RESEARCH ARTICLE

Clinical course, long-term outcomes, and chemotherapy toxicity profile in B-cell Non-Hodgkin Lymphoma in children: Single institution experience of Pakistan

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Abstract

Objective: To analyse the disease presentation, clinical course and long-term outcomes of children diagnosed with B-cell non-Hodgkin lymphoma.

Method: The retrospective descriptive study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan and comprised data of patients diagnosed with B cell non-Hodgkin lymphoma between January 2012 and December 2016, with follow-up time of 4 years post-treatment. Data was collected from the institutional database. Data was analysed using SPSS 20.

Results: Of the 286 patients, 217(75.6%) were males and 69(24.1%) were females. The overall mean age at presentation was 7.6±4.1 years (range: 1-16 years). Burkitt lymphoma was diagnosed in 194(67.8%) patients, and diffuse large B cell in 83(29.0%). Majority of patients had presented with stage III disease 159(55.6%). Complete remission was achieved in 173(60.5%) patients, while 90(31.5%) died during treatment. The 4-year overall survival observed was 67.1%, whereas event-free survival was 60.5%.

Conclusion: Majority of the paediatric patients presented with extensive disease. Measures are needed for early recognition, identification, and prompt referral to paediatric cancer institute.

Keywords: B cell origin, Children, Non-Hodgkin lymphoma, Outcome. (JPMA 72: 1988; 2022)

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Introduction

Among childhood malignancies, paediatric lymphomas are the third most common.[1] Non-Hodgkin lymphoma (NHL) comprises almost 50% of paediatric lymphomas whereas the rest are Hodgkin's lymphoma (HL).[2] Over the last three decades, there has been significant improvement in the outcome of NHL, with current survival rates being 80-90%.[3] The incidence of NHL increases with age and the outcome is slightly less favourable in infants and adolescents compared to children.[4] Among the histological subtypes, Burkitt lymphoma (BL) and lymphoblastic lymphoma (LBL) have better outcomes in children compared to adolescents.[5] In high-income countries (HICs), the cure rate of NHL is >85%, whereas in low- and middle-income countries (LMICs) it is <50%. Majority of the NHLs diagnosed worldwide belong to LMICs, so even slightest improvement in the outcomes would decrease the disease morbidity and mortality worldwide.[6]

The current study was planned to analyse the disease presentation, clinical course and long-term outcomes of children diagnosed with B cell NHL (BCNHL).

Materials and Methods

The retrospective descriptive study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Lahore, Pakistan and comprised data of patients aged 1-18 years diagnosed with BCNHL between January 2012 and December 2016, with follow-up time of 4 years post-treatment. Cases of T-cell lymphomas (TCLs) and anaplastic large cell lymphomas (ALCLs) were excluded. Data was retrieved from the electronic database after approval from the institutional ethics review board exemption.

The diagnosis of BCNHL was made on the morphological and immunophenotyping appearance. Disease staging was done according to the St. Jude classification.[7] Risk stratification and treatment protocol used at the centre is the United Kingdom Children's Cancer Study Group (UKCCSG) NHL 2003 based on the FAB/LMB (French American British /Lymphome Malins De Burkitt) protocol.[8] Completely resected tumours (stage I) or completely resected abdominal stage II tumours along with lymph nodes were placed in Group A. Group B included unresected stage I and stage II tumours related to those with stage III disease. Group C included patients with tumour involving any site along with any with involvement of central nervous system (CNS) cerebrospinal fluid (CSF) or bone marrow.

Group A treatment regimen consisted of cyclophosphamide 250mg/m^2 every 12 hourly for the first 3 days, vincristine 2mg/m^2 2 doses, prednisolone

