

Case report

## Role of recombinant human erythropoietin in the treatment of cancer-related anaemia

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### ABSTRACT

Anaemia is one of the most frequently diagnosed complications in cancer patients and also occurs during the course of cancer treatment. The condition can be observed in as many as 60–70% of patients who receive chemotherapy or radiotherapy. As a cancer symptom, it is found in 30% of cases and is particularly severe when accompanied by kidney failure. In patients undergoing cancer therapy, anaemia is treated with PRBC transfusions and/or recombinant human erythropoietin.

The article discusses 3 case studies of patients with late-stage cancer (pleural mesothelioma, urothelial kidney carcinoma, and lung carcinoma), who suffered from moderate to severe anaemia during aggressive treatment with chemo- and radiotherapy. All 3 patients were treated with erythropoietin, which made it possible for them to stay on chemotherapy and/or undergo radiotherapy. Thanks to erythropoietin, they did not require PRBC transfusions and their general condition and quality of life improved. They tolerated the treatment well and no complications were observed.

**Key words:** anaemia, chemotherapy, erythropoietin, radiotherapy

## INTRODUCTION

Cancer and oncological treatment (chemotherapy, radiotherapy) disrupt the functioning of the hematopoietic system and frequently lead to anaemia. The condition is diagnosed in as many as 30% of untreated patients and its risk further increases with treatment. It can affect as many as 60–70% of all cancer patients [1]. Important risk factors include:

- myelotoxic chemotherapy (e.g. platinum compounds, anti-metabolites, gemcitabine) [2]
- radiotherapy of the pelvic bone
- eating disorders
- nephrotoxic cytotoxic drugs [3].

The choice of therapy depends on the severity of anaemia, ongoing cancer treatment, cancer type and other co-morbidities, and may include active observation, a packed red blood cells (PRBC) transfusion, or the administration of recombinant human erythropoietins.

Under physiological conditions, erythropoietin is a glycoprotein hormone synthesized primarily by the interstitial fibroblasts of the kidney (c. 90%). Three recombinant human erythropoietins with similar mechanisms of action are currently in use: epoetin  $\alpha$ , epoetin  $\beta$ , and darbepoetin  $\alpha$ . Erythropoietin treatment carries a high risk of adverse effects, including thromboembolic complications, but, in most cases, allows to continue cancer therapy and reduces the frequency of PRBC transfusions [4].

## CASE 1. ANAEMIA ASSOCIATED WITH CHEMOTHERAPY IN PLEURAL MESOTHELIOMA

A 59-year-old female patient was admitted for diagnosis because of a tumour in her right lung; a CT scan revealed a subpleural lesion of 40 × 28 mm in the sixth segment, with a smooth polycyclic outline, uneven contrast enhancement, and proliferative features. The lesion adhered to the pleura with the possibility of infiltration.

Since bronchoscopy did not reveal any lesions, the patient was referred for surgery. Trocars were introduced into the thorax and a tumour was discovered; the lesion adhered to the thoracic wall and there was a suspicion of possible infiltration. In addition, several nodular foci were observed in the parietal pleura; macroscopically, these corresponded to metastatic lesions. Intraoperative examination allowed to diagnose a poorly differentiated malignant tumour. Due to the advanced stage of the disease (stage IV), the anatomical resection of the lower lobe tumour was not performed. A post-surgery histopathological assay narrowed the diagnosis down to *mesothelioma malignum*.

The patient was referred to the oncology ward. Following additional assessment with the Zubrod-ECOG-WHO scale (0), as well as further lab tests and diagnostics, a multidisciplinary medical council qualified her for treatment with pemetrexed (500 mg/m<sup>2</sup>) and cisplatin (75 mg/m<sup>2</sup>), administered in cycles spaced at intervals of 21 days.

Before the start of treatment, the patient's blood parameters were within the normal range, with haemoglobin levels (HBG) at 13.3 g/dL, red blood cells (RBC) at 4.24 mln/mm<sup>3</sup>, and haematocrit (HCT) at 38.8%.

The patient received the first cycle of chemotherapy at prescribed doses. During the first 3 cycles, her blood parameters remained stable; a slight decrease in haemoglobin levels (11.2 g/dL) was judged as clinically insignificant.

After the third cycle, CT was used to assess the effectiveness of treatment. Based on RECIST 1.1. criteria, the disease appeared to have stabilized. Considering the positive outcome, high tolerance of treatment, and the good general condition of the patient (1 on the Zubrod-ECOG-WHO scale), three more cycles were prescribed in accordance with the previous treatment scheme.

