ORIGINAL ARTICLE

Chemotherapy-related infectious complications in patients with Hematologic malignancies

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Background: The objective of the present study was to determine the association between chemotherapy and infectious complications in patients diagnosed with Hematologic malignancies (HMs). **Materials and Methods:** The study included 463 patients diagnosed with HMs multiple myeloma (MM), Hodgkin's lymphoma (HL), non-HL (NHL), acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia, between January 2014 and June 2015. The patients were followed for 1 year after inclusion, to record the infectious complications. The collected data included age, sex, type of chemotherapy regimen, and several blood tests at admission. All patients received prophylactic treatment with antibiotics and antifungal agents. For each infection, we recorded the microbiological diagnosis and the day of occurrence since HMs diagnosis. **Results:** In patients with MM, we found that the treatment with growth factors (hazard ratio [HR] 2.2; confidence interval [CI] 95%: 1–4.6; $P = 0.03$) was associated with a higher chance of infectious complications. In patients with non-Hodgkin lymhoma (LNH), the following drugs were associated with a higher infectious incidence: cytarabine (HR: 2.3; CI 95%: 1–5; $P = 0.03$), methotrexate (HR: 2.1; CI 95%: 1.8–4; $P = 0.01$), dexamethasone (HR: 1.7; CI 95%: 0.9–3; $P = 0.06$), growth factors (HR: 1.7; CI 95%: 0.9–3.2; $P = 0.001$), and etoposide (HR: 2.5; CI 95%: 1.5–4.2; $P = 0.002$). Cytarabine (induction) (HR: 2; CI 95%: 1.1–3.7; $P = 0.01$), cytarabine (consolidation) (HR: 2.1; CI 95%: 1.3–3.5; $P = 0.01$), and growth factors (HR: 2.1; CI 95%: 1.3–3.5; $P = 0.002$) were often on the therapeutic plan of patients with AML, which developed infections. **Conclusion:** Regarding the chemotherapy regimen, the highest incidences of infectious complications were observed for growth factors and cytarabine.

Key words: Chemotherapy, hematologic malignancies, infectious complications

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INTRODUCTION

The prevalence of Hematologic malignancies (HMs) has been constantly increasing in developed countries,[1] due to earlier diagnosis and improved treatment efficacy and patient care. The treatment of HMs is based on a wide range of chemotherapeutics, small molecules, or antibodies, which are often associated by toxic side effects ranging from nausea and vomiting to diarrhea and mucositis to life-threatening myelosuppression.[2] The extensive research carried out in the last decades has been translated in several breakthrough therapies, which have substantially transformed this field.

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The introduction of chemoimmunotherapy (the fludarabine, cyclophosphamide, and rituximab regimen) for chronic lymphocytic leukemia (CLL) has shown excellent disease control, with a progression-free survival of 56.8 months.[3,4] In the case of chronic myeloid leukemia (CML), the introduction of the first tyrosine kinase inhibitors (TKIs), imatinib, has drastically improved the prognosis of this disease. Moreover, second-generation TKIs (dasatinib, nilotinib, and bosutinib)[5,6] and third-generation TKI (ponatinib) [7] have further improved the outcome of treatment for refractory cases. In the case of Hodgkin's lymphoma (HL), conventional combination chemotherapy regimens such

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as doxorubicin, bleomycin, vinblastine, and dacarbazine or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone and radiotherapy attained a 20-year overall survival of approximately 80% in a Swedish HL cohort.[8]

Acute forms of HMs, such as acute myeloid leukemia (AML), continue to have a rather poor prognosis. Despite several promising drugs which are currently evaluated in clinical trials, the classical approach based on intensive induction chemotherapy with 7 days of cytarabine and 3 days of an anthracycline (7 + 3), followed by consolidation chemotherapy or hematopoietic cell transplant (HCT), continues to remain the upfront treatment for AML.