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60mg/m^2 in 2 divided doses for 5 days then reduced to zero over 3 days, and doxorubicin (60mg/m^2) (COPAD). Groups B and C received initial cytoreductive chemotherapy vincristine 1mg/m^2, cyclophosphamide 300mg/m^2, prednisolone 60mg/m^2 in 2 divided doses for 7 days, and intrathecal chemotherapy with methotrexate (MTX) and hydrocortisone (COP- vincristine). Group B patients received two cycles of induction chemotherapy cyclophosphamide 250mg/m^2 every 12 hourly for 3 days, vincristine 2mg/m^2, prednisolone 60mg/m^2 in 2 divided doses for 5 days then reduced to zero over 3 days, MTX 3gm/m^2 along with folinic acid rescue and two doses of intrathecal chemotherapy with MTX, hydrocortisone (COPADM) followed by 2 cycles of consolidation chemotherapy cytarabine-100mg/m^2, 24-hour infusion for 5 days, high dose MTX 3gm/m^2 along with folinic acid rescue and intrathecal MTX, hydrocortisone and cytarabine for 2 days (CYM). Group C patients received extremely high doses of MTX 8000mg/m^2 and cyclophosphamide 1000mg/m^2 /day for 3 days during the induction phase, followed by folinic acid rescue and high doses of cytarabine 3000mg/m^2 for 3 days and etoposide 200mg/m^2 in the consolidation phase (CYVE), whereas CNS-positive patients also received high dose MTX 8000mg/m^2 along with folinic acid rescue, followed by 4 cycles of maintenance chemotherapy. Rituximab was not administered because of limited resources and availability.

Complete remission was defined as disappearance of all measurable or evaluable lesion, no L3 blast cells in the CSF and bone marrow. Incomplete response was defined as 20-99% reduction in the product of the largest two diameters of the measurable lesions, whereas non-response was defined as having <20% reduction of the product of the two largest diameters of the measurable lesions. The non-responders in group B were escalated to group C. Further response status was seen after CYM in Group B and after CYVE in Group C. Complete remission was defined as the complete disappearance of all measurable lesions, no L3 blast cells in the bone marrow and CSF. Persistent disease was defined as any existence of histologically proven residual disease, whereas disease progression or relapse was defined as any progression of >25% in the product of the two largest diameters of measurable lesions or appearance of new lesions or L3 blast cells in the CSF or bone marrow. Disease response was also assessed at the end of therapy. Data collected was also collected on chemotherapy-related toxicity, neutropenic complications and causes of death. Patients were followed up for 4-years after the end of therapy.

Data was analysed using SPSS 20. Descriptive statistics were reported as frequencies and percentages for quantitative data. Pearson's chi-square test was applied for the association between the extent of disease and outcome. P<0.05 was considered statistically significant. Overall survival (OS) and event-free survival (EFS) were calculated using Kaplan-Meir curve method. The EFS was calculated from the date of diagnosis until the first event, including death from any cause, progression of disease, relapse, second malignancy and abandonment of treatment. OS was calculated as the percentage of patients who were alive on last follow-up.

Results

Of the 293 patients diagnosed with BCNHL, 7(2.4%) had refused treatment and their data was excluded. The final sample, as such, comprised 286(97.6%) patients; 217(75.6%) males and 69(24.1%) females. The overall mean age at presentation was 7.6±4.1 years (range: 1-16 years). Majority of the patients belonged to remote areas of the country (n=127) (44.4%) and from the neighbouring Afghanistan (n=24) (8.4%). BL was diagnosed in 194(67.8%) patients, and diffuse large B cell lymphoma (DLBCL) in 83(29.0%). Majority of patients had presented with stage III disease 159(55.6%) (Table).

Bone marrow involvement was seen in 30 (10.4%) patients, combined bone marrow and CSF in 6 (2%), bone

Table: Clinical features seen in patients with B cell non-Hodgkin lymphoma.

	Clinical Features Seen In Patients With NHL Histological Subtypes			
Patient Characteristics	**Burkitt Lymphoma**	***Diffuse Large B Cell Lymphoma**	**B Cell Non-Specific**	**P value**
Patients (n=286)	194 (%)	83 (%)	9 (%)	
Gender				
Male	143 (50)	67(23.4)	7(2.4)	0.45
Female	51 (17.8)	16(5.5)	2(0.6)	
Site of Disease				
Abdomen	150(52.4)	48(16.7)	6(2)	
Cervical lymph nodes	18 (6.2)	16(5.5)	2(0.6)	
Maxillary Sinuses	17 (5.9)	4(1.3)	0	
Tonsils	6 (2)	4(1.3)	0	0.000
Spine	1 (0.3)	2(0.6)	0	
Mediastinal	2 (0.6)	2(0.6)	1(0.3)	
Other	0	7(2.4)	0	
Stages of disease				
Stage I	1(0.3)	3(1)	0	
Stage II	27(9.4)	17(5.9)	2(0.6)	0.20
Stage III	108(37.7)	45(15.7)	6(2)	
Stage IV	58(20.2)	18(6.2)	1(0.3)	
Overall survival	63.90%	73.50%	77.80%	
Event-free survival	59.80%	60.20%	77.80%	

*Four Patients with diffuse large B cell lymphoma (DLBCL) had primary central nervous system (CNS) disease.