Shortly before the fourth cycle of chemotherapy with pemetrexed and cisplatin was due to begin, the patient was admitted to the ward with a slight decrease in muscle strength and general malaise. Her general condition was estimated as 2 on the Zubrod-ECOG-WHO scale and lab tests revealed a moderate anaemia (HGB 8.6 g/dL; RBC 2.86 mln/mm<sup>3</sup>; HCT 27.4%). As a consequence, the next cycle of chemotherapy was put on hold and a PRBC transfusion was considered. In the end, considering the low severity of symptoms, erythropoietin treatment was introduced, in accordance with the guidelines laid down by cancer science associations.

In accordance with the guidelines published by the NCCN (*National Comprehensive Cancer Network*) in 2015 [5], following the recommendations of the ASCO (*American Society of Clinical Oncology*) from 2010 [6], patients who undergo chemotherapy should be put on erythropoietin treatment whenever their haemoglobin levels fall below 11 g/dL or decrease by more than 2 g/dL between two successive lab tests. The ESMO (*European Society of Medical Oncology*) sets the threshold at 10 g/dL and below [7], while the EORTC (*European Organization for Research and Treatment of Cancer*) recommends the cut-off point of 9 g/dL [8].

Before treatment, the patient underwent further testing to assess the risk of possible thromboembolic complications. The physical exam, interview, and additional lab assays (coagulation parameters – normal, d-dimer levels – 337 ng/mL) did not suggest any contraindications for treatment with recombinant human erythropoietin and the drug was introduced (erythropoietin  $\beta$ , administered s.c. every 7 days at doses of 30,000 IU). After 2 weeks, important blood parameters considerably improved (HGB 9.3 g/dL; RBC 3.09 mln/mm<sup>3</sup>; HCT 29.6%). In light of the good general condition of the patient (1 on the Zubrod-ECOG-WHO scale), good tolerance of treatment, and the positive outcome, the therapy was continued. Following 2 more doses of 30,000 IU s.c. erythropoietin  $\beta$ , HGB levels rose to 9.8 g/dL, and the next cycle of chemotherapy with pemetrexed + cisplatin, at 75% of the original dose, was initiated, while erythropoietin treatment continued as before. The weekly administration of erythropoietin made it possible for the patient to stay on chemotherapy; in total, she received 6 cycles and her anaemia never got worse than moderate according to WHO classification. The patient did not require a PRBC transfusion at any time.

A follow-up CT scan revealed partial response to chemotherapy. The patient was referred for palliative radiotherapy with 20 Gy applied to the thoracic wall. She was kept on the previous dose of erythropoietin throughout the treatment.

Erythropoietin was terminated 4 weeks after the end of radiotherapy, in accordance with the guidelines that recommend its discontinuation after cancer treatment (as it may increase the likelihood of death) [9, 10]. The patient continued to suffer from moderate anaemia (RBC 3.78 mln/mm<sup>3</sup>; HGB 9.7 g/dL; HCT 32.1%). She has been under observation for the past 2 months; her cancer has not progressed, there have been no significant changes in blood parameters, and her moderate anaemia persists, albeit without clinical symptoms.

## CASE 2. ANAEMIA ASSOCIATED WITH CHEMOTHERAPY IN KIDNEY CANCER

A 51-year-old female patient was admitted for the diagnosis of a tumour discovered in her left kidney during an abdominal ultrasound. The woman had previously observed symptoms of impaired immunity, recurrent fevers, and pain under the left rib (6 points on the VAS, Visual Analog Scale). The patient was put on analgesic treatment, including non-steroidal anti-inflammatory medication, and her pain decreased to 3 points on the VAS.

The CT scan revealed the following: "Left kidney with a lesion in the inferior extremity (63 × 65 × 59). The tumour directly adheres to the left iliac major muscle (suspected malignant infiltration). Enlarged right lumbar lymph nodes with necrotic features and a tendency to form packages that encompass the root of the left kidney and displace the non-dilated left ureter slightly to the side."

The patient underwent transabdominal left nephrectomy and periaortic lymphadenectomy. The histopathological report diagnosed: "Urothelial carcinoma with squamous differentiation. High Grade (G3). Carcinoma with extensive necrosis (c. 50%), infiltrates the renal pelvis, parenchyma in the lower renal extremity, the fat tissue of the hilus, and the adipose capsule. Tumour cell embolisms are present in numerous lymphatic and individual blood vessels. PT4 pN1."

The patient was referred to the oncology ward. In light of her general condition (1 on the Zubrod-ECOG-WHO scale), further lab assays and imaging tests that aimed to determine the baseline tumour stage before surgery, as well as earlier treatment, she was qualified for PG chemotherapy (cisplatin 75 mg/m<sup>2</sup> + gemcitabine 1000 mg/m<sup>2</sup> on the first and eighth day of the cycle), in cycles administered at 21-day intervals, with evaluation scheduled after 3 cycles (a total of 6 were prescribed).

