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Research Article

Infectious complications in pediatric patients with hematologic malignancies

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Abstract. Objective: The present study was to determine the association between chemotherapy and infectious complications in pediatric patients diagnosed with HM. Material and Method: The study included 32 pediatric patients diagnosed with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), between January 2014 and December 2015. Patients were followed with a median of 49.7 (32.7; 62.8), after inclusion, infectious complications were reported. Data collected were: age, sex, type of infection, type of chemotherapy (induction, consolidation, maintenance). All patients received prophylactic treatment with antibiotics, antivirals and antifungal agents. For each infectious complication, microbiological diagnosis and the day of MH diagnosis were recorded. Results: The type and incidence of infectious complications in pediatric HM were: 31.3% bacterial infections, 50% fungal infections, 28.1% viral infections and 65.6% total infectious complications. In pediatric patients diagnosed with MH, we found the following: induction therapy with vincristine, L-asparaginase, Cytosar; reinduction therapy with: dexamethasone, doxorubicin, cyclophosphamide; maintenance therapy with: methotrexate and purinethol; first-line therapy with vinblastine, bleomycin and dacarbazine, as associated with a greater chance of developing fungal infections. In patients with pediatric MH we found: cytoreductive therapy with Cytosar and 6-thioguanine; induction therapy with Cytosar and etoposide; consolidation therapy with mitoxantrone and Cytosar; first line therapy with vinblastine, doxorubicin, bleomycin and dacarbazine, as more likely to develop bacterial infections. Conclusion: The highest risk of developing fungal and / or bacterial infections was in the case of induction therapy with Cytosar and first-line therapy with vinblastine, bleomycin and dacarbazine.

Key Words:pediatric patients, hematologic malignancies, infectious complications

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Introduction

Hematologic malignancies (HM) are a heterogeneous group of diseases that affect the immune system and represent 40% of pediatric neoplastic processes (Stiller et al 2006).

Transformation of a normal haematopoietic cell during hematopoiesis involves: an interruption during the normal proliferation and differentiation process, resistance to apoptosis signals and an augmentation of the self-renewal process that associates with mutations. Malignant hematopoietic cells accumulate persistently in the bone marrow and gradually replace hematopoietic cells (Jim et al 2017). This causes medullary failure, associated with severe anemia, bleeding and infection.

Infection is the second leading cause of death among pediatric oncology patients, and not only does it contribute to mortality, but it also delays chemotherapy, prolongs hospitalization, and requires the administration of costly and often toxic antimicrobial compounds (Lehrnbecher et al 2005).

Recent studies have shown an approximately 13% increase in the incidence of childhood cancer worldwide (Stelirova-Foucher et al 2017).

In the USA, the incidence of leukemias in children diagnosed with cancer is of 49.6% (Noone et al 2018), and in Europe 46.7% (Gatta et al 2014). Acute lymphoblastic leukemia (ALL) is the most common pediatric malignant hemopathy, accounting for about 25% of all childhood cancers and about 80% of childhood leukemias. Acute myeloid leukemia (AML) among children is less common than ALL and accounts for up to 20% of childhood leukemias.

In the USA, the incidence of lymphomas in pediatric patients diagnosed with cancer is of 25% (Noone et al 2018), and in Europe 12.3% (Gatta et al 2014). Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL) represent 11% of all cases of cancer diagnosed in children, twice as many cases being diagnosed in boys. HL accounts for about 45% of all lymphomas diagnosed in children; the incidence increases steadily after the age of 2 until the last years of childhood, when there is a much higher increase, more than two-thirds of all childhood HL being diagnosed in children aged 10-14 years. NHL represents more than half (53%) of all lymphomas in children, with a sudden increase in incidence in early childhood, followed by a gradual increase with age.

Infections in children with leukemia or lymphoma are polymicrobial (bacterial - gram positive and / or gram negative, viral and fungal) ranging from 5% to 60% of infections (Baily et al 2009). All studies have consistently reported that younger

patients appear to have an increased risk of infection than elderly patients (Bailey et al 2009; Alexander et al 2012).
Five-year or ten-year survival rates for pediatric malignant hemopathies have improved significantly since 1990(Rich et al 2012). For example, in the early 1970s, less than 10% of children with ALL survived for 10 years after diagnosis, while today 80% of children survive (Pulte et al 2008). This improvement in survival was attributed to the development of effective chemotherapy regimens, greater risk stratification, the use of targeted therapies and the progress in haematopoietic stem cell transplantation (Smith et al 2010).
The objective of this study was to determine the association between chemotherapy and infectious complications in pediatric patients diagnosed with HM.

