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## High-risk febrile neutropenia and its management in children with solid tumors and lymphoma

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**Background/aim:** The clinical characteristics and treatment results of febrile neutropenia attacks that occurred in patients with lymphoma and solid tumors were analyzed.

**Materials and methods:** A total of 50 patients with 94 high-risk attacks were evaluated for malignant diseases in this study.

**Results:** The fever etiology was determined as clinical (50%), microbiological (5.31%), clinical-microbiological (5.31%), or unknown (39.3%). A few of the attacks (21.3%) were observed in lymphoma cases and 77.7% were observed in patients with solid tumors. Patients who were in remission had 59.6% of the attacks, and 39.4% occurred in patients not in remission. Among the groups tested, 73% (the imipenem/amikacin group) and 47.9% (the piperacillin-tazobactam/amikacin group) of patients were in remission. Glycopeptide addition rates in these groups were 22.2% and 40.8% and antifungal addition rates were 8.8% and 18.3%, respectively.

**Conclusion:** Clinical progress was more problematic in patients who were not in remission during the attacks. This was due to the fact that some patients had other factors that placed them in the high-risk group, as well as increased C reactive protein and procalcitonin values on the first day. Therefore, it may not be accurate to associate the success achieved in the different treatment regimens with antibiotics alone.

**Key words:** Childhood, febrile, high risk, neutropenia

### 1. Introduction

Neutropenia is a condition where the absolute neutrophil count (ANC) is lower than 1500 cells/ $\mu$ L or is expected to drop below 500 cells/ $\mu$ L within a 48-h time period. When classifying the condition, 1000–1500 ANC/ $\mu$ L is accepted as mild, 500–1000 ANC/ $\mu$ L is accepted as intermediary, and less than 500 ANC/ $\mu$ L is accepted as severe neutropenia. On the other hand, neutropenic fever is a condition where the body temperature is greater than 38 °C for more than 1 h or is measured to be higher than 38 °C twice during a 12-h period (1). The signs and occurrence of infection in a neutropenic patient are also evaluated as febrile neutropenia (FN), even if there is no fever (2).

In this study, clinical characteristics, treatment results of the FN attacks occurring in our patients with lymphoma and solid tumors factors treated due to FN, and factors influencing clinical pursuit and treatment results were compared with the literature.

### 2. Materials and methods

#### 2.1. Ethical declaration

Ethical approval of the study was granted by the scientific research ethics board of our university.

#### 2.2. Patients

In this study, 94 high-risk FN attacks that occurred in 50 pediatric patients were examined retrospectively. Patients with lymphoma and solid tumors received chemotherapy for malignant disease in the Pediatric Hematology and Oncology Clinic between the years of 2011 and 2013.

#### 2.3. Criteria for exclusion from the study

Patients with one of the following factors were excluded from the study: leukemia, a neutrophil count and fever that did not comply with the criteria described below, the source of fever being thought to be noninfectious, the patient being older than 18, the patient having had received antibiotics during the last 10 days, and the administration of glycopeptide (GP) at the beginning.

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## 2.4. Clinic and laboratory evaluation

When patients with FN were admitted to our clinic, their histories were evaluated rapidly and physical examinations were made. Afterwards, materials were taken for complete blood, biochemical (glucose, urea, creatinine, transaminase, electrolytes, lactate dehydrogenase, and alkaline phosphatase), peripheral smear, C reactive protein (CRP), procalcitonin (PCT), and complete urine and culture tests (blood and from the other suspected regions) and direct chest radiography. Body temperature was measured and accepted as fever if the temperature was greater than 38 °C at least once or measured to be greater than 37.5 °C for longer than 1 h by an axillary method. In addition, neutropenia was diagnosed when ANC levels were less than 500 cells/mm<sup>3</sup>.

Patients were placed in the high-risk group (Group 1) if the ANC value was less than 100 cells/mL with the expectation of it lasting more than 7 days, liver or renal failure (aminotransferase levels >5 times normal or creatinine clearance <30 mL/min, respectively), hemodynamic instability, mucositis causing swallowing malfunction, abdominal pain, nausea, vomiting, diarrhea, newly beginning neurological and mental situation changes, intravascular catheter infection, new pulmonary infiltrations, hypoxemia and underlying chronic lung illness, infant acute lymphoblastic leukemia, acute myeloid leukemia, or being in the first 30 days following a stem cell transplantation.

