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ORIGINAL ARTICLE

Chemotherapy-related toxicity in childhood neoplasia

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Summary

Purpose: *To evaluate the incidence and time of occurrence of chemotherapy-related toxic events in 100 children admitted to the Hematology-Oncology Ward of "Sfanta Maria" Children's Emergency Hospital in Iasi, Romania, over a 4-year period.*

Methods: *An analytical, descriptive and comparative, retrospective and prospective study covering a 4-year period on the incidence of chemotherapy side effects, was performed on 100 children admitted for solid tumors or hematologic malignancies. The probability of each adverse event to appear and the time period from chemotherapy initiation to the moment of side effect appearance were assessed.*

Results: *The most frequent toxicity was alopecia (79.5%), followed by medullary aplasia (71.1%), oral candidiasis (65.3%), diarrhea and emesis (64% each), toxic hepatitis (61%), and Cushing's syndrome (21.5%). Oral herpes and thrush were less frequent (13.2% and 12.2%, respectively). Remissions of the underlying disease were achieved in 69.9% of the cases. Alopecia, medullary aplasia and oral candidiasis developed during the first 14 months of treatment. Mucositis, emetic syndrome and toxic hepatitis were diagnosed within the first 12 months of treatment. Diarrhea and oral herpes or thrush appeared during the first 15 months, while Cushing's syndrome developed during the first 6 months. All remissions were obtained during the first 4 months of treatment.*

Conclusions: *While alopecia and medullary aplasia were the most frequent side effects of chemotherapy in our study group, the earliest were Cushing's syndrome, emetic syndrome and toxic hepatitis.*

Key words: *chemotherapy, childhood, neoplasia, toxicity*

Introduction

Cancer accounts for 10% of all deaths in childhood, and leukemia is the most frequent malignancy in children (20-30% of childhood neoplasias) [1]. After the first temporary remission in acute lymphoblastic leukemia (ALL) obtained by Farber et al. using a folic acid antagonist in 1948 [2], agents like corticosteroids, 6-mercaptopurine, vincristine, methotrexate (MTX), L-asparaginase and anthracyclines (doxorubicin and daunorubicin) were discovered in 1950s and 1960s. Thereafter, the first clinical trials demonstrated that combinations of two or more agents were superior to single-agent chemotherapy [3].

Therapeutic regimens for the treatment of hematologic malignancies and solid tumors create complications like febrile neutropenia, nausea, infusion reactions, mucositis, diarrhea, anemia/pancytopenia from medullary aplasia, neuropathy, arthropathy, cardiomyopathy, second malignancy, iatrogenic Cushing's syndrome, toxic hepatitis, digestive candidiasis, with variable incidence and severity.

This article estimated the incidence and the time of onset of various types of chemotherapeutic complications for leukemia, lymphoma or solid tumors in children.

Methods

We performed an analytical, descriptive and comparative, retrospective and prospective study covering a 4-year period which involved 100 children admitted to the Hematology-Oncology Ward of Children's Emergency Hospital in Iasi.

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All the data were retrieved from the Hospital's registry system. The evaluated parameters included cancer type and the time lapse (months) until one or more of the following chemotherapy adverse reactions occurred: Cushing's syndrome, alopecia, mycositis, medullary aplasia, diarrhea, toxic hepatitis, candidiasis, emetic syndrome, herpes or thrush. Time to disease remission (months) was also evaluated.

Because age at disease onset is correlated with different risks, children were divided into 4 age groups: 0-3, 4-6, 7-10 and 11-18 years.

Statistics

We used the Kaplan-Meier method to estimate the probabilities for events to appear and the time interval from the beginning of chemotherapy administration until 25%, 50% or 75% (quartiles) of the patients developed the side effect in question. We chose Kaplan-Meier method because it allows to measure time intervals and because it has the advantage of being able to extrapolate data even if information is incomplete (not all patients developed all side effects, therefore quartiles might not be possible to be estimated in some cases). Comparisons of Kaplan-Meier curves were performed using log-rank test. Standard error and 95% confidence interval (95% CI) were also used. Statistical significance was set at $p<0.05$. The analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL).

Results

The study group consisted of patients with acute lymphoid leukemia (ALL) (47%), Hodgkin's lymphoma (9%), osteosarcoma (9%), neuroblastoma (8%), non-Hodgkin's lymphoma (8%), Wilms tumor (7%), acute myeloid leukemia (AML) (4%), chronic lymphoid leukemia (CLL) (2%), myelodysplastic syndrome (1%), PNET tumor (1%), ovarian tumor (1%), histiocytosis (1%), fibrosarcoma (1%) and gastric tumor (1%). There were 29 children aged 0-3 years, 21 aged 4-6 years, 13 aged 7-10 years and 37 aged 11-18 years.