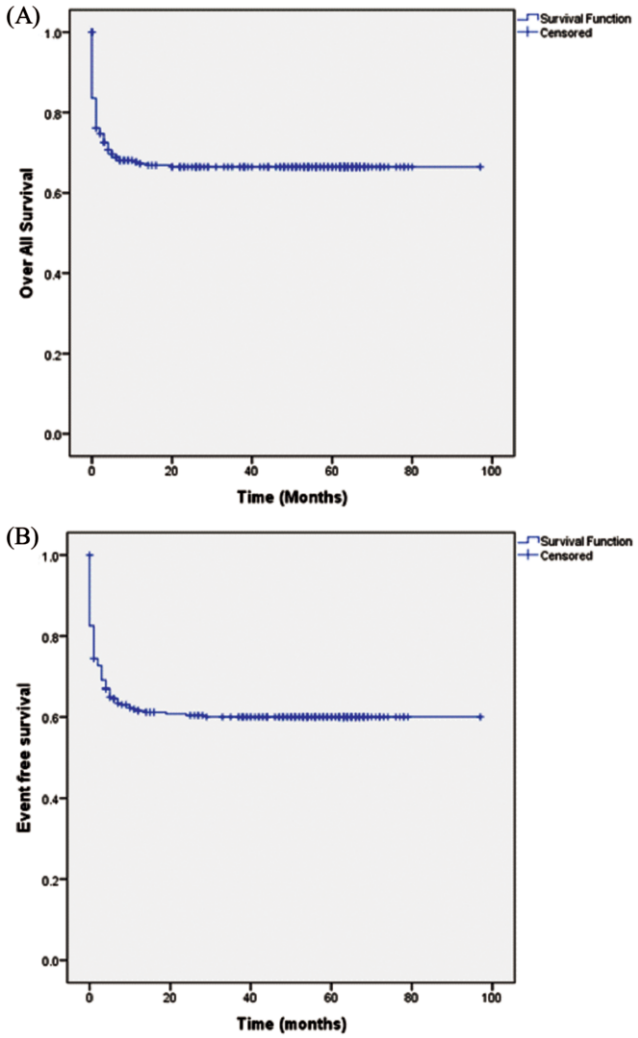

Figure-1: (A) Overall survival (OS); (B) Event-free survival (EFS).
EFS was calculated from the time of presentation till the onset of event (death, relapse, disease progression, abandonment).