Life-threatening infectious events due to malignancy and treatment-related immunosuppression are important factors that contribute to the mortality of HMs, especially in the case of acute HMs and patients who received HCT. Chemotherapy-induced neutropenia represents an important toxic side effect, which has been associated with increased morbidity, mortality, and treatment costs.[8] Moreover, many neutropenic patients develop life-threatening infections with minimal symptoms and signs, due to their inability to respond immunologically. Infectious complications can be reduced using prophylactic antibacterial, antiviral, and antifungal agents in patients at significant risk, but the incidence of infections remains increased. Prophylactic therapy is especially recommended for high-risk patients such as those with anticipated prolonged (>7-day duration) and profound neutropenia (absolute neutrophil count ≤100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical comorbid conditions including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes.[9] The risk of infectious complications depends on several factors including the prescribed chemotherapy, the type of HM, sex, and living conditions (rural/urban area).

The objective of the present study was to determine the association between chemotherapy and infectious complications in patients diagnosed with HMs.

MATERIALS AND METHODS

A prospective, observational, analytical, longitudinal, cohort study was conducted at the "Ion Chiricuţă" Oncology Institute Cluj-Napoca, Romania. It included 463 patients admitted to the Department of Hematology, diagnosed with HMs, between January 2014 and June 2015. The study protocol was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy. The study protocol was in accordance with the Helsinki Declaration of 1975, as revised in 2000. All patients signed an informed consent form prior the study inclusion.

The inclusion criteria were age over 18 years, who provided written informed consent and were diagnosed with multiple myeloma (MM), HL, non-HL (NHL), AML, acute lymphocytic leukemia (ALL), CLL, and CML according to the current European LeukemiaNet guidelines. The exclusion criteria were the presence of autoimmune disorders or solid malignancy and patients who were only colonized with microorganisms without signs of infection.

The patients were followed for 1 year after inclusion, to record the infectious complications. The collected data included age, sex, type of chemotherapy regimen (including the goal of the chemotherapy: curative or relapse), and several blood tests at admission including complete blood count, blood urea, creatinine, aspartate transaminase, and alanine transaminase. All patients received prophylactic treatment with antibiotics and antifungal agents.

The infectious complications were diagnosed based on blood culture, sputum culture, throat swab culture, nasopharyngeal culture, vaginal culture, stool culture, central venous catheter tip culture, and by Galactomannan assay, chest X-ray, and clinical examination, in accordance with current guidelines. For each infectious complication, we recorded the microbiological diagnosis and the day of occurrence since HMs diagnosis.

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 were characterized by frequency and percent. Differences between groups were tested using Chi-square test or Fisher's test, whenever appropriate. The risk of infectious complications was estimated using Kaplan–Meier analysis. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 463 adult patients affected by HMs were collected (MM, $n = 75$; HL $n = 32$; NHL, $n = 164$, AML, $n = 100$; ALL, $n = 26$; and chronic leukemia [CL], $n = 66$).

The type and incidence of infectious complications, for each HMs, were in MM 42.7% total infectious complications, 26.7% bacterial infections, 9.3% fungal infections, 5.3% viral infections, and 17.3% infections of unknown etiology; in HL 34.4% total infectious complications, 21.9% bacterial infections, 9.4% fungal infections, 3.1% viral infections, and 6.3% infections of unknown etiology; in NHL 39.6% total infectious complications, 25.6% bacterial infections, 12.2% fungal infections, 3.7% viral infections, and 17.7%

infections of unknown etiology; in AML 70% total infectious complications, 52% bacterial infections, 31% fungal infections, 1% viral infections, and 12% infections of unknown etiology; in ALL 73.1% total infectious complications, 53.8% bacterial infections, 30.8% fungal infections, 3.8% viral infections, and 11.8% infections of unknown etiology; and in CL 25.8% total infectious complications, 9.1% bacterial infections, 9.1% fungal infections, 3.0% viral infections, and 12.1% infections of unknown etiology.