Cushing's syndrome

All iatrogenic Cushing's syndrome cases appeared during the first 6 months of treatment, except for one case (36 months). Because only 21.5% of the patients developed this complication, the quartiles could not be estimated (Figure 1).

Alopecia

All cases of post chemotherapy alopecia appeared during the first 14 months, except one case that appeared at 48 months. Fifty percent of the cases appeared during the first 4 months and 25%

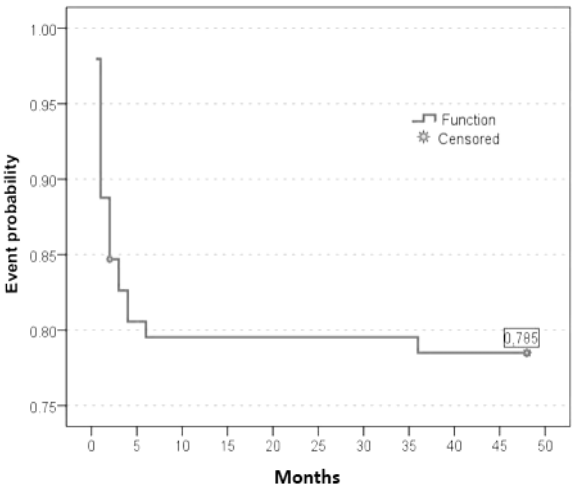

Figure 1. Time evolution curve of the event of patients not having Cushing's syndrome (78.5%).

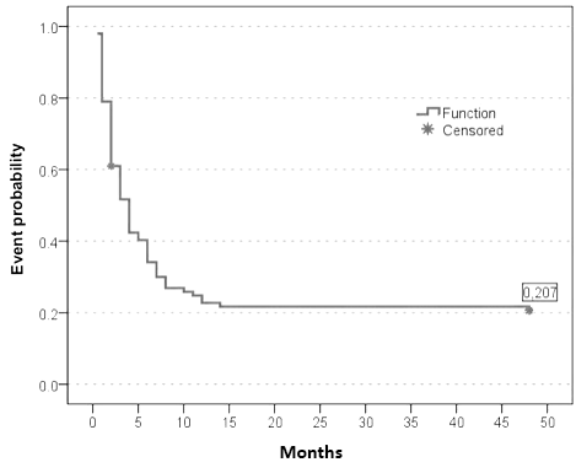

Figure 2. Time evolution curve of the event of patients not having alopecia (20.7%).

appeared during the first 2 months and 75% during the first 11 months. In total 79.3% of the patients developed alopecia (Figure 2).

Mucositis

Mucositis developed in 65.3% of the patients. This condition appeared during the first 12 months of treatment. Half of the cases appeared during the first 3 months and 25% during the first month (Figure 3).

Medullary aplasia

All cases of medullary aplasia appeared during the first 14 months, except a single case, which appeared at 48 months. Fifty per cent of the cases appeared during the first month. The total percentage of this complication was 71.1% (Figure 4).

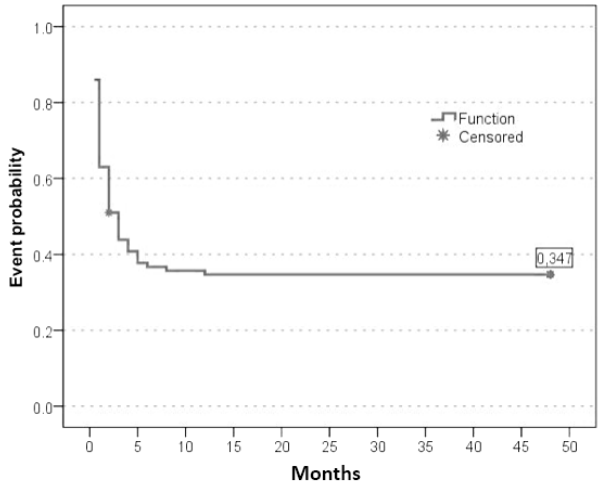

Figure 3. Time evolution curve of the event of patients not having mucositis (34.7%).