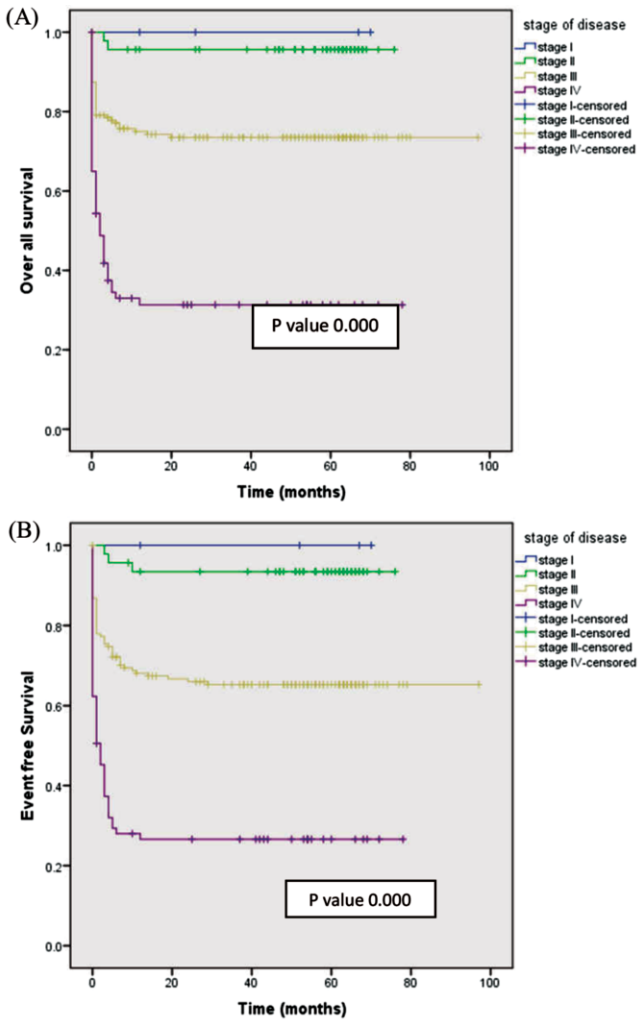

Figure-2: (A) Overall survival (OS) in relation to the disease stage; (B) Event-free survival (EFS) in relation to the disease stage.

marrow along with CNS in 8 (2.7%), both CNS and CSF in 2 (0.6%), CNS disease alone in 29(10.1%), and CSF alone was 3 (1%) patients.

The most common site of disease involvement was abdomen 204(73.1%) patients. Among them 144(70.5%) patients had upfront laparotomy whereas diagnostic biopsy was done in 6230.3%). Majority of the patients with abdominal disease had upfront laparotomy, though no statistical correlation could be found with open laparotomy versus biopsy on disease outcome (p=0.22).

Further, 72(25.2%) patients had head and neck involvement, mediastinum 5(1.7%) and primary CNS 4(1.4%) among whom 1(25%) patient had intracranial disease and 3(75%) presented with spinal cord compression.

Of the total patients, 11(3.9%) were treated in Group A, 199(69.8%) in Group B and 75 (26%) in Group C. One patient (0.3%) presented one year after completely resected abdominal disease and was kept on close surveillance without any treatment. In Group B, 9(4.5%) patients had minimal response, and the treatment was escalated to Group C.

On re-evaluation scans, complete remission was seen in 152(53.1%) patients, disease progression in 7(2.4%), and partial response in 35(12.2%) patients out of whom 28(14%) belonged to Group B and 7(9.3%) to Group C.

At the end of treatment, Complete remission was achieved in 173(60.5%) patients, while 90(31.5%) died during treatment. Disease progression was seen in 7(2.4%) patients, and 6 patients (out of 7) (85.7%) of them died because of disease burden, while 1 patient (14.2%) was shifted to palliative care. Moreover, 8(2.8%) patients

