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## Results of a retrospective study on assessment of routine approaches to the treatment of anaemia in cancer patients

*Relevance. Anaemia remains an acute problem of oncology given the importance of maintaining a good quality of life of patients during antitumour therapy. The incidence of anaemic syndrome in cancer patients is about 40%.*

*The aim of the study was to estimate the incidence of anaemia in cancer patients during chemotherapy and the methods of its correction used in the routine oncological practice.*

*Results. The paper provides the results of retrospective analysis of data obtained from the Almaty Oncology Center (Almaty) and the Zhambyl Region Oncology Dispensary (Taraz city). The obtained data evidences the urgency of this problem for Kazakhstan.*

*Almost a third (28.9%) of patients receiving chemotherapy showed a decrease in haemoglobin. In 85.9% of cases, anaemia was associated with 5 groups of drugs: platins, anthracyclines, fluoropyrimidines, taxanes, and periwinkle alkaloids. The reduction of haemoglobin to the level corresponding to the toxicity degrees 1 and 2 was not seen as a basis for the administration of anti-anaemia therapy in 76.8% and 65.8% of cases, respectively. Drug therapy to adjust the blood values was administered only in 26.8% of cases. Of them, 77.2% of patients received only iron preparations, 22.8% of patients were received erythropoietin. Erythropoietin was equally administered as monotherapy or in combination with iron preparations. Iron preparations were administered equally in oral and parenteral forms.*

*Conclusion. A fairly high proportion of anaemic syndrome in cancer patients receiving treatment in two oncology dispensaries, their low coverage with antianemic therapy, and a list of drugs most often used to correct anaemia indicate an unsatisfactory level of doctors' awareness of modern protocols for treating this pathology and an urgent need to develop national protocols of accompanying therapy in oncology.*

**Keywords:** malignant tumours, chemotherapy, cytostatics, anaemia, haemoglobin, iron preparations, erythropoietins.

**Introduction.** Modern approaches in treatment cancer diseases allow not only to actually increase the life expectancy of patients with an advanced tumour process, but to say about complete cure of patients with small tumours. Still, the issues of maintaining a satisfactory quality of life of patients during treatment remain acute. One of the factors closely related to the concept of «quality of life of a cancer patient» is anaemia which is manifested in reduced physical activity of the patient, weakness, decreased ability to work. The frequency of anaemic syndrome in cancer patients is about 40% [1]. Sometimes, the underestimation of the importance of this factor does not only reduces the objective status of the patient but affects the final result of antitumour therapy.

The development of anaemia in cancer patients can be associated with a variety of different factors, including antitumour therapy, since chemo- and radiotherapy have a direct inhibitory effect on haematopoiesis [2,3]. According to the data presented in the "Practical recommendations for the treatment of anaemia in cancer patients" RUSSCO, 40% patients with solid neoplasms have anaemia associated with chronic diseases; anaemia develops in 54% of cases of chemo- and radiotherapy [1].

It is important that the myelosuppressive effect of chemotherapeutic agents may accumulate in repeated cycles of chemotherapy leading to a gradual increase in anaemia, as was proven by ECAS study. According to Ludwig H., van Belle S. et al., the frequency of anaemia has increased from 19.5% after the first course of chemotherapy to 46.7% on the fifth course of treatment [4, 5].

Several studies have provided evidence that anaemia and the hypoxia of tumour tissue caused by it may cause tumour resistance to chemotherapy stimulating genetic mutations and angiogenesis that hinder the control of tumour growth [2, 6]. As a result, effective treatment of anaemia may not only improve the life quality but increase the survival of patients with malignancies.

**Materials and Methods.** Retrospective study on the basis of two oncological dispensaries was conducted to assess the real situation in the country on the urgency of the problem of anaemia in cancer patients, vigilance of doctors in developing this syndrome and the methods of its correction.

**Purpose of the study** was to assess the frequency of anaemia in cancer patients during chemotherapy and the methods of its correction used in the routine practice of oncologists.

In its design, the study was a descriptive, retrospective and cohort. The study population: patients over 18 years of age with various cancer cases receiving chemotherapy in 2015 in two oncological dispensaries: Zhambyl regional oncological dispensary (ZhROD, the town of Taraz) and the day patient department of chemotherapy of Almaty Cancer Center (ACC).