First, antibiotic dosages were administered within approximately 1.5–2 h after the patients applied to the hospital. On the following 3rd, 5th, and 7th days, complete blood counts and peripheral smear tests were repeated. In addition, CRP and PCT tests were repeated on the seventh day. The etiology of the fever was classified as clinical, microbiologic, clinical-microbiological infection, or fever with unknown reasons.

## 2.5. Antibiotherapy

The selection of antibiotics that were administered was completely random. A regime [imipenem/amikacin (IA)] was applied for all patients between certain dates. Later, another regime [piperacillin-tazobactam/amikacin (PA)] was applied. Clinical treatment success was accepted if there were no signs of fever for 5 days, no need for modification of the treatment, loss of clinic and laboratory symptoms, eradication of the developed bacteria, and nonrecurrence of the infection in the first 7 days after cessation of the treatment. On the other hand, failure was determined if the patient died, had persistent bacteremia or new bacterial production, and if there was any modification or addition to the initial treatment. If there were indications that it was necessary (1), or if fever persisted longer than 72 h, then GP was added to the initial treatment (3). When fever persisted until the end of the fifth day, thorax tomography

was conducted and an antifungal (AF) was included in the treatment (3). Among the medicines, imipenem was administered as 15 mg/kg per dose (4 doses), piperacillin-tazobactam as 80 mg/kg per dose (4 doses), amikacin as 7.5 mg/kg per dose (2 doses), liposomal amphotericin B as 4 mg/kg per dose (1 dose), voriconazole as 7 mg/kg per dose (2 doses), and caspofungin as 70 mg/m<sup>2</sup> per dose on the first day and 50 mg/m<sup>2</sup> per dose (1 dose) later.

## 2.6. Duration of the treatment

No modification was made in the initial treatment for patients whose fever dropped during the first 3 days if there was no growth in their cultures as well. Once the ANC was greater than 500 µL, the treatment was continued for at least 48 h. Clinical symptoms and patient recovery were evaluated for the decision to terminate the treatment. Treatment was continued for at least 4–5 days after the patient's ANC value increased above 500 cells/µL. If the fever still did not drop GP and AF were added to the initial treatment as long as there was no growth in the cultures. The treatment was discontinued when there was clinical improvement in patients (the ANC was determined as under 500 cells/µL at the end of the 14th day).

## 2.7. Statistical analysis

Statistical analysis of the study was done using SPSS 16. In group comparisons for parameters for which a normal distribution approach could not be achieved, the Mann-Whitney test was used as a nonparametric test.

For parameters for which a normal distribution approach could be achieved, an independent t-test was used as a parametric test. Categorical data were analyzed using a crosstabs Fisher exact test. Correlation coefficients for some related parameters were evaluated by the Spearman rank correlations technique and some identifier characteristics were evaluated by the aid of identifying statistical tests.  $P < 0.05$  was accepted as statistically significant.

## 3. Results

The sex representation of our study was 46% boys and 54% girls. Attacks occurred in 52.1% of the boys and 47.9% of the girls. A few of the attacks (21.3%) were observed in lymphoma cases and 77.7% were observed in patients with solid tumors. There was no significant difference determined in any of the parameters when values of these groups were compared.

In 56.4% of all attacks, the number of risk factors placing the patients in the high-risk group was greater than 3. In this group, the number of days with fever and AF starting rates were significantly higher in comparison to the other group (Table 1).

Patients who were not in remission had 39.4% of the attacks. In this group, initial creatinine (Cr) and CRP values on the 1st and 7th days, PCT values on the 7th day, and number of days with fever were significantly high.

**Table 1.** Parameters found as significant when compared according to the number of risk factors patients had ( $\leq 2$  and  $\geq 3$ ).

Parameter	NRF $\leq 2$ (42.6%)		NRF $\geq 3$ (56.4%)		P-value
	Mean	Interval	Mean	Interval	
DWF	2.2 $\pm$ 1.6	1.0–7.0	3.1 $\pm$ 2.1	1.0–7.0	0.020
AF given	5.0%		20.8%		
AF not given	95.0%		79.2%		0.027

AF: Antifungal, DWF: number of days with fever, NRF: number of risk factors.