Additional tests showed increased levels of CA 125 and CEA markers: 146.8 U/mL and 6.61 ng/mL, respectively. Before treatment, the patient's blood parameters were in the normal range (RBC 3.3 mln/mm<sup>3</sup>; HGB 10.5 g/dL; HCT 31.4%). She started the first cycle of chemotherapy in the prescribed dosage.

Following 3 cycles, a CT scan was performed to evaluate the effectiveness of treatment; based on RECIST 1.1 criteria, the disease appeared to have stabilized. Considering the positive outcome, high tolerance of treatment, and the good general condition of the patient (1 on the Zubrod-ECOG-WHO scale), 3 more cycles were prescribed in accordance with the previous treatment scheme.

Shortly before the sixth cycle of chemotherapy was due to begin, the patient was admitted to the oncology ward with severe weakness and exertional dyspnea; she was pale and sweat profusely, complained of tinnitus and acute chest pain (her general condition was evaluated as 3 on the Zubrod-ECOG-WHO scale). The X-ray exam revealed the presence of fluid in the right pleural cavity; drained, it yielded 1500 mL of a blood-coloured discharge. Moderate anaemia (HGB 6.9 g/dL) was treated with a transfusion

of 3 units of PRBC, which allowed to stabilize haemoglobin levels (HGB 8.7 g/dL) and improve the general condition of the patient (2 on the Zubrod-ECOG-WHO scale).

A subsequent CT scan revealed metastatic lesions in the parenchymal organs: lungs and liver. PG chemotherapy was discontinued (after 5 cycles in total) and the patient was qualified for MVA treatment (methotrexate, vinblastine, adriamycin).

Since the patient's general condition had improved to 1 on the Zubrod-ECOG-WHO scale after the PRBC transfusion, drainage of the pleural fluid, and anti-inflammatory treatment, including low doses of corticosteroids, and she suffered from moderate anaemia (HGB 8.5 g/dL), she was soon put on erythropoietin  $\beta$  (administered in subcutaneous doses of 30,000 IU every 7 days).

After 4 weeks, the patient's blood parameters improved (RBC 3.84 mln/mm<sup>3</sup>; HGB 9.8 g/dL; HCT 33.1%), her biochemical and coagulation parameters stayed within normal limits, and her general condition was 1 on the Zubrod-ECOG-WHO scale. Chemotherapy was reintroduced, based on the MVA scheme; the patient received 3 full cycles, while erythropoietin treatment continued as before. A follow-up CT scan revealed a slight decrease in the size of metastatic lesions in the liver (based on RECIST 1.1 criteria, the outcome was described as stabilization). The decision was taken to continue with chemotherapy and administer 2–3 more full cycles in prescribed doses. The patient tolerated the treatment well and her anaemia did not deteriorate. She had to have the fluid in her left pleural cavity drained at regular intervals. After the termination of chemotherapy, she was qualified for further erythropoietin treatment (up to 4 weeks post-treatment) and palliative care.

The high severity of anaemia observed in the patient may have been related to the fact that she lacked a kidney, which increased the toxicity of cisplatin. Erythropoietin made it possible for the patient to stay on chemotherapy, prevented additional PRBC transfusions, improved her general condition, and had a positive impact on her quality of life during aggressive cytotoxic treatment.

### CASE 3. ANAEMIA ASSOCIATED WITH CHEMOTHERAPY IN LUNG CANER

A 59-year-old female patient had already been treated (8 years ago) for a tumour in the right breast, which required the partial excision and biopsy of the sentinel lymph node in the right armpit. The histopathological report stated: "Carcinoma ductale in situ typus noncomedocarcinoma et solidum cum microcalcificationibus. N.G-2".

The sentinel lymph node proved free from cancer cells. Receptor tests were also performed: ER (+++); PGR (+++); HER2-negative (0). Follow-up treatment included radiotherapy and hormonal therapy with tamoxifen for 5 years. Currently, there are no signs of relapse in the breast.

The patient was admitted to the oncology ward to undergo chemotherapy for a stage IIIb (pT2aN3M0) left lung tumour. The treatment of breast cancer had started three years earlier.

The CT scan performed before surgery revealed a 3 × 2 cm nodular lesion with an irregular outline and strand-like outgrowths along the circumference at the apex of the left lung (segment 1/2); at the right arc of the aorta, a lymph node package could be observed, c. 3.2 × 1.3 cm large. Other mediastinal lymph nodes were not enlarged.

Left lobectomy was then performed. The histopathological report described a tumour of 3.5 × 2.5 × 2 cm. Diagnosis: "Adenocarcinoma tubulare pulmonis CK7(+), TTF1(+), CK20(-), ER(-), PGR(-), peribronchial lymph node – adenocarcinoma metastaticum, lymph node conglomerate: N5-adenocarcinoma metastaticum."

The cancer was diagnosed at stage IIIb (N3 – the tumour had spread to the mediastinal lymph nodes on the side opposite to the primary lesion). A post-surgery CT scan showed no signs of relapse or distant metastatic sites.

