 10–20 years ago [40, 41]. There was an inverse correlation of anemia with tumor stage (table 2) [42]. Due to ultrasound-based screening, tumors are detected in earlier stages today. This may be the main reason why preoperative anemia is not frequently seen today: in our own experience 14% of all renal tumors present with a hemoglobin concentration of <7.4 mmol/l (equal to 11.9 g/100 ml); however, based on the WHO criteria of anemia, we did not see any anemic patients in a recent analysis of 30 consecutive patients (data not shown). It is currently not celar whether preoperative anemia is an indicator of an unfavorable prognosis in RCC [40, 41]. Tumor-induced preoperative anemia is probably explained by iron shortage that has been found to increase with tumor stage [42]. Loughlin et al. [43] suggested that low levels of serum iron were caused by the iron-binding protein transferrin. They base their assumption on a clinical study where they found an inverse correlation of the serum iron and transferrin concentration detected in tumor tissue. Moreover, ferritin has been found to be elevated in RCC by several groups [44–46].

Table 2. Proportion of anemic patients in relation to tumor stage

Robson stage	Anemic patients, %
I	18
II	24
III	42
IV	46
All stages	31

Anemia was defined as a hemoglobin concentration of <7.4 mmol/l (equal to 11.9 g/100 ml) [40].

Table 3. Frequency of anemia observed in immunotherapy of renal cell carcinoma

Drug	n	anemia %	Grade	References
IL-2 i.v.	199	14	n.a.	MacFarlane [53], 1995
IL-2 i.v. + LAK	42	88	n.a.	Ettinghausen et al. [54], 1987
IL-2 s.c.	15	2	n.a.	Atzpodien et al. [55], 1993
IL-6	49		n.a.	Nieken et al. [51], 1995
IFN-α $3–6 \cdot 10^6$ U	20	7	2	Schomburg et al. [56], 1993
IFN-α $10 \cdot 10^6$ U	41	75	2/3	Tsavaris et al. [57], 1993
IL-2/IFN-α/5-FU	215	0		Lopez et al. [58], 1996

n.g. = Not available.

Treatment-Related Anemia

Major therapeutic options for RCC consist of surgery for patients with organ-confined disease and/or medical therapy for metastatic disease which is mostly done in clinical trials. With the exception of very large tumors or large thrombi in the vena cava, surgery for RCC carries no significant risk for intraoperative blood loss. Transfusion rates of 81%, as reported in series in the 1970s and early 1980s appear very high compared to contemporary standards [47]. In our own series we had a transfusion rate of 14% (data not shown). Since massive blood loss is an infrequent event in surgery of renal cancer, it does not seem to be necessary to institute alternative measures such as autologous blood transfusion or autotransfusion by cell savers [48, 49].

It is controversial, whether intraoperative transfusions have an impact on the patient's survival [47, 50].

No standards exist for therapy of metastatic RCC. The majority of study protocols are based on cytokines alone or in combination with chemotherapeutic drugs such as 5-fluorouracil. Anemia was observed in almost all patients treated with regimens based on high dose interleukin-2 and lymphokine-activated killer cells (table 2). Using low-dose interleukin-2, anemia is a rare event. Reversible anemia is observed in almost all patients treated with interleukin-6 [51]. In constrast, anemia is a rarely seen in protocols based on 5-fluorouracil [52].

In conclusion, anemia is an infrequent clinical problem in RCC (table 3). This is mainly due to an increasing proportion of tumors detected in an early stage. Protocols for systemic therapies for metastatic RCC are mostly based on cytokines and chemotherapeutic drugs in concentrations that usually do not induce anemia. Thus, EPO treatment in RCC is not indicated.

Anemia in Patients with Testicular Germ Cell Tumors

P. Albers

Tumor-Related Anemia

Testicular germ cell tumors (GCTs) are highly proliferative tumors that usually are not diagnosed by anemia in the first place. In only a few very advanced tumors bone metastasis may occur and be responsible for anemia at first diagnosis. In general, tumor-related anemia is negligible in GCTs.

Treatment-Related Anemia – Chemotherapy

After cisplatin-based chemotherapy with more than 3 cycles (total dose >600 mg) 40% of patients will need blood transfusions because of myelotoxicity-related anemia [59]. The anemia in these cases is induced by a direct toxicity of cisplatin derivates to EPO producing interstitial renal cells [60]. Prophylactic treatment with EPO is justified, if the cisplatin dose is >75 mg/m^2/cycle [61]. In a randomized trial of 62 patients with breast cancer, prophylactic EPO treatment before 6 cycles of cyclophosphamide-based chemotherapy was able to avoid blood transfusions in the treatment group, whereas 16 of 31 patients in the placebo group had to be treated by transfusions [62]. However, a significant difference in transfusion rates in 32 patients before cisplatin-based chemotherapy was only shown if the time of post-chemotherapy anemia exceeded 3 months [63].

There is an indication for EPO therapy of chemotherapy-related anemia in general oncology. Two trials with over 100 anemic patients were able to show a significant increase in hemoglobin with EPO treatment versus placebo [64, 65]. However, only 15% patients with <3 cycles of

cisplatin-based chemotherapy in the treatment of GCTs will need blood transfusions [66]. With conventional salvage chemotherapy (e.g. PEI) the rate increases to 48% [67]. High-dose chemotherapy always leads to chemotherapy-related anemia that needs to be treated.

In summary, patients with GCTs benefit from prophylactic treatment with EPO only if the planned chemotherapy regimen exceeds 3 cycles (intermediate and poor prognosis patients according to the IGCCCG classification). Another group that justifies prophylactic EPO therapy consists of patients who will need salvage chemotherapy after 3 cycles of standard chemotherapy.

The lower limit of hemoglobin that can be tolerated without blood transfusions still remains unclear. In general, the patients are very young and the tumor has a very high cure rate. Thus, long-term toxicities of transfusions (like infections) are an extremely important consideration in this group of patients. A lower limit of 8.0 g% of hemoglobin after complete remission (without following salvage treatment or surgery) seems to be justified before blood transfusions are indicated.

However, an indication for EPO treatment is if a patient with a chemotherapy-related anemia needs either surgical or chemotherapy salvage treatment.

Treatment-Related Anemia – Surgery

From several studies in patients with orthopedic surgery (like hip replacement), it is known that prophylactic treatment with EPO in initially anemic patients enables preoperative blood donations for autologous transfusions. Postoperative anemia can be treated by EPO if the serum EPO level is low.

In patients with GCTs, the rate of blood transfusions after primary retroperitoneal lymph node dissection is $<10\%$. In post-chemotherapy retroperitoneal lymph node dissection the rate increases to about 40% of patients. Thus, prophylactic EPO treatment is justified in patients after chemotherapy who will need a post-chemotherapeutic surgical resection of residual masses.

In summary, only about 20% of patients with GCTs will have an indication for prophylactic or therapeutic EPO treatment. In Germany, the incidence of GCT patients is about 8/100,000 (3,000 patients/year).

Important general considerations of EPO treatment in patients with GCTs are: (1) usually young patients with a curable disease are treated. This group of patients will potentially suffer from long-term toxicities of blood transfusions like transmission of infectious diseases. (2) Quality of life aspects are of utmost importance in the treatment of these patients and reintegration in their social surroundings and time to get back to work are important aspects.

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