In the same group, AF starting rates and the number of factors placing the patients in the high-risk group were significantly high (Table 2).

The reason for the fever was evaluated as clinical in 50% of the attacks, microbiological in 5.31%, and clinical-microbiological in 5.31%. The cause of the fever was not able to be determined in 39.3% of the attacks (Table 3).

PCT values on the 1st and 7th days, number of days with fever, and AF starting rates were significantly higher in the group who had a CRP level of  $>100$  mg/L on the first day (Table 4).

In the group that had PCT values greater than 0.61 ng/mL, the CRP values on the 1st and 7th days along with the number of days with fever were significantly high. On the first day, thrombocyte values were significantly low. In addition, the AF starting rate and the number of factors placing the patients in the high-risk group were significantly increased in the same group (Table 5).

Patients who started with PA as an initial treatment had significantly higher CRP values on the 1st and 7th days, PCT values on the 7th day, and number of days with fever when compared to the other group. A majority of the patients in the IA group were in remission (73.3%), while in the PA group this percentage was 47.9% (Table 6).

The number of total attacks for which IA was started was 45 (40% of total). Out of these, 22.2% were administered GP initially and 4 of these 40% were started with AF. When 45 patients were evaluated, the AF starting rate was 8.8% in this group. The number of total attacks for which PA was started was 49. Out of these, 40.8% were administered GP initially, and 45% started with AF. When a calculation was made based on 49 patients, the AF starting rate in the group receiving PA was 18.3%. Of all attacks, 13.8% were given AF treatment. CR and CRP values on the 1st and 7th days, PCT values on the 7th day, and number of days with fever and neutropenia in patients receiving AF were

**Table 2.** Parameters found as significant when attacks of those whose malignant diseases were in remission or not in remission were compared.

Parameter	Those in remission (59.6%)		Those not in remission (39.4%)		P-value
	Mean	Interval	Mean	Interval	
Cr (mg/dL)	0.5 $\pm$ 0.2	0.3–1.4	0.6 $\pm$ 0.2	0.4–1.9	0.045
Day 1 CRP (mg/L)	46.3 $\pm$ 45.7	2.0–168	82.6 $\pm$ 57.8	4.0–204.0	0.001
Day CRP 7 (mg/L)	19.7 $\pm$ 27.6	2.0–142	59.2 $\pm$ 67.3	2.0–211.0	<0.001
Day 1 PCT (ng/mL)	0.2 $\pm$ 0.4	0.01–2.8	2.3 $\pm$ 4.1	0.05–16.2	0.001
DWF	2.3 $\pm$ 1.5	1.0–7.0	3.3 $\pm$ 2.2	1.0–7.0	0.018
NRF ( $\leq 2$ )	53.6%		27.0%		
NRF ( $\geq 3$ )	46.4%		73.0%		0.010
AF given	7.1%		24.3%		0.022
AF not given	92.9%		75.7%		

AF: Antifungal, Cr: creatinine, CRP: C reactive protein, DWF: number of days with fever, NRF: number of risk factors, PCT: procalcitonin.

**Table 3.** Fever etiology, diagnostic method, rates, produced effects, and production locations in all patient groups.

Diagnosis method of infection					
Clinical	Microbiological		Clinical-microbiological		FUO
n = 47 (50%)	n = 5 (5.31%)		n = 5 (5.31%)		n = 37(39.3%)
Infection area	The field produced	Agent produced	Infection area	The field produced	Agent produced
URT: 39	Blood	<i>Str. oralis</i>	GIS	Blood	SE
GIS: 6	Urine	EC	URT	Blood	<i>Klebsiella</i>
LRT: 2	Urine	EC	URT	Blood	SE
	Urine	EC	URT	Blood	SE
	Urine	Enterococci	URT	Urine	EC

EC: *Escherichia coli*, FUO: fever of unknown origin, GIS: gastrointestinal system, LRT: lower respiratory tract, SE: *Staphylococcus epidermidis*, URT: upper respiratory tract.