**Results and Discussion.** 983 clinical records were studied. Of them, 521 patients received chemotherapy in ZhROD, and 462 – in the day patient department of ACC in 2015.

Out of 983 cases, 284 (28.9%) patients had a decrease in haemoglobin during chemotherapy. In 61 (21.5%) cases, they were men whose average age was 61.4 years (21-81 years). Women had anaemia more often – in 223 (78.5%) cases. At that, the average age of women with anaemia associated with antitumour drug therapy was 55.9 years (25-79 years).

During 2015, the patients of the two oncological dispensaries have received different number of courses of chemotherapy which resulted in anaemia. All 284 pa-

tients underwent one course, 133 (46%) patients underwent 2 courses, 92 (32.4%) patients – 3 courses, 63 (22.2%) patients – 4 courses, and 28 (9.9%) patients – 5 courses of chemotherapy.

Nearly  $\frac{3}{4}$  of patients, 209 (73.6%), who had a decrease in haemoglobin on the background of antitumour therapy, received treatment for breast cancer (BC), stomach cancer (SC), lung cancer (LC), ovarian cancer (OC), colorectal cancer (CRC) and lymphomas. The distribution of patients by localization of malignant tumours was as follows: 78 (27.5%) patients had BC; 56 (19.7%) patients had OC; 29 (10.2%) patients had LC, 23 (8.1%) – SC; 12 (4.2%) – CRC and 11 (3.9%) had lymphomas. 75 (26.4%) of patients had other singular localizations of cancer. During treatment, the patients received different chemotherapy regimens which included this or that drugs with varied frequency. In total, 284 patients have received 987 injections of various drugs which were studied for their association with anaemia. Table 1 shows the distribution of drugs by groups and analogues.

**Table 1** – List of antitumour drugs associated with the development of anaemic syndrome in patients receiving chemotherapy

| Name of the drug, group of drugs | Frequency of use | %    |
|----------------------------------|------------------|------|
| Platins                          | 256              | 25.9 |
| Cyclophosphamide                 | 150              | 15.2 |
| Anthracyclines                   | 177              | 17.9 |
| Fluoropyrimidines                | 122              | 12.4 |
| Taxanes                          | 69               | 7.0  |
| Periwinkle alkaloids             | 74               | 7.5  |
| Methotrexate                     | 45               | 4.6  |
| Gemcitabine                      | 20               | 2.0  |
| Dacarbazine                      | 13               | 1.3  |
| Natriopholine                    | 11               | 1.1  |
| Bevacizumab                      | 9                | 0.9  |
| Pemetrexed                       | 9                | 0.9  |
| Etoposide                        | 14               | 1.4  |
| Temozolomide                     | 6                | 0.6  |
| Irinotecan                       | 4                | 0.4  |
| Rituximab                        | 3                | 0.3  |
| Cytarabine                       | 2                | 0.2  |
| Bleomycin                        | 2                | 0.2  |
| Trabectedine                     | 1                | 0.1  |
| TOTAL                            | 987              | 100  |

Table 1 shows that in most cases, 85.9%, anaemia was associated with 5 groups of drugs: platins (Cisplatin, Carboplatin, Oxaliplatin), anthracyclines (Doxorubicin, Epirubicin), fluoropyrimidines (5-fluorouracil, Capecitabine), taxanes (Docetaxel, Paclitaxel) and vinca alkaloids (Vinorelbine, Vincristine, Vinblastine) which we combined for the convenience of analysis.

Quite often the combination of chemotherapy drugs which lead to a decrease in haemoglobin included Meth-

otrexate – 4.6% in patients treated for lymphomas. The remaining 12 drugs were in single cases associated with haematological complications associated with a decrease in haemoglobin.

A decrease in haemoglobin in patients was revealed not only during treatment but also before chemotherapy. Table 2 shows the decrease in haemoglobin in 284 patients included in the study.