Materials and methods

We conducted a cohort, prospective, observational, analytical, longitudinal study at Ion Chiricuta Institute of Oncology in Cluj-Napoca. The study included 32 patients from the Department of Pediatric Oncology diagnosed with HM , defined according to the International Classification for Childhood Cancer (Stellarova-Foucher 2005), between January 2010 and December 2015. The study protocol was approved by the Ethics Committee of Iuliu Hatieganu University of Medicine and Pharmacy.
Inclusion criteria were as follows: 1.patients diagnosed with ALL, AML, NHL, HL and treated according to protocols: ALL IC-BFM 2009, AML-BFM 2004, B-NHL BFM 2004, GPOH-HD 2002; 2.patients under the age of 18 at the time of diagnosis; 3. informed consent of the parent or guardian of the patient and / or of the patient in accordance with national law.
Exclusion criteria: 1. other simultaneous malignancies; 2. concomitant severe conditions (eg, immunodeficiency syndrome); 3. HIV positive; 4. pregnancy and / or lactation.
Patients were followed with a median of 49.7 (32.7; 62.8), and infectious complications were reported. Data collected were: age, gender, type of infection, type of chemotherapy (induction, consolidation, maintenance). All patients received prophylactic treatment with antibiotics, antivirals and antifungal agents. Infectious complications were diagnosed based on haemocultures, sputum cultures, nasopharyngeal cultures, vaginal cultures, stool cultures, central venous catheter tip cultures, thoracic radiographs and clinical examinations in accordance with current guidelines. For each infectious complication, microbiological diagnosis and the day of MH diagnosis were recorded. Statistical analysis was performed using the MedCalc statistical software version 17.5.5 (MedCalc Software bvba, Ostend, Belgium, http://www.medcalc.org, 2017). Nominal data was characterized by frequency and percentage. Differences between groups were tested using the Chi-square test or Fisher's test, as appropriate. The risk of infectious complications was estimated using the Kaplan-Meier method. A p value of less than 0.05 was considered statistically significant.

Results

Of the 32 pediatric patients with HM : 6 had AML, 8 had ALL, 7 had NHL and 11 had HL.
The type and incidence of infectious complications in pediatric HM were: 31.3% bacterial infections, 50% fungal infections, 28.1% viral infections and 65.6% total infectious complications. In the case of patients who developed fungal infections: 52.9% were boys and 46.7% were girls; 52.6% were from urban areas and 46.2% were from rural areas. Of the fungal infections, the most common was *Candida albicans* (13 cases), one case of *Candida krusei* and one case of *Candida famata*. Of patients with HL, 9.1% had fungal infections, compared with other diseases (71.4%) (p = 0.003).

Table 1. Patient characteristics

Variable		Cases (percentage)
Mean age		9 (7;13)
Gender	F	15 (46.87%)
	M	17 (53.13%)
Environment	U	19 (59.37)
	R	13 (40.63)
Pathology	AML	6 (18.75%)
	ALL	8 (25%)
	NHL	7 (21.87%)
	HL	11 (34.38)
Infections	Bacterial	10 (31.3%)
	Fungal	16 (50%)
	Viral	28.1%
	Total infections	65.6%

In pediatric patients diagnosed with MH, we found the following: induction therapy with vincristine, L-asparaginase, Cytosar; reinduction therapy with: dexamethasone, doxorubicin, cyclophosphamide; maintenance therapy with: methotrexate and purinethol; first-line therapy with vinblastine, bleomycin and dacarbazine, as associated with a greater chance of developing fungal infections (Table 2).
The mean age for bacterial infections was 7 (3.5; 10.5), compared with the mean age of those who did not have bacterial infections, which was 10.5 (7; 15) with a p value of 0.045, showing that younger patients have an increased risk of developing bacterial infections.
In terms of bacterial infections, there were 2 cases of infections with *Staphylococcus aureus* (nasal secretion, blood culture), *Staphylococcus hominis* (blood culture), *Clostridium difficile, Enterococcus faecalis* (blood culture, urine culture) and 1 case of infection with *Mycoplasma pneumoniae* (blood culture), *Koch bacillus* (sputum culture), *Pseudomonas aeruginosa* (sputum culture), *E. coli* (urine culture).
In patients with pediatric MH we found: cytoreductive therapy with Cytosar and 6-thioguanine; induction therapy with Cytosar and etoposide; consolidation therapy with mitoxantrone and Cytosar; first line therapy with vinblastine, doxorubicin, bleomycin and dacarbazine, as more likely to develop bacterial infections. [Table 3]
Herpes simplex virus (HSV) - 6 cases and varicella zoster virus (VZV) - 3 cases were the most common causes of viral infections. In HL there were 3 HSV cases, in NHL there were 2 HSV cases, and 1 case in AML.