**Table 4.** Parameters found as significant when patients were compared according to day 1 CRP.

Parameter	CRP = 5.1–100 (72.9%)		CRP > 100 (27.1%)		P-value
	Mean	Interval	Mean	Interval	
Day 1 PCT (ng/mL)	1.1 ± 3.8	0.07–28.1	5.5 ± 16	0.1–75.0	0.046
Day 1 PCT (ng/mL)	0.6 ± 2.3	0.04–16.2	2.5 ± 3	0.05–12.1	0.015
DWF	2.4 ± 1.8	1.0–7.0	3.7 ± 2	1.0–7.0	0.008
AF given		9.7%		30.4%	0.025
AF not given		90.3%		69.6%	

AF: Antifungal, CRP: C reactive protein, DWF: number of days with fever, PCT: procalcitonin.

**Table 5.** Parameters found as significant when patients are compared according to day 1 PCT.

Parameter	PCT = 0.11–0.60 (66.3%)		PCT ≥ 0.61 (33.7%)		P-value
	Mean	Interval	Mean	Interval	
Day 1 CRP (mg/L)	42.3 ± 43	2.0–163.0	101.3 ± 48	21.0–204.0	<0.001
Day 7 CRP (mg/L)	18.4 ± 30	2.0–192.0	68.6 ± 67	2.0–211.0	<0.001
Day 1 PLT	78.9 ± 57	3000–233,000	54.3 ± 47	7000–195,000	0.043
DWF	2.3 ± 1	1.0–7.0	3.8 ± 2	1.0–7.0	0.003
NRF (≤2)		49.1%		27.6%	0.045
NRF (≥3)		50.9%		72.4%	
AF given		7.0%		31.0%	0.005
AF not given		93.0%		69.0%	

AF: Antifungal, CRP: C reactive protein, DWF: number of days with fever, NRF: number of risk factors, PCT: procalcitonin, PLT: platelets.

**Table 6.** Parameters with significant differences when the values of the groups treated with IA and PA were compared.

Parameter	IA (47.9%)		PA (51.1%)		P-value
	Mean	Interval	Mean	Interval	
Day 1 CRP (mg/L)	49.3 ± 47.5	2.0 - 204.0	71.8 ± 57	4.0–175.0	0.044
Day 7 CRP (mg/L)	23.1 ± 41.4	2.0 - 211.0	46.2 ± 56	2.0–201.0	0.034
Day 7 PCT (ng/mL)	0.3 ± 0.5	0.01–2.8	1.8 ± 3	0.04–16.2	0.011
DWF	2.2 ± 1.8	1.0–7.0	3.2 ± 2	1.0–7.0	0.012
Those in remission		73.3%		47.9%	0.011
Those not in remission		26.7%		52.1%	

CRP: C reactive protein, DWF: number of days with fever, IA: imipenem/amikacin, PA: piperacillin-tazobactam/amikacin, PCT: procalcitonin.

significantly higher in comparison to the group that did not receive AF (Table 7).

#### 4. Discussion

It was previously reported that FN was found most frequently in hematological malignancies (4), osteosarcoma, and Ewing's sarcoma (ES) (5). In our study, attacks were determined most frequently in non-Hodgkin lymphoma, ES, and rhabdomyosarcoma, respectively. When the number of attacks per patient was evaluated, the ranking changed to rhabdomyosarcoma, ES, and neuroblastoma. When the values of the patients with lymphoma and other solid tumors were compared, there was no significant difference determined in any of the parameters. The situation and ranking differences observed in the studies indicate that malignancy type is not a determinant for FN on its own.

The patients were divided into 2 risk groups: high and low, based on the evaluations (1). In our study, it was determined that the number of days with fever

and, therefore, the AF starting empirical rate increased significantly as the number of factors placing the patients in the high-risk group increased. Because of this, we propose that the risk factor number may give us ideas about the clinical course that may be encountered and may guide the selection of initial antibiotic.

Patients whose malignant diseases were not in remission were placed in the high-risk group according to their treatment guides (1). In our study, it was observed that the CRP value on the 1st day, number of days with fever, and AF onset rates were higher in the patients who were in nonremission for malignant disease. This situation was probably caused by severe myelosuppression originating from the increase in the chemotherapeutic medicine load, resulting from chemotherapy protocol extension or changes to new protocols. Furthermore, the fact that a difference occurred on the 7th day, when there was no difference between the 1st day PCT values of both groups, made us think that the patients who were in remission reached lower PCT values on the 7th

**Table 7.** Parameters estimated to be significantly different when the values of the patient groups receiving AF and not receiving AF were compared.

