ORIGINAL ARTICLE

INCIDENCE OF INFECTION DURING SALVAGE CHEMOTHERAPY REGIMENS IN PATIENTS WITH RELAPSED/ REFRACTORY LYMPHOMAS: AN EXPERIENCE OF A TERTIARY CARE CENTER

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ABSTRACT

Background: Mortality from lymphomas has improved over the years with newer chemotherapy regimens. However, life-threatening infections caused by immunosuppression due to chemotherapy remain a major cause of morbidity and mortality. Due to patients being lost-to-follow-up in developing countries, it is difficult to accurately quantify the incidence of infection. Thus, this prospective study aims to assess the rate of infection in lymphoma patients on salvage chemotherapy.

Material and Methods: A prospective study was conducted at a tertiary care hospital in Karachi, Pakistan. Patients aged 16-65 years of both gender and appropriate organ function were included. Patients with pre-existing cardiovascular disease and active infections were excluded. STATA version 16 was used to analyze the data.

Results: A total of 98 patients were included. The mean age of participants was 43.7 ± 15.5 years. Males were 73.7% of all patients and females were 26.3%. Febrile neutropenia was found in 4.1% of patients, all of whom had DLBCL (refractory in 2 patients and relapsed in 2 patients). The mean age of patients was 41.7 ± 13.5 years. Sepsis was found in 14.1% of patients, of which 8 had NHL and 6 had HL. Half of all patients with sepsis had late relapse. The mean age of all patients with sepsis was 47.4 ± 18.2 years, which was not statistically significant from the remainder of the sample.

Conclusion: Infectious complications are high in lymphoma patients on salvage chemotherapy. Often, they may progress to sepsis, with its associated high morbidity and mortality in this vulnerable patient population.

Keywords: Infection, Sepsis, Salvage chemotherapy, Lymphoma

BACKGROUND

Lymphoma is the sixth most common cancer in the world. A recent study has shown that, globally, 2.8% of people are diagnosed with NHL with 2.6% mortality, and 0.4% are diagnosed with HL, with 0.2% mortality.[1] Mortality from lymphomas has improved over the years with newer chemotherapy regimens and better control of some severe complications of chemotherapy, including immunosuppression causing life-threatening infections. However, infections remain a major problem in lymphoma treatment.[2] An example is chemotherapy-induced neutropenia, which is associated with significant morbidity and mortality[3]. Added to this is the additional hospital stay, burden on healthcare, and other associated costs.[3, 4] Such infections often develop insidiously, and are hence are a diagnostic challenge and increase morbidity and mortality.[3,5] An added concern is emerging microbial resistance that can cause further mortality.[6]

While chemotherapy-induced infections are a major cause of morbidity in lymphoma patients, it is difficult to accurately quantify in our set-up due to problems of loss-to-follow-up. With no centralized health information system to connect patients across hospitals, it is impossible to identify whether patients developed infections. This is especially true for tertiary-care hospitals, where crippling medical expenditure can deter readmission for evaluation of infection. Thus, to accurately qualify the incidence of infections in lymphoma patients on salvage chemotherapy, a prospective study is required. We present a

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prospective report of infectious complications in patients with lymphoma on salvage chemotherapy.

MATERIAL AND METHODS

A prospective study was conducted at a tertiary care hospital in Karachi, Pakistan. Data from January 2019 to December 2020 was extracted after institutional ethical approval and informed consent of all participants. Early relapse was classified as a complete remission lasting three months but not twelve months, and late relapse was defined as a complete remission lasting twelve months. Refractory lymphoma defined as, who failed to response on 2 line of standard chemotherapy.