Table 2. Factors associated with fungal infections in HM among children

Chemotherapy	Fungal infections (%)	No fungal infections (%)	p
Prednisone (induction)	11 (78.6)	5 (27.8)	0.01
Vincristine (induction)	12 (80)	4 (23.5)	0.005
Daunorubicin (induction)	11 (78.6)	5 (27.8)	0.01
Epirubicin (induction)	3 (60)	13 (48)	0.5
L-asparaginase (induction)	12 (80)	4 (23.5)	0.005
Cyclophosphamide (induction)	10 (76.5)	6 (31.6)	0.03
Cytosar (induction)	13 (72.2)	3 (21.4)	0.006
Etoposide (induction)	3 (75)	13 (46.4)	0.3
Purinethol (induction)	2 (66.7)	14 (48.3)	0.5
Dexamethasone (reinduction)	11 (84.6)	5 (26.3)	0.004
Vincristine (reinduction)	10 (76.9)	6 (31.6)	0.03
Doxorubicin (reinduction)	11 (78.6)	5 (27.8)	0.006
L-asparaginase (reinduction)	9 (81.8)	7 (33.3)	0.02
Cyclophosphamide (reinduction)	11 (78.6)	5 (27.8)	0.006
Cytosar (reinduction)	10 (76.9)	6 (31.6)	0.01
6-thioguanine (reinduction)	8 (72.7)	8 (38.1)	0.06
Methotrexate (consolidation)	10 (76.9)	6 (31.6)	0.03
Cytosar (consolidation)	5 (83.3)	11 (42.3)	0.08
Mitoxantrone (consolidation)	3 (75)	13 (46.4)	0.3
Purinethol (consolidation)	10 (76.9)	6 (31.6)	0.01
Methotrexate (maintenance)	12 (85.7)	4 (22.2)	0.001
Purinethol (maintenance)	12 (85.7)	4 (22.2)	0.001
Cytosar (cytoreductive)	3 (60)	13 (48.1)	0.5
6-thioguanine (cytoreductive)	3 (60)	13 (48.1)	0.5
Doxorubicin (first-line)	1 (11.1)	15 (65.2)	0.01
Bleomycin (first-line)	1 (10)	15 (68.2)	0.008
Pharmarubicin (first-line)	0	16 (51.6)	0.5
Adriblastin (first-line)	0	16 (51.6)	0.5
Vincristine (first-line)	0	16 (53.3)	0.2
Vinblastine (first-line)	1 (10)	15 (68.2)	0.008
Prednison (first-line)	0	16 (51.6)	0.5
Dexamethasone (first-line)	0	16 (59.3)	0.05
Hydrocortisone hemisuccinate (first-line)	0	16 (55.2)	0.1
Cyclophosphamide (first-line)	0	16 (53.3)	0.2
Etoposide (first-line)	0	16 (51.6)	0.5
Rituximab (first-line)	0	16 (51.6)	0.5
Dacarbazine (first-line)	1 (10)	15 (68.2)	0.008
Procarbazine (first-line)	0	16 (51.6)	0.5