Regarding the most frequent fungal infections, we recorded the following: *Candida albicans* was found more frequently in MM (5.3%), NHL (7.2%), AML (17.0%), ALL (26.6%), and CL (4.5%) and *Aspergillus* in NHL (3.6%), AML (6.0%), and ALL (15.4%). As for the most frequent bacterial infections, *Escherichia coli* was more common in MM (5.3%), NHL (6%), AML (14%), ALL (15.4%), and CL (3.0%); *Clostridium difficile* in MM (5.3%), HL (9.4%), NHL (4.8%), AML (15%), and ALL (15.4%); and *Klebsiella pneumoniae* in NHL (6%) and AML (10%). Herpes simplex virus was more common in NHL (2.4%) and varicella-zoster virus in CL (3.0%).

In patients diagnosed with MM, we found that the treatment with growth factors, Adriablastin, and liposomal doxorubicin was associated with a higher chance of infectious complications of any type [Table 1].

In patients diagnosed with HL, only vincristine was more likely to be associated with an infectious complication [Table 2]. This may be from the small number of HL cases.

In patients with NHL, the following drugs were associated with a higher infectious incidence: cytarabine, methotrexate, dexamethasone, growth factors, etoposide, and cisplatin [Table 3].

Cytarabine, idarubicin, etoposide, dexamethasone, growth factors, and fludarabine were often on the therapeutic plan of patients with AML, which developed infections [Table 4].

In the patients diagnosed with CL that received growth factors, we recorded frequent infectious complications [Table 5].

For the drugs that were associated with infectious complications in previous analysis, we calculated the hazard ratio: growth factors (curative) in MM was 2.2 (confidence interval [CI]: 95% 1–4.6; $P = 0.03$); methotrexate (curative) in NHL was 2.1 (CI 95%: 1.8–4; $P = 0.01$); etoposide (curative) in NHL was 2.5 (CI 95%: 1.5–4.2; $P = 0.002$); cytarabine (relapse) in NHL was 2.3 (CI 95%: 1–5; $P = 0.03$); dexamethasone (relapse) in NHL was 1.7 (CI 95%: 0.9–3; $P = 0.06$); growth factors (relapse) in NHL was 1.7 (CI 95%: 0.9–3.2; $P = 0.001$); cytarabine (induction) in AML was 2 (CI 95%: 1.1–3.7; $P = 0.01$); cytarabine (consolidation) in AML was 2.1 (CI 95%: 1.3–3.5; $P = 0.01$); growth factors (consolidation) in AML

Table 1: Factors associated with infectious complications in multiple myeloma patients

Chemotherapy regimen	Infectious complication (%)	Without infectious complication (%)	*P*
Vincristine	18 (56.2)	20 (46.5)	0.5
Epirubicin	0	3 (7)	0.3
Cyclophosphamide	23 (71.9)	26 (60.5)	0.4
Doxorubicin	13 (40.6)	11 (25.6)	0.2
Pharmorubicin	2 (6.2)	1 (2.3)	0.7
Dexamethasone	30 (93.8)	38 (88.4)	0.6
Medrol	7 (21.9)	12 (27.9)	0.7
Growth factors	10 (31.2)	4 (9.3)	0.035
Adriblastin	5 (15.6)	1 (2.3)	0.09
Bortezomib	27 (84.4)	43 (79.1)	0.7
Lomustine (CCNU)	4 (12.5)	2 (4.7)	0.4
Melphalan	10 (31.2)	12 (27.9)	0.9
Liposomal doxorubicin	6 (18.8)	2 (4.7)	0.1

Table 2: Factors associated with infectious complications in Hodgkin lymphoma patients