Parameter	AF given (13.8%)		AF not given (85.1%)		P-value
	Mean	Interval	Mean	Interval	
Day 1 CRP (mg/L)	105.1 ± 49	18.0–175.0	53.3 ± 50	2.0–204.0	0.001
Day 7 CRP (mg/L)	112.5 ± 64	14.0–201.0	22.3 ± 34	2.0–211.0	<0.001
Day 7 PCT (ng/mL)	4.2 ± 5	0.2–16.2	0.5 ± 1	0.01–9.4	<0.001
DWF	6.5 ± 0	1.0–7.0	2.1 ± 1	1.0–7.0	<0.001
Neutropenic days	6.4 ± 0	4.0–7.0	5.0 ± 1	2.0–7.0	0.001

AF: Antifungal, CRP: C reactive protein, DWF: number of days with fever, PCT: procalcitonin.

day and their responses to the treatment were better. In approximately 1/3 of all neutropenic attacks that developed after chemotherapy, fever occurred (6). Infection was not the root cause for approximately 31% of them (7). In approximately 50% of all the attacks, the infection was documented as microbiological and clinical (8). In our study, infection was identified as clinical in 50% of the attacks, microbiological in 5.31%, and clinical-microbiological in 5.31%. In 39.3% of attacks, the fever was accepted to be of unknown origin. Infections identified in FN (apart from blood) were reported as lung, skin and soft tissue, urinary system, sinus and oropharynx, skeletal system, enteric track, and meninx (9). In the present study, 52 attacks were determined as clinically infectious. Infection regions were the upper respiratory tract, gastrointestinal system, and lower respiratory track when ranked according to frequency. The number of attacks shown as microbiological was 10, and 5 of these 10 cases were of urine origin, while the rest were of blood origin.

Although gram-negative bacteria were the most frequent factors (10), increased usage of antimicrobial agents and venous catheters have contributed to an increase in gram-positive factors. It was reported that 46% of bacteremia attacks were gram-positive, 42% were gram-negative, and 12% were polymicrobial (10). However, gram-negative dominance was reported in Israel, Singapore (11), and Turkey (12), as well. The most frequent gram-positive pathogens are coagulase-negative *Staphylococcus*, *Streptococci viridans*, and *Staphylococcus aureus*. In bacteremic episodes caused by aerobic gram-negative bacilli, *Escherichia coli* was the factor in approximately 1/3 to 1/2 of the cases, as well as other contributors (including *Klebsiella* spp., *Pseudomonas* spp., *Acinetobacter* spp., and *Enterobacter* spp.) (13). In our study, 60% of the producible factors were gram-negative. Gram-negative pathogens were *Escherichia coli* (66.6%), *Klebsiella* (16.6%), and *Enterococcus* (16.6%). Gram-positive pathogens were *Staphylococcus epidermidis* (75%) and *Streptococcus oralis* (25%).

CRP elevation sensitivity in infection was 56%–100%. However, the 24–48 h required to see any significant increase and the interaction between the primary disorder and CRP are disadvantages for this marker (14). On the other hand, PCT increases in sepsis, multiple organ failure, and bacterial, fungal, and parasitic infections and remains extremely low in neoplastic disorders (15). Furthermore, its level is comparative to the degree of microbial invasion, and it increases rapidly in comparison to CRP (16).

In our investigation, the group with higher CRP values on the first day had PCT values on the 1st and 7th days that were significantly higher in comparison to the other group. The group with higher PCT values on the 1st day had CRP values on the 1st and 7th days that were significantly

higher in comparison to the other group. This illustrates that both parameters progress in parallel. They increase as an answer to infection and drop as an answer to treatment. In the groups with higher CRP and PCT values on the 1st day, the higher number of days with fever and higher AF administration rates illustrate that both parameters increase in parallel to the intensity of the infection and that 1st day values can give an idea about the expected clinical progress.