Table 3. Factors associated with bacterial infections in HM among children

Chemotherapy	Bacterial infections (%)	No bacterial infections (%)	p
Prednisone (induction)	5 (35.7)	5 (27.8)	0.4
Vincristine (induction)	6 (40)	4 (23.5)	0.2
Daunorubicin (induction)	5 (35.7)	5 (27.8)	0.4
Epirubicin (induction)	4 (80)	6 (22.2)	0.04
L-asparaginase (induction)	6 (40)	4 (23.5)	0.2
Cyclophosphamide (induction)	6 (46.2)	4 (21.1)	0.1
Cytosar (induction)	10 (55.6)	0	0.003
Etoposide (induction)	4 (100)	6 (21.4)	0.006
Purinethol (induction)	1 (33.3)	9 (31)	0.6
Dexamethasone (reinduction)	5 (38.5)	5 (26.3)	0.3
Vincristine (reinduction)	4 (30.8)	6 (31.6)	0.6
Doxorubicin (reinduction)	5 (35.7)	5 (27.8)	0.4
L-asparaginase (reinduction)	5 (45.5)	5 (23.8)	0.1
Cyclophosphamide (reinduction)	5 (35.7)	5 (27.8)	0.4
Cytosar (reinduction)	6 (46.2)	4 (21.1)	0.1
6-thioguanine (reinduction)	4 (36.4)	6 (28.6)	0.4
Methotrexate (consolidation)	5 (38.5)	5 (26.3)	0.3
Cytosar (consolidation)	5 (83.3)	5 (19.2)	0.006
Mitoxantrone (consolidation)	4 (100)	6 (21.4)	0.006
Purinethol (consolidation)	5 (38.5)	5 (26.3)	0.3
Methotrexate (maintenance)	6 (42.9)	4 (22.2)	0.1
Purinethol (maintenance)	6 (42.9)	4 (22.2)	0.1
Cytosar (cytoreductive)	4 (80)	6 (22.2)	0.04
6-thioguanine (cytoreductive)	4 (80)	6 (22.2)	0.04
Doxorubicin (first-line)	0	10 (43.5)	0.05
Bleomycin (first-line)	0	10 (45.5)	0.03
Pharmarubicin (first-line)	0	10 (32.3)	0.6
Adriblastin (first-line)	0	10 (32.3)	0.6
Vincristine (first-line)	0	10 (33.3)	0.4
Vinblastine (first-line)	0	10 (45.5)	0.03
Prednisone (first-line)	0	10 (32.3)	0.6
Dexamethasone (first-line)	0	10 (37)	0.1
Hydrocortisone hemisuccinate (first-line)	0	10 (34.5)	0.3
Cyclophosphamide (first-line)	0	10 (33.3)	0.4
Etoposide (first-line)	0	10 (32.3)	0.6
Rituximab (first-line)	0	10 (32.3)	0.6
Dacarbazine (first-line)	0	10 (45.5)	0.03
Procarbazine (first-line)	0	10 (32.3)	0.6

Discussion

Infectious complications are an important problem in HM among children, which most of the time require emergency hospitalization and therapy with broad-spectrum antimicrobials, antifungal therapy and antiviral therapy.

The present study shows that younger patients have an increased risk of developing infectious complications.

Over the past decade pediatric patients with malignant hematologic diseases have a particularly high risk for infectious complications related to new chemotherapy regimens. The greatest risk of developing both bacterial infections and fungal infections in our study was in the case of induction therapy with Cytosar and first-line therapy with vinblastine, bleomycin and dacarbazine.

In the case of bacterial infections, in terms of etiology, we identified both gram-positive bacteria (*Staphylococcus aureus, Enterococcus faecalis, Clostridium difficile*) and Gram-negative bacteria (*E coli, Pseudomonas aeruginosa, Klebsiella*).

In a study by Urrea et al (2004) the most common microorganisms isolated from children with hematologic neoplasms were gram-positive bacteria (78.6%).

During induction chemotherapy in childhood ALL, there were 5 cases of *Staphylococcus aureus*, 9 cases of *Pseudomonas aeruginosa* and 5 cases of *E. coli* (Rajeswari et al 2018).

Children with haematologic neoplastic disease are more likely to develop nosocomial infections as they face a longer period of low immunity, undergo a longer period of hospitalization, and there is a greater chance that they require central venous catheterization, urinary catheterization and orotracheal intubation.

A retrospective study showed that nosocomial infections with gram-positive microorganisms accounted for 64.5% of pathogens (*Staphylococci* 71.5%, *Streptococci* 16%), while gram-negative microorganisms accounted for 30% of pathogens (*E. coli* 48.6%, *Klebsiella* 15.7 %, *Pseudomonas* 35.7%) (Al-Tonbary et al 2011).

Our study shows that the greatest risk of developing fungal infections is in the treatment of ALL (BFM-2009 protocol) and HL (GPOH-HD 2002 protocol). The most commonly isolated pathogenic agent was *Candida albicans* (13 cases).

In their study, among the etiological agents of fungal infections, Badiee et al. found 5 cases of *Candida albicans* and 1 case of *Candida krusei* in children with MH (Badiee et al 2017).

Another study showed that 5 out of 82 patients developed fungal infections in those with leukemia treated with the BFM regimen (Yilmaz et al 2008).