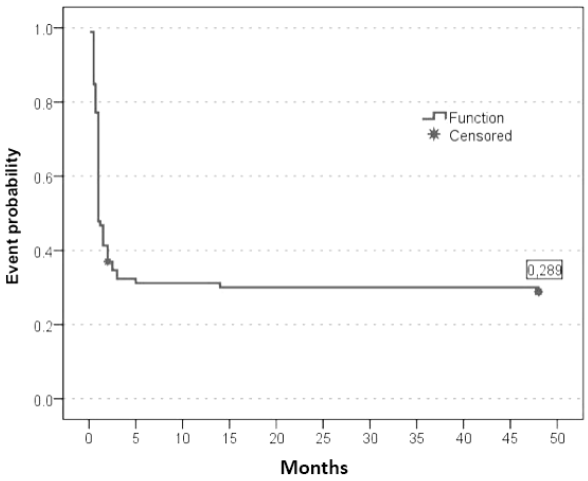

Figure 4. Time evolution curve of the event of patients not having medullary aplasia (28.9%).

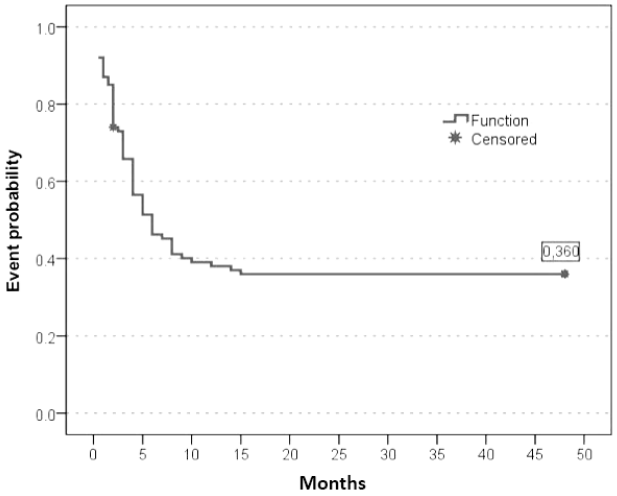

Figure 5. Time evolution curve of the event of patients not having diarrhea (36%).

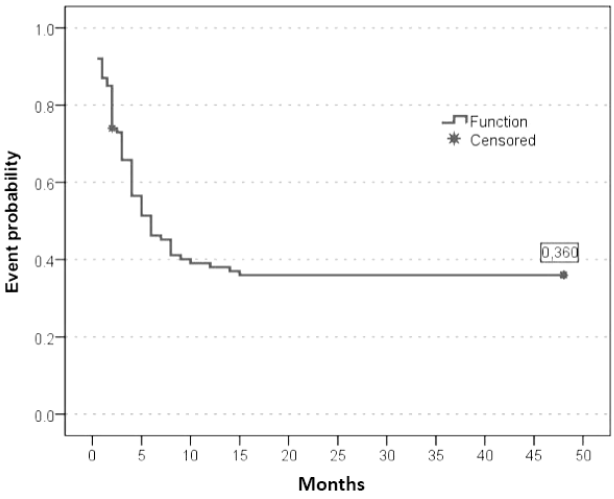

Figure 6. Time evolution curve of the event of patients not having toxic hepatitis (39%).

Diarrhea

All diarrhea cases appeared during the first 15 months of therapy. Fifty per cent of the cases developed during the first 6 months and 25% during the first 2 months. Sixty four per cent of all patients developed post chemotherapy diarrhea (Figure 5).

Hepatitis

Sixty one per cent of the patients developed toxic hepatitis and all cases appeared during the first 12 months, except one case that appeared 48 months after the beginning of treatment. Fifty per cent of the cases appeared during the first 10 months and 25% appeared during the first 2 months (Figure 6).

Candidiasis

All candidiasis cases appeared during the first 14 months of treatment. Only 12.2% of the patients developed this complication, therefore quartiles could not be estimated (Figure 7).

Emesis

Chemotherapy-induced emetic syndrome appeared in 64% of the patients. All cases appeared during the first 12 months, 50% of the cases during the first 4 months and 25% of the cases during the first 2 months (Figure 8).

Herpes/thrush

Post chemotherapy oral herpes or thrush appeared in 13.2% of the patients. All cases appeared during the first 15 months (Figure 9).

Remission

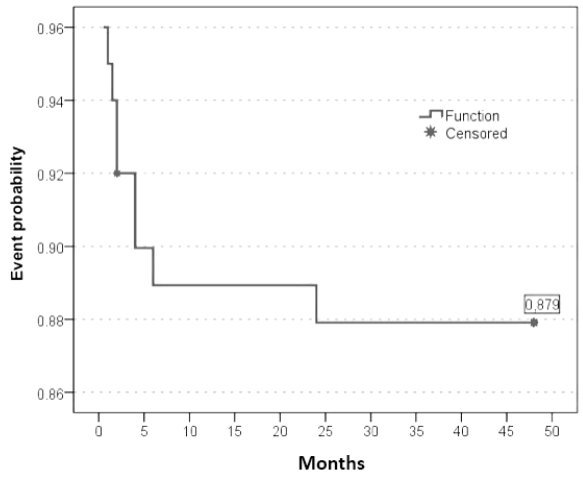

Figure 7. Time evolution curve of the event of patients not having digestive candidiasis (87.9%).