Chemotherapy regimen	Infectious complication (%)	Without infectious complication (%)	*P*
Cytosar	1 (9.1)	1 (4.8)	1
Cyclophosphamide			
Curative	5 (45.5)	5 (23.8)	0.3
Relapse	0	1 (4.8)	1
Epirubicin	1 (9.1)	1 (4.8)	1
Doxorubicin	9 (81.8)	15 (71.4)	0.8
Pharmorubicin	1 (9.1)	5 (23.8)	0.5
Adriblastin	4 (36.4)	15 (71.4)	0.1
Vincristine	9 (81.8)	10 (47.6)	0.1
Vinblastine	5 (45.5)	14 (66.7)	0.4
Vinorelbine			
Curative	1 (9.1)	2 (9.5)	1
Relapse	1 (9.1)	1 (4.8)	1
Dexamethasone			
Curative	9 (81.8)	13 (61.9)	0.4
Relapse	2 (18.2)	1 (4.8)	0.5
Medrol			
Curative	3 (27.3)	6 (28.5)	1
Relapse	1 (9.1)	0	0.7
Etoposide	5 (45.5)	5 (23.8)	0.3
Ifosfamide			
Curative	1 (9.1)	2 (9.5)	1
Relapse	1 (9.1)	1 (4.8)	1
Bleomycin	10 (90.9)	21 (100)	0.7
Growth factors			
Curative	7 (63.6)	16 (76.2)	0.7
Relapse	2 (18.2)	1 (4.8)	0.5
Rituximab (Mabthera)	0	1 (4.8)	1
Procarbazine	4 (36.4)	5 (23.8)	0.7
Dacarbazine	9 (81.8)	17 (81.0)	1
Cisplatin	1 (9.1)	1 (4.8)	1

Table 3: Factors associated with infectious complications in non-Hodgkin's lymphoma patients

Chemotherapy regimen	Infectious complication (%)	Without infectious complication (%)	*P*
Cytarabine			
Curative	14 (21.5)	10 (10.1)	0.07
Relapse	7 (10.8)	2 (2.0)	0.04
Methotrexate			
Curative	13 (20)	8 (8.1)	0.04
Relapse	3 (4.6)	3 (3.0)	0.9
Cyclophosphamide			
Curative	60 (92.3)	91 (91.9)	1
Relapse	5 (7.7)	4 (4.0)	0.5
Epirubicin			
Curative	12 (18.5)	11 (11.1)	0.2
Doxorubicin			
Curative	27 (41.5)	48 (48.5)	0.4
Pharmorubicin			
Curative	10 (15.4)	24 (24.2)	0.2
Adriblastin			
Curative	14 (21.5)	22 (22.2)	1
Vinblastine			
Curative	6 (9.2)	12 (12.1)	0.7
Relapse	1 (1.5)	1 (1.0)	1
Vincristine			
Relapse	6 (9.2)	4 (4.0)	0.3
Vinorelbine			
Relapse	1 (1.5)	0	0.8
Dexamethasone			
Curative	65 (100.0)	95 (96.0)	0.2
Relapse	15 (23.1)	10 (10.1)	0.04
Medrol			
Curative	27 (41.5)	50 (50.5)	0.3
Maintenance	6 (9.2)	18 (18.2)	0.1
Relapse	3 (4.6)	0	0.1
Rituximab			
Curative	40 (61.5)	67 (67.7)	0.5
Maintenance	7 (10.8)	20 (20.2)	0.1
Relapse	5 (7.7)	8 (8.1)	1
Growth Factors			
Curative	47 (72.3)	43 (43.4)	0.001
Relapse	13 (20.0)	8 (8.1)	0.04
Etoposide			
Curative	24 (36.9)	13 (13.1)	0.001
Relapse	10 (15.4)	8 (8.1)	0.2
Bleomycine			
Curative	4 (6.2)	2 (2.0)	0.3
Procarbazine			
Curative	1 (1.5)	0	0.8
Relapse	1 (1.5)	1 (1.0)	1
Dacarbazine			
Curative	1 (1.5)	0	0.8
Ifosfamide			
Curative	1 (1.5)	0	0.8
Relapse	6 (9.2)	4 (4.0)	0.3
Lomustine (CCNU)			
Relapse	6 (9.2)	4 (4.0)	0.3
Carboplatin			
Relapse	5 (7.7)	5 (5.1)	0.7
Cisplatin			
Relapse	6 (9.2)	3 (3.0)	0.1