Patients aged 18-65 years of both gender with normal renal, hepatic and cardiac function were included. Patients with previous cardiovascular disease and active infections were excluded. Febrile neutropenia was defined as "single oral temperature greater than or equal to 101 F, or a temperature greater than or equal to 100.4 F for at least an hour, with an absolute neutrophilic count (ANC) of less than 1500 cells/microliter" (7). Sepsis was defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (8) and "namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36 °C), and leukocytosis, leukopenia, or bandemia (white blood cells >1,200/mm3, <4,000/mm3 or bandemia ≥10%)" (9). STATA version 16 was used to analyze the data. Patient were monitored throughout salvage chemotherapy regimen.

Using non-probability convenience sampling, total 99 lymphoma patients after 1st line chemotherapy, who received DHAP (dexamethasone, cytarabine cisplatin), ICE (ifosfamide, carboplatin, etoposide), R-benda (rituximab, bendamustine), IGEV (ifosfamide, gemcitabine, vinorelbine and prednisone), R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, prednisone), GDP (gemcitabine, dexamethasone, cisplatin), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), R-DHAP (rituximab, dexamethasone, cytarabine cisplatin), and CHOP (cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, prednisone).were included in the study. Numeric variables were presented as mean and SD. Categorical variables were presented as frequency and percentage.

RESULTS

Out of a total of 99 patients with refractory or relapsed lymphoma, the mean age of participants who developed febrile/non-febrile neutropenia and/or sepsis was 43.7 ± 15.5 years. Males were 73.7% of all patients and females were 26.3%. Diabetes and hypertension were the common co morbid accounting for 26.3% and 14.1% of the cases respectively.

Diffuse large B-cell lymphoma (DLBCL) sub-type of NHL was present in 41.4% patients, and nodular sclerosis was the most frequent subtype (29.3%) in patients with HL. At the time of diagnosis, most of the patients (80.1%, n=80) presented with stage IV lymphoma, while 19.2% (n=19) presented with stage III lymphoma.

Regarding disease course, who developed hematologic complication, 14.1% (n=14) patients presented with early relapse, while 45.4% (n=45) presented with late relapse and 25.3% (n=25) had refractory disease. A total of 43 patients (43.4%) had ECOG status 1 and 13 patients (13.1%) had ECOG status 2. Nodal metastasis were found in 24.2% (n=24) patients.

A total of 38.4% (n=38) received DHAP, 18.2% (n=18) received ICE, 11.1% (n=11) received R-benda, 6.1% (n=6) received IGEV, 4.0% (n=4) received R-CHOP, 4.0% (n=4) received GDP, 3.0 (n=3) patients received ABVD, 2.0% (n=2) received R-DHAP and 1.0% (n=1) received CHOP

Febrile neutropenia was found in 4 patients in total, as shown in figure 1. The mean age of patients was 41.7 ± 13.5 years. Of these, 3 patients were males and 1 was female. All patients were diagnosed with DLBCL (refractory in 2 patients and relapsed in 2 patients). Half of these patients had stage 4 disease and received ICE salvage chemotherapy.

Sepsis was found in 14 patients (14.1%), as depicted in Figure-1. The mean age of all patients with sepsis was 47.4 ± 18.2 years, which was not statistically significant from the remainder of the sample. Females comprised 35.7% (n=5) of the sample, while 64.3% (n=9) were males. Of all patients, 8 had NHL and 6 had HL. Half of all patients with sepsis had late relapse. The majority (71.4%, n=10) had stage 4 malignancy, and 8 (57.1%) received DHAP, while 2 (14.3%) received R-benda, 1 (7.1%) received ICE and 1 (7.1%) received GDP. Majority of patient had

neutropenic bacterial sepsis, managed with intravenous antibiotics, few had gastrointestinal symptoms related to mucositis and only two patient developed pulmonary symptoms.

Table-1:General demographics.