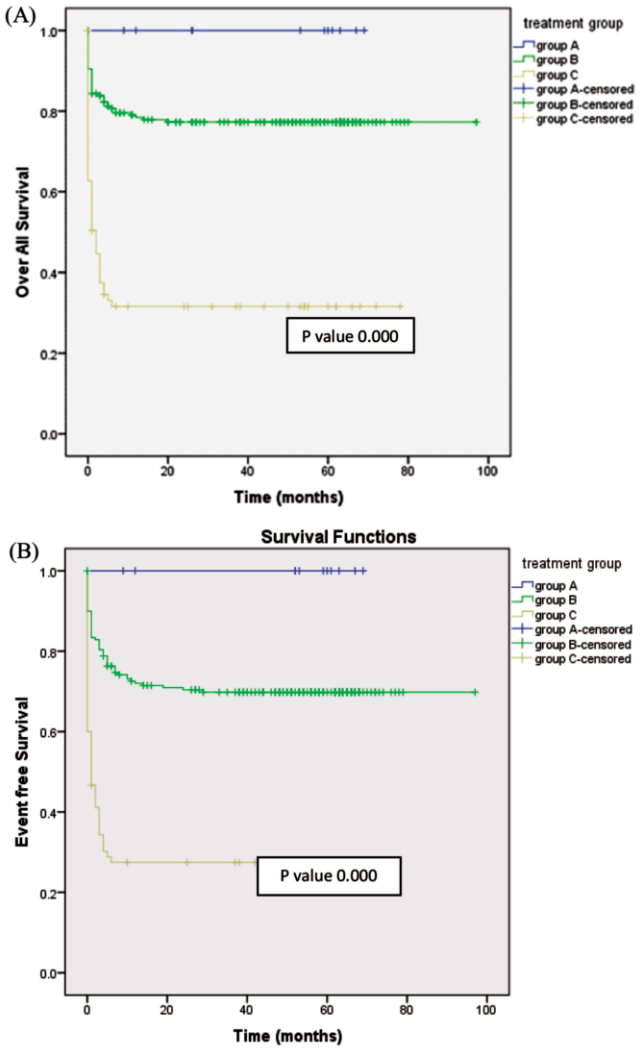

Figure-3: (A) Overall survival (OS) in relation to treatment group; (B) Event-free survival (EFS) in relation to treatment group.

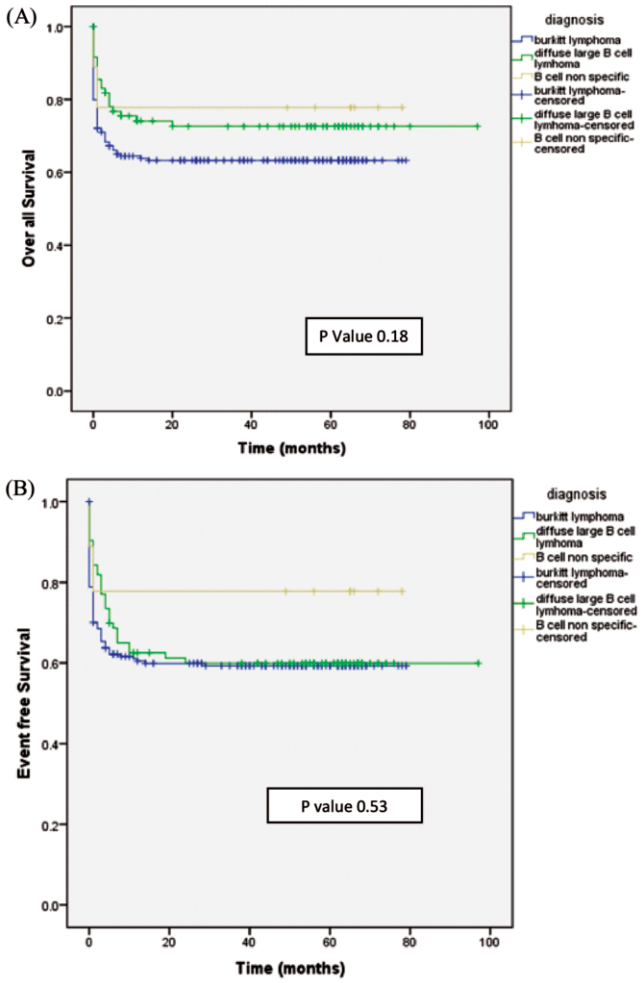

Figure-4: (A) Overall survival (OS) in relation to diagnosis; (B) Event-free survival (EFS) in relation to diagnosis.

had relapse disease, and another 8(2.8%) abandoned treatment.

The common cause of death was neutropenic colitis observed in 50 patients (52.6%), diagnosed clinically and radiologically on computed tomography (CT) scan of the abdomen. The most common microorganisms cultured from blood in patients who suffered from neutropenic colitis was multi-drug resistance Escherichia (E.) coli present in 32 (29.1%) blood cultures, followed by Klebsiella (K.) pneumoniae present in 31(28.2%), Acinetobacter in 17 (15.5%) and Pseudomonas (P.) aeruginosa in 18 (16.4%) blood cultures.

Increased number of febrile neutropenia episodes led to mortality (p=0.02). Death due to high disease burden and tumour lysis syndrome was seen in 20(21.3%) patients. Multiorgan dysfunction syndrome due to treatment toxicity was observed in 17(18.1%) patients, 6(6.4%) died because of disease progression, and 2(2.1%) patients died because of cardiotoxicity. Patients having advance disease stages III and IV with CNS and bone marrow involvement had poor outcome (p<0.005).

The 4-year OS was 67.1%, whereas EFS was 60.5% (Figure-1). Both parameters were compared in terms of disease stage (Figure-2), treatment group (Figure-3) and diagnosis (Figure-4).