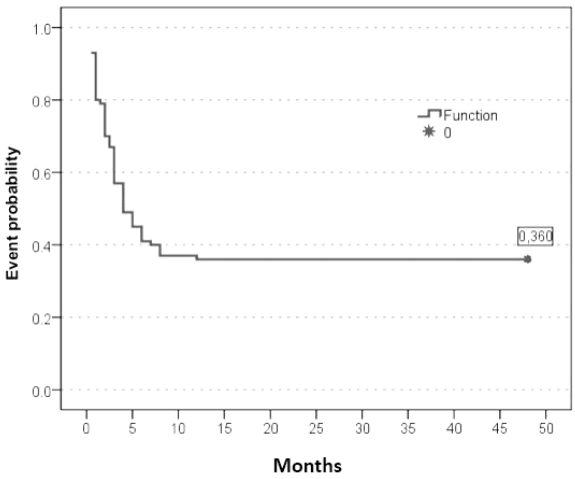

Figure 8. Time evolution curve of the event of patients not having emetic syndrome (36%).

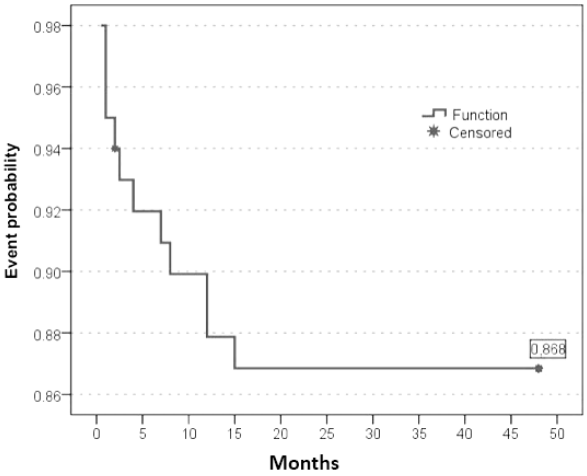

Figure 9. Time evolution curve of the event of patients not having oral herpes or thrush (86.8%).

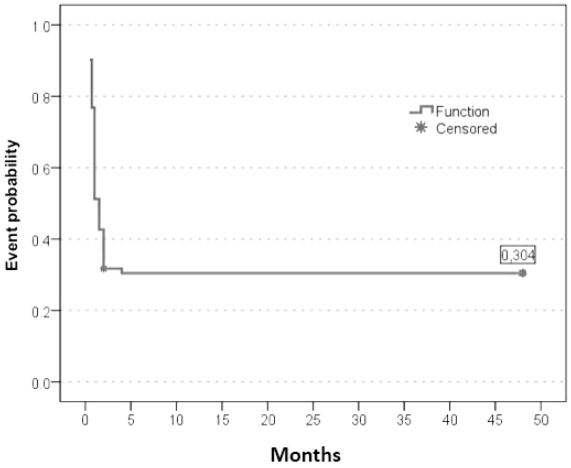

Figure 10. Time evolution curve of the event of patients not having remission of malignancy (30.4%).

Remission of the underlying malignancy occurred in 69.6% of the patients. All cases with remission appeared during the first 4 months of chemotherapy. Fifty per cent of the cases appeared during the first 1.5 months and 25% during the first month of treatment. Remissions occurred in leukemia and lymphoma patients, not in those with solid tumors, thus, due to study group heterogeneity, the remission rate was relatively low (Figure 10).

Event comparison

Cushing's syndrome, emesis and toxic hepatitis were the earliest side effects. Alopecia and medullary aplasia were the most frequent side effects while oral herpes or thrush and oral candidiasis were the most infrequent side effects (Figure 11).

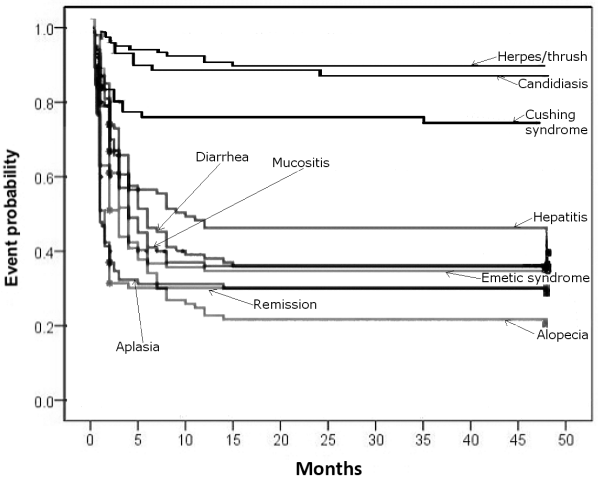

Figure 11. Comparison between time evolutions of all studied events.