was 2.1 (CI 95%: 1.3–3.5; $P = 0.002$); and growth factors in CL was 3.5 (CI 95%: 1.3–9.3; $P = 0.009$). The treatment with etoposide and growth factors determined the highest chance of infections. Cytarabine and growth factors were correlated with infections in almost every HMs.

DISCUSSION

Infectious complications represent an important issue for the patients diagnosed with HMs. The study showed that patients diagnosed with acute forms of leukemia had the highest incidence of infectious complications (AML – 70% and ALL – 73.1%), whereas in the case of chronic forms of leukemia (CL), the incidence was comparatively lower (9.1%).

The majority of the infectious complications were of bacterial etiology, a trend which was particularly obvious in the case of ALL, AML, and MM. Regarding specific nosocomial infections, the data show that, among patients diagnosed with acute HMs, the incidence of *E. coli* and *C. dificille* infections was around 27%–30%. A study conducted by Neofytus *et al*. with AML patients (48.4%) developed an invasive fungal infection.[10] ALL patients developed 3.3% invasive aspergillosis.[11]

Marin *et al*. found infections of C. dificille in 1.4% patients with HMs.[12]

In a study regarding the use of supplements, as a trend toward a benefit, probiotics were indicated on hematologic and immunologic parameters in patients with pelvic malignancies.[13]

Physicians must be aware of the infectious risks posed by chemotherapy-induced neutropenia and to promptly intervene with prophylactic antibiotics when needed. Often, fever can be the only sign of an underlying infection, since other symptoms are attenuated by the neutropenia. In the case of high-risk patients with fever, the Infectious Diseases Society of America guidelines recommend empirical intravenous therapy with antipseudomonal antibiotics such as cefepime, carbapenem, or Piperacillin-Tazobactam, whereas low-risk patients should receive combination ciprofloxacin plus amoxicillin-clavulanate, orally.[14]

Table 4: Factors associated with infectious complications in acute myeloid leukemia patients

Chemotherapy regimen	Infectious complication (%)	Without infectious complication (%)	*P*
Hydroxyurea	24 (34.3)	11 (36.7)	1
Cytarabine			
Induction	56 (80.0)	15 (50.0)	0.005
Consolidation	31 (44.3)	1 (3.3)	<0.001
Maintenance	3 (4.3)	0	0.6
Relapse	10 (14.3)	0	0.06
Methotrexate			
Induction	1 (1.4)	2 (6.7)	1
Consolidation	1 (1.4)	0	1
Maintenance	3 (4.3)	0	0.6
Idarubicin			
Induction	29 (41.4)	7 (23.3)	0.1
Consolidation	7 (10.0)	0	0.1
Relapse	2 (2.9)	0	0.8
Etoposide			
Induction	14 (20.0)	2 (6.7)	0.9
Consolidation	7 (10.0)	1 (3.3)	0.4
Relapse	8 (11.4)	0	0.1
Vincristine			
Induction	1 (1.4)	0	1
Consolidation	1 (1.4)	0	1
Dexamethasone			
Induction	24 (34.3)	5 (16.7)	0.1
Consolidation	7 (10.0)	0	0.1
Relapse	3 (4.3)	0	0.6
Mitoxantrone			
Induction	0	1 (3.3)	0.6
Consolidation	5 (7.1)	1 (3.3)	0.7
Relapse	4 (5.7)	0	0.4
Tretinoin			
Induction	5 (7.1)	3 (10.0)	0.9
Maintenance	1 (1.4)	0	1
Decitabine			
Induction	3 (4.3)	1 (3.3)	1
6-Mercaptopurine			
Induction	1 (1.4)	0	1
Consolidation	2 (2.9)	0	0.8
Maintenance	5 (7.1)	0	0.3
Relapse	2 (2.9)	0	0.8
Growth factors			
Consolidation	46 (65.7)	6 (20.0)	<0.001
Relapse	4 (5.7)	0	0.4
Fludarabine			
Relapse	8 (11.4)	0	<0.001
Gemcitabine			
Relapse	3 (4.3)	0	0.6