Overall, 18(6.3%) patients had chemotherapy-related toxicity> MTX-related neurotoxicity was observed in 11(3.8%) patients, 6 (2%) patients had posterior reversible leukoencephalopathy and 5 (1.7%) patients developed seizure disorder despite the fact folinic acid rescue was given along with regular serum MTX monitoring. Treatment modification was done in 1 (0.3%) patient and only 6 cycles of COP were given. Cardiotoxicity was seen

in 7(2.4%) patients, and 3 of them died due to treatment-related complications.

Discussion

There was male predominance in the current study, with male-to-female ratio being 2.7:1, which was almost the same as reported in literature.[9] Majority of the patients presented age 1-15 years, which correlated with other studies.[10] The histological subtypes of NHLs can vary geographically,[11] and BL is the common histological subtype reported in Asia, which was also evident in current data. The common site of presentation among patients with BL and DLBCL was abdominal disease which is in line with literature.[12] The factors affecting the outcomes was extensive disease at presentation. Patients presented belonged to the remote areas of the country and some from neighbouring countries, hence there was delay in referral. Delayed presentation due to financial constraints and lack of awareness for prompt referral to oncologist are the factors seen in developing countries.[13] The most common disease site seen was abdomen, and majority of them had open laparotomy either for resection or for biopsy, before being referred to the study centre, which reflects poor awareness among healthcare providers and the families. The extent of disease was the main prognostic indicator in patients with abdominal lymphoma. Surgery plays a role where there is complete resection of localised disease and in management of emergencies, like intuscception/obstruction, but no clear association between debulking surgery and the outcome has been established.[14]

The OS of the BCNHLs has dramatically increased over the years in the developed world because of intensive chemotherapy regimens and better supportive care.[15,16] In the current study, OS was 67.1%, which is like other developing countries.[17] Based on the age of the patients, the EFS was 62.0% in children and 61.1% in adolescents, whereas Cairo MS et al. reported 3-year EFS in paediatric patients aged <15 years to be 89% and in those aged >15 years 84%.[18] Marked differences were observed in the outcome of NHLs, likely due to increased episodes of febrile neutropenia and infection-related mortality and morbidity. Majority of the current patients presented with advanced disease and were treated on intensive -dose chemotherapy regimens (Groups B and C), which resulted in increased episodes of febrile neutropenia (p=0.001). It is well known that the combined administration of doxorubicin and MTX induces mucositis that can lead to neutropenic colitis, although six hours of doxorubicin infusion has resulted in reduced complications. Perhaps we can also adopt protocol without doxorubicin or with reduced dose, in advance disease for better outcomes.[19]

Better supportive care strategies can reduce the risk of febrile neutropenia episodes and complications. Therefore, the departmental supportive guidelines were modified and granulocyte colony stimulating factor (GCSF) was incorporated as primary prophylaxis in 2017, the aim being to reduce infection-related complications. Latest research has shown that outcomes in NHLs, especially DLBCL type, are further improved with the incorporation of rituximab in upfront chemotherapy. The addition of rituximab in both paediatric and adult regimens of BCNHL has been proven to be beneficial.[20]

Treatment-related neurotoxicity and cardiotoxicity observed in the patients was acute at onset. It has been seen that the cardiology follow-up of cancer survivor patients is important, and cumulative incidence of adverse cardiovascular outcomes in childhood cancer survivor patients by the age of 45 years are significantly higher.[21] Unfortunately, the current data lacked the long-term follow-up needed to assess chemotherapy-induced adverse effects.

The OS of patients who completed the treatment was acceptable, taking into the consideration the advanced disease at presentation, nutritional status, and other co-morbidities. Low-stage disease has better outcomes, hence early identification of the disease, timely referral and better supportive care can improve outcomes. A significant number of patients in the current study had abandoned treatment, and almost similar results of abandonments had been reported from other resource-limited countries.[22] Factors contributing to the abandonment are low socioeconomic status, lodging expenses and fear of chemotherapy.

Conclusion

Paediatric NHL patients were found to have the same presentation and outcomes compared to their counterparts in other resource-limited countries. The patients who tolerated chemotherapy well had better outcomes. However, better supportive care is essential along with intensive chemotherapy protocols that may improve outcome of infection-related morbidity and mortality. A nationwide chemotherapy protocol for advanced disease can be helpful.

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