	Minimum	Maximum			
Age	18	65			
Gender	Male	Female			
ECOG	<2	2			
Type of Lymphoma	Relapsed/Refractory Hodgkins	Relapsed/Refractory Non-Hodgkins			
Renal Function	Creatinine normal per BSA				
Liver Function	Normal SGPT and total bilirubin				
Cardiac function	Normal EF and ECG				
Active infection	No active bacterial or viral infection				
Chemotherapy regimen	DHAP	ICE	IVEG	BENDA	GDP
SOFA score	<2	>2			

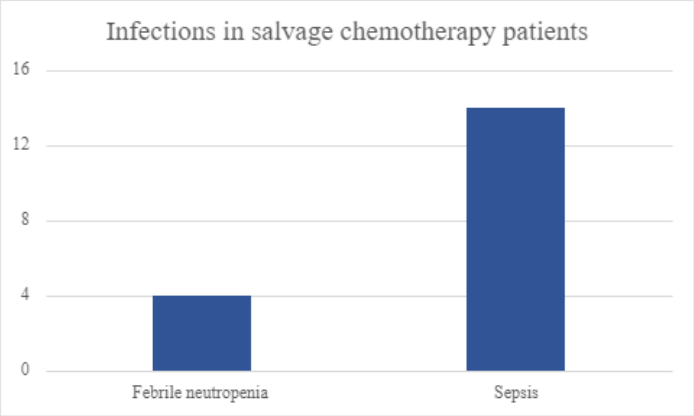

Figure-1: Febrile neutropenia and sepsis in patients on salvage chemotherapy.

DISCUSSION

Infections due to chemotherapy for lymphoma are a major contributor to morbidity, mortality and healthcare costs. We found a 14.1% and 4.1% of sepsis and febrile neutropenia in our population, respectively.

In literature, infectious complications are more frequent than our observation. Rusu *et al*. found infections in 34.4% of patients with HL and 39.6% of patients with NHL.[2] The most common infectious organisms were bacteria, followed by fungi and then viruses.[2] Many causes of infection remain unknown despite extensive diagnostic tests.[2] However, studies have varied with regards to which infectious agents are more common in lymphoma, with some studies suggesting higher rates of fungal infections.[10] Overall, literature has not adequately identified specific infections to be associated with specific chemotherapy regimens. Despite this, it is known that the presence and severity of neutropenia is a major clinical factor in development of a life-threatening infection, which is then difficult to control and treat. Early identification and prophylactic treatment are required[2,15] to prevent infections.

In Pakistan, like many other developing countries, healthcare expenditure is primarily out-of-pocket, where patients pay for healthcare costs at the point of treatment.[11]This leads to, inevitably, catastrophic expenditure and impoverishment. Clearly, cancer treatments are a large expense to be borne by patients. Added to this is the cost of complications, such as infections, which require prolonged hospitalization, extensive diagnostic tests, and often expensive treatments due to widespread microbial resistance. Factors associated with a longer length of stay and greater mortality include the age of the patient and patient factors such as vital instability and dehydration[4], and early identification of such high-risk groups can help reduce such complications and their associated morbidity and costs.[12,13,14]

Our study is limited by sample size from a single tertiary-care center. With a small sample size, and

limited resources, we could not quantify the type of infection further. However, this is a prospective study, thus, we collected and included patients with complete data, excluding those who were loss-to-follow-up during their treatment, providing more accurate data. Further studies based on a prospective design are required, especially for our set-up, where patient data from other hospitals is not available and parallel treatments are not recorded centrally, so that a large sample size is used to identify the incidence of infectious complications in lymphoma patients on salvage chemotherapy.

CONCLUSION

Infectious complications are high in lymphoma patients on salvage chemotherapy. Often, they may progress to sepsis, with its associated high morbidity and mortality in this vulnerable patient population.

AUTHOR CONTRIBUTION

Kanta Devi: Conception, the acquisition, analysis, interpretation of data and manuscript writing
Muhammad Usman Shaikh: Conception, Analysis and interpretation of data
Maria Khan: Data collection and analysis
Natasha Ali: Revised critically for important intellectual content
Salman Naseem Adil: Revised critically for important intellectual conten

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