In our study, the initial CRP values were normal in 7.44% of all the attacks, and there was no need for the addition of GP in any of them. The lowest CRP value for which GP was added was 18.5 mg/L, and the lowest CRP value for which AF was added was 37.4 mg/L. On the other hand, the initial PCT values were normal in 5.31% of 94 attacks, and the need for modification arose only in 1 of them. In addition, the lowest PCT value for which AF was added was 0.29 ng/mL and the lowest PCT value for which AF was added was 0.30 ng/mL. The initial false negative values were close. Since there was a GP requirement in a patient with a normal PCT value, and the lowest PCT values for which GP and AF were added were close to each other, it was thought that CRP could be a little more advantageous in comparison to PCT in the current manifestation and for illustrating expected clinical progress. However, in the group with higher day 1 PCT values, the fact that the number of factors placing the patients in a high-risk group was greater implies an advantage on behalf of PCT as well.

In patients with neutropenia and bacteremia, the death rate was 40% during the first 48 h following identification of the fever (17), and the mortality diminished due to empirical antibiotic treatment that was started immediately (18).

Although gram-positive pathogens are more frequent, gram-negatives are more vital because of their virulence and their relationship with sepsis (19). Therefore, the Infectious Diseases Society of America proposed a combination of an aminoglycoside and an antipseudomonal beta-lactam in the initial empirical treatment for high-risk patients (3). The beta-lactam agent could be a 3rd or 4th generation cephalosporin, a beta-lactam with beta-lactamase inhibitor, or a carbapenem. On the other hand, if there are data available about sensitivity, the aminoglycoside should be gentamicin, tobramycin, or netilmicin. If sufficient data are lacking, amikacin should be used because it is the least resistance-developing member (20).

Piperacillin is a broad spectrum ureidopenicillin. Tazobactam is a beta-lactamase inhibitor and an effective agent against many gram-positive and gram-negative pathogens, including anaerobic pathogens and *Pseudomonas aeruginosa* (21). Carbapenems have excellent activity against both gram-negative and gram-positive

bacteria, including beta-lactamase-producing gram-negatives (22). Aminoglycosides used in combination may cause an increase in nephrotoxicity and ototoxicity, especially in patients receiving chemotherapy. However, the combination has advantages, such as a synergic effect and the prevention of resistance development (23).

Studies comparing piperacillin-tazobactam and carbapenems ( $\pm$ amikacin) (24), piperacillin-tazobactam and imipenem (12), piperacillin-tazobactam + amikacin, and meropenem + amikacin (25) have reported equal levels of efficiency in the initial treatment. On the other hand, there are reports indicating that they reduce mortality in comparison to other beta-lactams containing carbapenems or piperacillin-tazobactam (26). In addition, more modification is required in patients receiving piperacillin-tazobactam in comparison to those who receive carbapenem (24). In another investigation, success rates in the initial treatment were reported to be 31% for cases treated with piperacillin-tazobactam ( $\pm$ amikacin) and 42% (27) for those treated with carbapenems. In our study, the success rate with the initial treatment in the group that started with PA was 59.1%, and it was 77.8% in the group that started with IA. However, this could be the result of lower remission rates (47.9%) in the PA group in comparison to the IA group (73.3%). The significantly higher day 1 CRP values in PA-started attacks in comparison to the IA-started group supports this notion, as well.

Modification rates with GPs have risen from 5%–8% up to 20% during recent years in parallel with central venous

catheter utilization. AF addition rate is 3%–10% (28). In our study, GP addition rate was 31.9% and AF addition rate was 13.8%.

Mortality has dropped to 0.4%–1% in FN, owing to empiric antibiotic treatment and improvement in care opportunities (29). Only one person died among the patients included in our investigation. This patient was a 16-year-old male with ES diagnostics. PA was started as the initial treatment; however, GP and AF were also added to the treatment regime later on. This patient was not in remission, and the infection source determined in his last attack was the upper respiratory tract. However, the manifestation developed towards sepsis and the patient was lost. Therefore, the mortality rate in our investigation was determined to be 1.06%.

In this study, clinical progress was observed as more problematic in patients who were not in remission during attacks. This resulted in the placement of patients with a higher number of factors in the high-risk group with high day 1 CRP and PCT values. Thus, it may be beneficial to consider these factors in the selection of the initial antibiotic regime. On the other hand, it may not be accurate to attribute the success attained by various treatment regimens only to antibiotics. It is possible that the response gained from the treatment may be influenced by many factors, including the remission state of the patient, number of risk factors, infection type, total dosage of the administered chemotherapeutics, and their myelosuppressive effects.

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