Discussion

Iatrogenic Cushing's syndrome often has a reserved prognosis due to corticoid resistance [4]. Adrenocorticotropic hormone (ACTH) can be excessively produced within the frame of a paraneoplastic syndrome. Alternatively, Cushing's syndrome may develop as a direct effect of high prednisone dosage included in some chemotherapy regimens. Neoplasm-induced ACTH may have a different structure from endogenous ACTH and immunohistochemical staining using polyclonal anti-ACTH antibodies may not be useful in tumor cells [5].

The incidence of post chemotherapy alopecia reported by several authors [6], is 65%, this percentage being in accordance with our study. Women and children have marked difficulties in coping with this side effect, sometimes either declining therapy or asking to stop it [7,8]. The process begins in weeks 2-4 of treatment and may be complete in 1-2 months [9].

Oral mucositis may limit the dose of some chemotherapeutic drugs. The incidence of mucositis is 31-85%, even higher if cervical region radiotherapy is delivered [10,11]. Intestinal mucositis quantification is difficult, with diarrhea as its sole clinical sign, as well as a non-specific one. Oral mucositis is associated with infectious episodes and gastrointestinal mucositis is accompanied by infection and bleeding [12]. The incidence of mucositis is higher in immunocompromised patients [13]. Ulcerative lesions may become infected with bacteria, viruses (herpes or thrush), and fungi (candidiasis); in our study, the incidence of these complications was 12.2% for oral candidiasis and 13.2% for herpes or thrush.

Medullary aplasia is a feared complication of many chemotherapeutic regimens. For instance, the average duration of febrile neutropenia after induction therapy in AML is 11-31 days [14,15], depending on the cytotoxic agent administered, hematopoietic growth factors used [16], patient age [17,18] and myelodysplasia [19,20]. In some studies 3-29% of the patients died of medullary aplasia [21,22]. This condition predisposes to infection, and during the last decades the etiology of infections has shifted from Gram-negative to Gram-positive microorganisms [22].

Toxic hepatic injuries consist of necrosis, steatosis, fibrosis, cholestasis and vascular lesions [23] and may be caused either by chemotherapy or by supportive medications including antibiotics, analgesics, and antiemetics. Preexisting conditions, tumors, immunosuppression, hepatitis viruses, nutritional deficiencies or total parenteral nutrition may influence patient susceptibility to hepatic toxic injuries. Therefore, it is difficult to attribute hepatic injury to toxic reactions solely [24,25]. Many hepatotoxic reactions are idiosyncratic, due to immunologic mechanisms of the host [26] and often they are not dose-dependent.

In our study, emetic syndrome did not always appear from the first chemotherapy administration. Nausea and vomiting may become worse from one administration to another [27,28] and may be so severe that the patient requests treatment withdrawal [29-32]. Nausea and vomiting may be acute, delayed or anticipatory. The most pro-emetic chemotherapeutics are cisplatin, carboplatin and doxorubicin [33].

The global remission rate of malignancies in our study was 69.6%, but one must consider the heterogeneous pathologies. If in the literature the remission rate of ALL could be as high as 85%, [34], statistics show remission in myelodysplastic syndromes may be as low as 28% [35].

Conclusion

The most frequent form of chemotherapy-related toxicity in children was alopecia (79.3%), appearing during the first 14 months of treatment, followed by medullary aplasia (71.1%), occurring in the same time interval, and mucositis (65.3%), occurring within the first 12 months of treatment. Diarrhea and emetic syndrome appeared in 64% of the cases each, during the first 15 and 12 months, respectively. Toxic hepatitis developed in 61% of the patients, during the first 12 months of treatment and Cushing's syndrome appeared in 21.5% of the cases, all of them during the first 6 months. Oral herpes or thrush and oral candidiasis were less frequent (13.2% and 12.2%, respectively) and appeared during the first 15 and 14 months, respectively. Remissions of malignancies were obtained in 69.6% of the cases, all of them during the first 4 months of treatment. While alopecia and medullary aplasia were the most frequent side effects, the earliest ones were Cuhsing's syndrome, emetic syndrome and toxic hepatitis.

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