Cent. Eur. J. Med. • 3(3) • 2008 • 341-345
DOI: 10.2478/s11536-008-0049-3

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Central European Journal of **Medicine**

Assessment of chemotherapy-induced anemia in children with cancer

Research Article

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Received 21 February 2008; Accepted 19 May 2008

Abstract: Anemia is a common cause of co-morbidity in children with cancer. We reviewed a series of 124 children with non-metastatic cancer to assess the relationship between chemotherapy intensity, severe anemia, and frequency of transfusion. In more than 60% of children who received intensive chemotherapy, transfusions were prescribed compared to 38% and 21% of children treated with standard and mild chemotherapy, respectively. In conclusion, our data suggest that the intensity and duration of chemotherapy constitute important factors in determining the onset of anemia.

Keywords: *Anemia • Chemotherapy-induced anemia • Children • Cancer • Transfusion*

1. Introduction

Anemia is a frequent and significant cause of co-morbidity in patients with cancer, that results in decrease in functional capacity and quality of life [1]. It is a common complication of myelosuppressive chemotherapy and children with anemia are often managed differently from adults. Different mechanisms for the pathogenesis of chemotherapy(CT)-induced anemia in children with cancer have been proposed. A direct cytotoxic effect of different chemotherapeutic agents on bone marrow erythroid progenitors and microenvironment has been suggested as the main cause of anemia [2,3]. Additionally, other antineoplastic agents, such as Cisplatin, have shown to have a direct toxic effect on the renal tubules leading to a decreased erythropoietin production [2].

Other factors such as therapeutic interventions, intensity of treatment, extent of disease, chronic nature of the disease itself, recurrent infections due to suppressed immunity, or impaired iron utilization appear to have a role as cofactors in the pathogenesis of anemia [4-7]. Anemia in children with cancer is generally a hyporegenerative, normocytic, normochromic anemia associated with reduced serum iron and transferrin saturation but elevated (or normal) ferritin levels (Table 1).

The most commonly used standard for the assessment of therapy induced toxicity, is the same in their classification of more severe grades of anemia (grade 3 and grade 4) but differ slightly in their classification of lesser grades (Table 2).

In our series, we have investigated the relationship between chemotherapy intensity, severe anemia and frequency of transfusions in order to determine the clinical impact of the therapeutic interventions in the treatment of CT-induced anemia.

2. Material and Methods

We conducted a retrospective chart survey of 124 children with non-metastatic solid tumour (72 males, 52 females) treated from 1997 to 2001 at the Division of Pediatric Oncology, Catholic University of Rome (Table 3). Patient characteristics are reported in Table 4. Patients with progressive disease were not included into the study.

The children were 1 to 21 years old. The survey comprised patients with a confirmed diagnosis of cancer

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Table 1. Differential diagnosis of iron depletion or cancer related anemia.

	Iron depletion	Cancer
Reticulocyte count	reduced	reduced
MCV	reduced	normal
MCHC	reduced	normal
Serum ferritin	reduced	normal-elevated
Serum iron	reduced	reduced-normal
Transferrin saturation	reduced	reduced-normal

who received chemotherapy for more than 3 cycles or 3 months. Patients with hematological tumors were excluded because of the possible contamination of peripheral blood by malignant cells. Each patient was included only once, without taking into account the exact number of transfusions for each of them.

Antineoplastic treatment included surgery and chemotherapy. Patients treated with radiotherapy were ruled out because of the possibility of modifying hemoglobin and platelets levels. Demographics and baseline disease characteristics were recorded, along with respective antineoplastic treatments.

Hemoglobin, heamatocrit, red blood cell, total white blood cell and differential counts, platelets and reticulocytes, were measured at the start, duration and end of the treatment phase.

Anemia was defined as mild (hemoglobin value > 10 and < 12 g/dl), moderate (hemoglobin value 8-10 g/dl), and severe (hemoglobin value < 8 g/dl). Red blood cell transfusion was considered for children with severe anemia (hemoglobin level ≤ 8 g/dl).

Patients were divided according to chemotherapy regimen: mild, standard and intensive chemotherapy, which consisted of 2, 3 or >3 cytotoxic agents prescribed at standard dosage, respectively.