**Table 2** – Reduction of haemoglobin levels in cancer patients before and after chemotherapy

| The level of haemoglobin               |   | Frequency | %     |
|--|---|-----------|-------|
| Before chemotherapy                    | Norm (Hb, men – 140 and above, women – 120 and above) | 42        | 15.2  |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 187       | 67.8  |
|  | Level 2 (Hb 80-100)                                   | 43        | 15.6  |
|  | Level 3 (Hb below 80 g/l)                             | 4         | 1.4   |
|  | Total   | 276       | 97.2  |
|  | Missed  | 8         | 2.8   |
|  |   | 284       | 100.0 |
| 1 <sup>st</sup> course of chemotherapy | Norm (Hb, men – 140 and above, women – 120 and above) | 16        | 6.9   |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 148       | 63.5  |
|  | Level 2 (Hb 80-100)                                   | 66        | 28.3  |
|  | Level 3 (Hb below 80 g/l)                             | 3         | 1.3   |
|  | Total   | 233       | 82.0  |
|  | Missed  | 51        | 18.0  |
|  |   | 284       | 100.0 |
| 2 <sup>nd</sup> course of chemotherapy | Norm (Hb, men – 140 and above, women – 120 and above) | 8         | 6.5   |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 85        | 69.1  |
|  | Level 2 (Hb 80-100)                                   | 28        | 22.8  |
|  | Level 3 (Hb below 80 g/l)                             | 2         | 1.6   |
|  | Total   | 123       | 100.0 |
| 3 <sup>rd</sup> course of chemotherapy | Norm (Hb, men – 140 and above, women – 120 and above) | 10        | 11.1  |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 66        | 73.3  |
|  | Level 2 (Hb 80-100)                                   | 14        | 15.6  |
|  | Total   | 90        | 100.0 |
| 4 <sup>th</sup> course of chemotherapy | Norm (Hb, men – 140 and above, women – 120 and above) | 5         | 10.0  |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 30        | 60.0  |
|  | Level 2 (Hb 80-100)                                   | 14        | 28.0  |
|  | Level 3 (Hb below 80 g/l)                             | 1         | 2.0   |
|  | Total   | 50        | 100.0 |
| 5 <sup>th</sup> course of chemotherapy | Norm (Hb, men – 140 and above, women – 120 and above) | 2         | 7.1   |
|  | Level 1 (Hb, men – 100-140, women – 100-120)          | 14        | 50.0  |
|  | Level 2 (Hb 80-100)                                   | 11        | 39.3  |
|  | Level 3 (Hb below 80 g/l)                             | 1         | 3.6   |
|  | Total   | 28        | 100.0 |

The table shows, that even before chemotherapy the majority of patients (84.8%) had this or that level of anaemia. Dynamics of changes in haemoglobin level by degree of toxicity from the start of treatment to the fifth course of chemotherapy shows a decrease in the proportion of patients with normal blood and with haemoglobin level corresponding to 1 degree of toxicity – from 15.2% to 7.1% and from 67.8% to 50.0%, respectively. At

the same time, during antitumour therapy the number of patients with level 2-3 haematological toxicity grew 2.5 times: from 17.0% to 42.9%.

The analysis of patients' treatment depending on the level of haematological toxicity for a total of 5 courses of chemotherapy has revealed 590 cases of registered reduction in haemoglobin level to a different extent in 284 patients receiving chemotherapy (Table 3).

**Table 3** – Appointment of corrective therapy depending on the reduction of haemoglobin levels

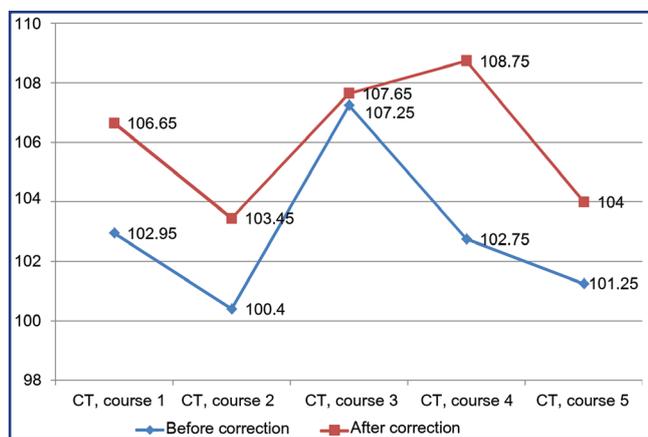
| HB indices  | Treatment status                               | No. of patients | %            |
|---|--|-----------------|--------------|
| Norm (Hb, men – 140 and above, women – 120 and above) | Received no treatment against anaemia          | 33              | 71.7         |
|   | Received only iron preparations                | 13              | 28.3         |
|   | <b>Total</b>                                   | <b>46</b>       | <b>100.0</b> |
| Level 1 (Hb, men – 100-140, women – 100-120)          | Received no treatment against anaemia          | 295             | 76.8         |
|   | Received only erythropoietins                  | 8               | 2.1          |
|   | Received only iron preparations                | 71              | 18.5         |
|   | Received erythropoietins and iron preparations | 10              | 2.6          |
|   | <b>Total</b>                                   | <b>384</b>      | <b>100.0</b> |