In light of the advanced stage of the disease, the histopathological report, the general condition of the patient (1 on the Zubrod-ECOG-WHO scale), as well as imaging tests and lab assays, the patient was qualified for PG chemotherapy: cisplatin 75–80 mg/m<sup>2</sup> and gemcitabine 1000 mg/m<sup>2</sup>, administered on the first and the eighth day of the cycle. 4–6 cycles were scheduled at intervals of 21 days, with evaluation after 4 cycles. Altogether, the patient received 4 cycles of PG and tolerated the treatment well, also in terms of blood parameters. Subsequently, she was referred to a radiotherapy centre for possible follow-up treatment; however, due to being tired with her disease and chemotherapy, she never showed up at the centre and refused further treatment.

She was admitted to the oncology ward again 2 years later due to resting dyspnea, weakness, and appetite loss; her weight had decreased by more than 10%. As the CT scan revealed, the cancer had spread (the state after the upper left lobectomy). Both lungs showed numerous dispersed metastatic lesions: the biggest one

in the right lung, 14 mm in diameter, was found in segment 4; the biggest one in the left lung, 11 mm in diameter, was observed in segment 7.

A sample of the metastatic lesions was taken to determine their source (breast cancer or lung cancer); microscopic analysis suggested medium-differentiated metastatic papillary adenocarcinoma.

Because the diagnostic process was taking a long time to complete, another CT scan was performed and confirmed severe progression. The number and size of metastatic lesions in the lungs visibly increased. Metastases are currently to 20 mm in diameter and larger lesions begin to merge together. The subcarinal and right lower paratracheal lymph nodes in the right pulmonary hilus reach up to 11 mm in diameter.

The patient was referred to the oncology ward. Following the assessment of her general condition (0 on the Zubrod-ECOG-WHO scale), as well as additional diagnostic tests and lab assays, a multidisciplinary medical council qualified her for chemotherapy in accordance with the *Treatment of Non-small Cell Lung Carcinoma* drug program: pemetrexed (500 mg/m<sup>2</sup>) + cisplatin (75 mg/m<sup>2</sup>), administered in cycles repeated every 21 days. A CT assessment was scheduled after 3 cycles, and 6 were planned in total.

The patient received 3 cycles of chemotherapy at the prescribed dose and tolerated the treatment well, without significant adverse effects.

Her response to treatment was assessed after the third cycle. The disease in the lungs had progressed and new distant metastatic lesions (3 cm and 1.5 cm in diameter) had appeared in the liver. Chemotherapy was terminated, followed by the molecular examination of a sample isolated from the metastatic pulmonary tumour; no mutation was found in the *EGFR* and *ALK* genes, which made the patient ineligible for treatment with tyrosine kinase inhibitors.

Second-line chemotherapy was introduced, based on the PN scheme (cisplatin 75–80 mg/m<sup>2</sup> administered orally on the first day, followed by vinorelbine 60 mg/m<sup>2</sup> on the first and eighth

day of the cycle), spaced at 21-day intervals and assessment scheduled after 3 cycles.

The patient was diagnosed with moderate anaemia related to previous chemotherapy (HGB 9.3 g/dL) and qualified for treatment with erythropoietin  $\beta$  (10,000 IU 3 times per week).

After one month of treatment, the patient's haemoglobin levels had increased considerably (HGB 9.8 g/dL) and no signs of toxicity were observed. Because all other lab parameters stayed within the normal range, the first cycle of PN chemotherapy was initiated at doses calculated for the current BSA.

A blood test performed before the next cycle showed a deterioration in the patient's anaemia (HGB 8.9 g/dL). Treatment with erythropoietin was thus continued at the same dosage as before and chemotherapy was put on hold until an improvement in blood parameters could be observed. After 2 weeks, haemoglobin levels increased (HGB 9.7 g/dL) and the next cycle of chemotherapy, at 75% of the original dosage, was introduced.

The therapy scheme was maintained alongside erythropoietin treatment. Altogether, the patient received 4 PN cycles and erythropoietin was terminated 3 weeks after the end of chemotherapy (HGB 9.8 g/dL).

The patient did not require a PRBC transfusion and underwent 4 cycles of PN chemotherapy, which helped stabilize the disease. She is currently under strict observation.

## CONCLUSIONS

The article discusses 3 case studies of patients with late-stage cancer (pleural mesothelioma, urothelial kidney carcinoma, and lung carcinoma), who suffered from moderate to severe anaemia during aggressive treatment with chemo- and radiotherapy. All 3 patients were treated with erythropoietin, which made it possible for them to stay on chemotherapy and/or undergo radiotherapy. Thanks to erythropoietin, they did not require PRBC transfusions and their general condition and quality of life improved. They tolerated the treatment well and no complications were observed.

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