Thirty-three (26.6%) patients received mild, 48 (38.7%) standard, and 43 (34.7%) intensive chemotherapy.

Secondly, chemotherapy regimens were separated into platinum-containing regimens and other chemotherapy.

Statistical significance was tested using χ^2 test.

Table 3. Tumor type.

Tumor	n
Medulloblastoma	19
Low-grade glioma	23
High-grade glioma	12
Germ cell tumors	20
Neuroblastoma	9
Rabdomyosarcoma	9
Wilms tumor	4
Soft tissue and bone sarcoma	6
p-PNET	8
Others	12

3. Results

Four patients (3.2%) had received transfusions prior to the start of chemotherapy because of their severe anemia at clinical presentation.

For the 65% of children who received intensive chemotherapy, transfusions were prescribed. Children who received standard and mild chemotherapy requested less frequent transfusions (38% and 21%, respectively) (Table 5). The mean cumulative transfusion rate for the transfused patient population only was 3.2±0.8 units 3 months. In univariate analysis, chemotherapy regimens was found to be significantly related (p = 0.000516) with the risk of red blood cell transfusion.

We observed a prevalence of severe anemia and transfusion requirement in patients receiving platinum-based chemotherapy. In the mild and standard CT group the need for transfusion increased from 21% of all patients to 50% (p = 0.022118), and from 38% of all patients to 50% (p = 0.296709) of children who received platinum compounds, respectively (Table 6). No significant differences were found in the group of patients treated with the intensive chemotherapy regimen. However, subgroup analyses were not performed, as the number of patients in each subgroup was relatively small, making it difficult to perform a subset analysis.

Table 2. Anemia severity criteria according to different Groups.

Grading	WHO	NCI	ECOG	EORTC
0 (WNL)	≥11,0 g/dl	WNL	WNL	WNL
1 (mild)	9,5-10,9 g/dl	10 g/dl to WNL	10 g/dl to WNL	10 g/dl to WNL
2 (moderate)	8,0-9,4 g/dl	8,0-10,0 g/dl	8,0-10,0 g/dl	8,0-10,0 g/dl
3 (severe)	6,5-7,9 g/dl	6,5-7,9 g/dl	6,5-7,9 g/dl	6,5-7,9 g/dl
4 (life threatening)	< 6,5 g/dl	< 6,5 g/dl	< 6,5 g/dl	< 6,5 g/dl

WHO: World Health Organization; NCI: National Cancer Institute; ECOG: Eastern Cooperative Group; EORTC: European Organization for Research and Treatment of Cancer; WNL: Within Normal Limits (female: 12,-16,0 g/dl; male: 14,0-18,0 g/dl).

Table 4. Patient characteristics.

Total pts	124
Sex	
Males	72
Females	52
Age (years)	
< 2	15
2-6	39
> 6	76
Therapy	
CT	124
CT + surgery	95

Extended duration of chemotherapy tended to increase the probability of developing moderate or severe anemia. After 3 months of treatment, approximately 45% of all the patients have experienced at least one episode of moderate or severe anemia; that prevalence increased to 68% of children after 8 months (p = 0.04) (Table 7).

4. Discussion

Many aspects of supportive care of the child with cancer deal strictly with the multiple hematological complications of the primary disease and its treatment. Emerging new data demonstrate that CT-induced anemia may have an adverse impact on the acceptance of cures and quality of life of children with cancer [8].

Severe anemia is generally treated with red blood cell transfusions, but mild to moderate anemia has traditionally been managed conservatively with little consideration of its impact on patient well-being. The clinical impact of anemia is more difficult to assess in young children since the normal hemoglobin range is lower compared to adults. In addition, children tend to tolerate low hemoglobin levels better than in adults, especially when the anemia develops over time [9].

Transfusion remains the standard therapy for treating CT-induced anemia. When anemia is mild to moderate, transfusion is postponed until the hemoglobin level decreases. Although the limit for administering red blood cell transfusion may differ among institutions, transfusion is generally prescribed when the hemoglobin level ≤ 8 g/dL, even in asymptomatic children. More controversial is whether transfusions should be administered to children with hemoglobin values in the 8 to 10 g/dL range. Several factors should be considered in assessing whether to give a transfusion, such as, the clinical status of the patient, comorbidity, and signs of an imminent hematological recovery. As in the case of mild anemia, unless the child with moderate anemia is symptomatic, transfusions should not be routinely prescribed if recovery from CT-induced myelosuppression is imminent.