|                           |  |            |              |
|---------------------------|--|------------|--------------|
| Level 2 (Hb 80-100)       | Received no treatment against anaemia          | 100        | 65.8         |
|                           | Received only erythropoietins                  | 9          | 5.9          |
|                           | Received only iron preparations                | 37         | 24.3         |
|                           | Received erythropoietins and iron preparations | 6          | 3.9          |
|                           | <b>Total</b>                                   | <b>152</b> | <b>100.0</b> |
| Level 3 (Hb below 80 g/l) | Received no treatment against anaemia          | 4          | 50           |
|                           | Received only erythropoietins                  | 2          | 25           |
|                           | Received only iron preparations                | 1          | 12.5         |
|                           | Received erythropoietins and iron preparations | 1          | 12.5         |
|                           | <b>Total</b>                                   | <b>8</b>   | <b>100.0</b> |

According to data analysis, in 13 (28.3%) cases out of 46 at normal haemoglobin parameters, patients received anti-anaemic treatment with iron preparations. At the same time, with a decrease in haemoglobin to levels below 1 and 2 degrees most of the patients, 295 (76.8%) and 100 (65.8%), respectively, received no corrective treatment at all. With a haemoglobin level below 80 g/l (grade 3 toxicity), antianemic therapy was prescribed only in 4 (50.0%) out of 8 cases. In total, only in 158 (26.8%) cases the patients received antianemic drugs. Of them, in 122 (77.2%) cases the patients were prescribed only iron preparations. 36 (22.8%) patients were prescribed erythropoietin which was equally often, in 18 (50%) cases, prescribes in mono or in combination with iron preparations.

Out of erythropoietins, in 2 (5.5%) cases the patients were prescribed Darbopoetin 500 IU, in 34 (94.5%) cases - Erythropoietin-Alfa (express) in a dose of 40 000 IU once a week. Iron preparations were oral in 50% of cases (Ferrovite, Ferrovite C, Forsinol), and parenteral in other 50% of cases. The latter included Cosmosphere i.v. in 28.4% of cases, and i.m. drugs – Novofer or Ferrum-Lek – in 21.4% of cases.

Analysis of the dynamics of changes in the average haemoglobin in patients on the background of correction did not show improvement in laboratory parameters of red blood (Fig. 1).



**Figure 1** - Effect of correction on the dynamics of changes in haemoglobin level against the background of chemotherapy courses

**Conclusions.** The analysis of data obtained from the retrospective study in two centres – Zhambyl Regional Oncological Dispensary and Almaty Cancer Center – as of 2015 has shown that:

1. 28.4% of cancer patient receiving chemotherapy had anaemic syndrome: 36.7% in ZhROD, and 20.1% in ACC.

2. The list of main chemotherapy drugs associated with haematological complication in the form of anaemia coincided according to the data of both centres. The highest share of anaemic syndrome developed on the background of chemotherapy on the basis of platins and anthracyclines. Other drugs to a lesser extent, but with varying frequency have contributed to the development of that complication.

3. Only 26.8% of patients with proven anaemia have received antianemic treatment during antitumour therapy.

4. In both centres, main treatment against anaemia associated with chemotherapy included iron preparations with the prevalence of oral dosage forms. Only 6.9% (ZhROD) and 5.9% (ACC) of patients received erythropoietins.

5. A retrospective analysis showed the low alertness of oncologists for anaemic syndrome in chemotherapy as one of the factors of unsatisfactory quality of life of patients and a possible reason of low efficiency of chemotherapy.

6. Drugs prescribed by doctors to correct anaemia testify to the insufficient level of information of doctors on modern protocols for the treatment of this pathology and the urgent need to develop Kazakhstan protocols of accompanying therapy in oncology.

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