A study of Teh *et al*. identified the use of melphalan and cyclophosphamide, and cumulative doses of corticosteroids were independently associated with an increased risk of infection.[15]

Table 5: Factors associated with infectious complications in CL patients

Chemotherapy regimen	Infectious complication	Without infectious complication	*P*
Cyclophosphamide	9 (52.9)	22 (44.9)	0.7
Vincristine	2 (11.8)	16 (32.7)	0.1
Vinblastine	1 (5.9)	1 (2.0)	1
Pharmorubicin	1 (5.9)	2 (4.1)	1
Dexamethasone	8 (47.1)	26 (53.1)	0.8
Medrol	2 (11.8)	13 (26.5)	0.3
Prednisone	1 (5.9)	0	0.5
Mabthera	4 (23.5)	19 (38.8)	0.4
Chlorambucil	3 (17.6)	3 (6.1)	0.3
Growth factors	9 (52.9)	9 (18.4)	0.015
Imatinib	1 (5.9)	9 (18.4)	0.3
Dasatinib	1 (5.9)	9 (18.4)	0.3
Nilotinib	1 (5.9)	5 (10.2)	0.9

CL = Chronic leukemia

Fungal infections were dominated by *C. albicans* and *Aspergillus*, which represented around 30% of the total infection in acute HMs. In a study with HMs, patient that used of cytotoxic chemotherapy had 79.3% risk factor for invasive fungal infection.[16]

Viral infections had a particular high incidence in MM patients (5.3%), and in those diagnosed with ALL (3.8%) and NHL (3.7%), with herpes simplex virus and Varicella-zoster viruses having the highest incidence. Patients with NHL who received chemotherapy had 24.45% infection with herpes zoster.[17]

The severity of the neutropenia, which in turn influenced the risk for developing an infectious complication, was partly determined by the chemotherapy regimen. In the case of MM, the incidence of infectious complications was highest in patients treated with growth factors.

A study conducted by Pugliese et al. on patients with AML found that 55.4% had neutropenic episodes with infections after chemotherapy.[18]

A similar situation was observed for patients diagnosed with LNH, the infectious complications being more frequent in the cases treated with methotrexate, etoposide, cytarabine, dexamethasone, and growth factors.

For AML, the incidence of the infectious complications was highest for cytarabine, which was 80% in the induction phase and 44.3% in the consolidation phase. Growth factors were associated with 65.7% infections in AML patients.

In a study, patients with CLL had 1.3% incidence of fungal infections, a lower risk comparative with MM (3.7%) and NHL (5.1%).[19]

Chronic types of leukemia were characterized by a comparatively lower incidence of infectious complications, probably due to the lower intensity of the chemotherapy regimens, and an overall better performance status of the patients. The incidence of infectious complications was 52.9% in the patients treated with growth factors.

This is the first study from this region that evaluates the risk of infectious complications from chemotherapy in patients with HMs. The study included patients only from one important regional hematologic center, but it followed a moderate/high number of patients for a year.

CONCLUSIONS

In our study, the incidence of infections depended on the type of HMs and on the employed chemotherapy regimen. Bacterial, fungal, and viral infections had the highest incidence in the case of acute HMs (AML and ALL). Regarding the chemotherapy regimen, the highest incidences of infectious complications were observed for growth factors and cytarabine.

RAR contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; DS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; DC contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; BN contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; MS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; SCV contributed in the conception of the work, performing the statistical analysis, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work; MP contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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There are no conflicts of interest.

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