Based on our results, it appears that the more intense the treatment, the greater the risk of anemia and the need of blood transfusions. However, it is interesting that a substantial percentage of our patients did not receive any treatment for anemia.

The policy to withhold transfusion until the hemoglobin level falls to < 8 g/dL might be inadequate in certain conditions. The reduced perception of present significant symptoms of moderate anemia contributes to the underestimation of the clinical influence anemia has on patients' social activities. Adolescents, for example, could experience debilitating symptoms such as fatigue or dyspnoea, similar to that observed in adults, at low hemoglobin levels ~7-8 g/dL. The current practice of

Table 5. Chemotherapy regimens and frequency of transfusions.

Chemotherapy regimen	**Patients n.**	**Transfusions**	
		yes	no
MILD	**33**	**7 (21%)**	**26 (79%)**
Low-grade glioma	23	5	18
Wilms tumor	4	1	3
Others	6	1	5
STANDARD	**48**	**19 (38%)**	**29 (62%)**
High-grade glioma	12	3	9
Germ cell tumors	20	8	12
p-PNET	8	4	4
Others	8	4	4
INTENSIVE	**43**	**28 (65%)**	**15 (35%)**
Medulloblastoma	19	13	6
Neuroblastoma	9	7	2
Rabdomyosarcoma	9	5	4
Soft tissue and bone sarcoma	6	3	3

Table 6. Platinum administration and frequency of transfusions.

Chemotherapy regimens	Patients n.	Transfusions	
		yes	no
MILD	33	7 (21%)	26 (79%)
Platinum-based chemotherapy	8	4 (50%)	4 (50%)
Nonplatinum-based chemotherapy	25	3 (12%)	22 (88%)
STANDARD	48	19 (38%)	29 (62%)
Platinum-based chemotherapy	16	8 (50%)	8 (50%)
Nonplatinum-based chemotherapy	32	11 (34%)	21 (66%)
INTENSIVE	43	28 (65%)	15 (35%)
Platinum-based chemotherapy	38	24 (63%)	14 (37%)
Nonplatinum-based chemotherapy	5	4 (80%)	1 (20%)

Table 7. Chemotherapy duration and frequency of transfusions.

Months	Patients n.	Transfusions	
		yes	no
After 3 months	99	45 (45%)	54 (55%)
>8 months	25	17 (68%)	8 (32%)

postponing blood transfusion may be due to potential risks associated with transfusion, such as transmitting infections, iron loading, and haemolytic reactions.

The real role of alternative treatment, such as the use of recombinant human erythropoietin, need to be clarified as anemia in children with cancer appears to be associated with decreased erythropoietic activity due directly to cytotoxic effect of chemotherapy rather than inadequate production of erythropoietin, in contrast with the pathogenesis of anemia in adults [2,10-13].

In this study, in order to assess the role of the chemotherapy regimens in predicting the risk of blood transfusion alone, patients with metastatic disease were left out, since it may affect the probability of requiring transfusion. Furthermore, children that experienced disease progression were removed from the study since low performance status may be a confounding factor in contributing to anemia. However, other co-morbidity factors, such as nutritional status or infections, may also be potential confounders. It is often difficult to predict which patients will develop anemia and require treatment. Our findings have assessed that the likelihood of receiving a transfusion is significantly related to the intensity of antineoplastic treatment. Additionally, the duration of the treatment and the administration of platinum compounds appear to be important factors in the onset of anemia.

Other studies have shown that patients receiving platinum-based regimens frequently require transfusions [14].

In conclusion, our data confirm that CT-induced anemia is a common complication of the myelosuppressive treatment in children with cancer. A significant percentage of patients receiving cytotoxic chemotherapy will become anemic and many will receive blood transfusions. Currently, transfusion is the standard treatment but larger randomized clinical trials are needed to ascertain the therapeutic role of human recombinant erythropoietin in the treatment of CT-induced anemia.

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