In an analysis of fungal infections in children with ALL, of 22 isolated fungal strains, 19 were detected in the induction phase of chemotherapy (Bakhshi et al 2009).

The most common viral etiology in our study was with HSV and VZV.

In MH patients, HSV reactivation is usually associated with mucocutaneous disease, localized most commonly in the orofacial region (85-90%) and less frequently in the inguinal region (Styczynshi et al 2009).

In pediatric patients with ALL, throughout therapy, Katsimpardi et al. diagnosed approximately 10% of viral infections, the most common of which were HSV and VZV (Katsimpardi et al 2006).

This is the first study in this region that evaluates the risk of infectious complications caused by chemotherapy in pediatric patients with MH. The study included children from a single department of pediatric oncology and followed a small number of patients for 6 years.

Conclusions

In our study, the type of infection depended on the type of chemotherapy regimen. The highest risk of developing fungal and / or bacterial infections was in the case of induction therapy with Cytosar and first-line therapy with vinblastine, bleomycin and dacarbazine.

References

Alexander S, Nieder M, Zerr DM, et al. Prevention of bacterial infection in Pediatric Oncology What do we know, what can we lern. Pediatric Blood Cancer 2012;59(1):16-20.

Al-Tonbary YA, Soliman OE, Sarhan MM et al. Nosocomial infections and fever of unknown origin in pediatric hematology/oncology unit:a retrospective annual study. World Journal Pediatric 2011;7(1):60-64.

Badiee P, Zareifar S, Haddadi B et al. Incidence of fungal infections in pediatric patients with hematologic neoplasm. Pediatric Infectious Deseases 2017.

Bailey LC, Reilly AF, Rheingold SP, et al. Infections in pediatric patients with hematologic malignancies. Seminar in Hematology 2009;46(6):313-324.

Bakhshi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia:an analyses of 222febrile neutropenic episodes. Pediatric Hematology and Oncology 2009;25(5):385-392.

Gatta G, Bott L, Rossi S, et al. Childhood cancer survival in Europa 1999-2007 results of EUROCARE-5-a population-based study. The Lancet Oncolgy 2014;15(1):35-47.

Jin M, Xu S, An Q. Pediatric haematopoiesis and related malignancies. Oncology letters 2017;14(1):10-14.

Katsimpardi K, Papadaks V, Pangalis A, et al. Infections in a pediatric patient cohort with acute lymphoblastic leukemia during entire course of treatment. Support Care Cancer 2006;14(3):277-284.

Lehrnbecher T, Laws HJ. Infectious complicatioans in pediatric cancer patients.Klinische Padiatrie 2005;217:3-8.

Noone AM, Howlader N, Kropecho M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute 2018.

Pulte D, Gondos A, Brenner H. Trends in 5-and 10-year survival after diagnosis with childhood hematologic malignancies in the United Statee, 1994-204.Journal of the National Cancer Institute 2008;100:1301-1309.

Rajeswari B, Nair RKS, Guruprasad CS, et al. Infections during induction chemotherapy in children with acute lymphoblastic leukemia-Profile and autcomes:Experience from a cancer center in South India. Indian Journal of Medical and Pediatric 2018;39(2):188-192.

Rich S, Ali S, Calkins G. Survival trends in childhood hematological malignancies. International Journal of Biomathematics 2012;5(6):9.

Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer:challenge for the twenty first century. Journal of Clinical Oncology 2010;28(15):2625-2634.

Stelirova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer 2001-2010:a population-based registry study. The Lancet Oncology 2017;18(6):719-731.

Stellarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood Cancer, third edition. Cancer 2005;103:1457-1467.

Stiller CA, Marcos-Gragera R, Ardanaz E, et.al. Geografical patterns of childhood cancer incidence in Europa, 1988-1997. Report from the Automated Childhood Cancer Information System project. European Journal of Cancer 2006;42(13):1952-1960.

Styczynshi J, Reusser P, Einsele H et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT:guidelenes from the Second European Conference on Infection in Leukemia. Bone Marrow Transplant 2009;43:757-770.

Urrea M, Rives S, Cruz O, et al. Nosocomial infections among pediatric hematology/oncology patients:results of a prospective incidence study. American Journal of Infection Control 2004;32(4):205-208.

Yilmaz S, Oren H, Demircioglu F et al. Assessment of fibril neutropenia episodes in children with acute leukemia treated with BFM protocols. Pediatric Hematology and Oncology 2008;25(3):195-204.

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