RESEARCH ARTICLE

Outcome of first relapse of Hodgkin lymphoma: single institution experience

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Abstract

Objective: To determine outcome of first relapse of Hodgkin lymphoma with standard dose chemotherapy, and to identify the prognostic factors predicting survival outcome in paediatric patients.

Method: The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of Hodgkin lymphoma patients who relapsed at least 3 months after the completion of initial treatment from January 2001 to December 2010. Probabilities of overall survival, event-free survival and cumulative incidence were calculated. Data was analysed using SPSS 21.

Results: Of the 43 patients, 31(72%) were males and 12(29%) were females. Mean age at relapse was 11±3.3 years (range: 4-17 years). In 31(72%) patients, early post-operative intraperitoneal chemotherapy was employed. Median follow-up of the cohort was 62 months (interquartile range: 4-187 months). Overall survival and event-free survival at 10 years was 23(54%) and 15(35%) respectively. On univariate analysis, initial disease stage (p=0.021), stage at relapse (p=0.003), treatment protocol (p=0.005), treatment responsiveness at initial two cycles of salvage chemotherapy (p=0.002) and at the end of treatment assessment (p=0.0009) were statistically significant factors. Multivariate cox regression analysis revealed disease stage at relapse (p=0.004), chemotherapy regimen (p=0.025) and end-of-treatment disease evaluation (p=0.005) as the significant variables.

Conclusion: Improved outcome with early post-operative intraperitoneal chemotherapy regimen was noted for Hodgkin lymphoma patients who had disease-free interval >2 years.

Keywords: B symptoms, Chemo-sensitivity, Mediastinal mass, Stage 4, Relapse Hodgkin lymphoma. (JPMA 71: 883; 2021)

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Introduction

Children with Hodgkin lymphoma (HL) have excellent outcome with 5 years survival rates between 80-90% by virtue of combined modality treatment. However, 10% patients with localised disease and 25% of those with advanced disease suffer relapse after first-line treatment.[1-4] Children with relapsed HL (rHL) have a substantial chance of cure depending on prognostic factors at the time of relapse. The backbone of salvage regimens is based on non-cross resistant drugs in combination with and without radiation.[5-7] Since the introduction of high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT), remission rate for relapsed HL patients has improved with reported overall survival (OS) and disease-free survival (DFS) of 65% and 60% respectively in the high-risk group.[8-10] In adults, shorter time to relapse, anaemia and higher stage at the time of relapse are considered poor predictors of outcome.[11] In paediatric series, previously identified predictors of poor survival included time to frontline treatment failure, presence of B-symptoms, mediastinal bulk, extra-nodal disease, advanced stage, anaemia at the time of treatment failure and chemo-sensitivity to salvage regimen. However, there is no uniform model for risk stratification and treatment assignment based on prognostic factors at the time of relapse.[7,12-14]

The current study was planned to examine outcome for first relapse of HL treatment with standard dose chemotherapy with and without radiation, but without HDCT and ASCT, and to identify prognostic factors that predicted survival outcome in paediatric rHL.

Materials and Methods

The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of HL patients who relapsed at least 3 months after the completion of initial treatment from January 2001 to December 2010. The data was retrieved after approval from the institutional ethics review board`. Relapsed HL was defined as diagnosis of HL at least 3 months after the completion of initial treatment where end-of-therapy evaluation had confirmed complete response (CR) on the basis of conventional imaging criteria. Data of patients with primary progressive/refractory disease was excluded.

Data was collected by reviewing electronic medical records (EMR) from the time of initial diagnosis and after the time of first relapse. In addition, records of multidisciplinary

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meetings (MDTS) were reviewed in cases where it was available. Disease-free interval (DFI) was calculated from the end of first-line treatment to the date of relapse. The age of the patients, disease stage, presence of B-symptoms, mediastinal mass and anaemia at the time of relapse were recorded. Treatment details for each case, including chemotherapy regimens and radiation therapy, were noted. Patients in CR had been followed according to the institutional surveillance guidelines comprising physical examination, X-ray chest, abdominal ultrasonography, erythrocyte sedimentation rate (ESR) and complete blood count (CBC) at each visit.

Prognostic factors about event-free survival (EFS) and OS after treatment of rHL, including time to relapse (DFI 3-12 months, and >12 months from the completion of first-line therapy), B-symptoms, extra-nodal disease, anaemia (haemoglobin [Hb] <10.5 g/dl for girls and <12g/dl for boys), bulky mediastinum (mediastinal mass greater than or equal to one-third of maximum diameter of thoracic wall), histopathology, stage 4 at the time of initial diagnosis and cycles of salvage chemotherapy, and at the end of the treatment.[15,16]

All relapses were histologically confirmed. The study focussed on two histological sub-types of classical HL; mixed cellularity and nodular sclerosis. The restaging was done in all relapsed patients according to the modified Anne Arbor staging system; with computed tomography (CT) scans and Gallium-67 whole-body scans or 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) scan; the latter imaging modality became available at our centre after 2007. Bone marrow biopsies were also performed in all relapsed cases to complete the restaging work-up.[17]

Most commonly used standard dose chemotherapy (SDCT) regimen (EPIC) comprising etoposide, prednisolone, ifosfamide and cisplatin.[18]

CR was defined as disappearance of all lymphoma-related clinical symptoms and complete radiological resolution of all measurable disease or non-measurable tumour volume (residual volume <25% of diagnostic nodal volume) or negative Gallium or PET scan. Partial response (PR) was defined as 50-74% reduction in tumour size in any axis of measureable nodal mass in a CT scan. Stable disease (SD) was defined as change in volume of <20%, whereas progressive disease (PD) was defined as appearance of any new lesion or >25% increase in any of the previous lesion with or without reappearance of disease-related symptoms.

Data was analysed using SPSS 21. OS was calculated from the date of relapse to the last contact or death from any cause. PD, second relapse (SR), treatment abandonment, second malignant neoplasm (SMN) and death from any cause were defined as events. The primary end-point was EFS, defined as the time from first relapse to event or last follow-up contact for patients who did not have an event. Probabilities of OS, EFS and cumulative incidence were calculated using Kaplan-Meier method. Log rank tests were used to compare survival curves and wald $p<0.05$ was considered significant. The impact of prognostic factors, including time to relapse, mediastinal mass, stage 4 at initial diagnosis and at relapse, presence of anaemia, response to salvage chemotherapy and effectiveness of chemotherapy regimens, were evaluated as independent variables. Proportional hazard assumption was determined using Schoenfeld residual method. Univariate analysis was carried out employing Log Rank (Mantel-Cox) for each stratum. Cox proportional hazard regression model was used for multivariate analysis in order to assess the independent prognostic factors influencing survival outcomes.

Results

Of the 43 patients, 31(72%) were males and 12(29%) were females. Mean age at relapse was 11±3.3 years (range: 4-17 years). There were 32(74%) cases of mixed cellularity and 11(26%) of nodular sclerosis (Table). Median follow-up of the cohort was 62 months (interquartile range [IQR]: 4-187 months).

Overall, 33(77%) patients had received frontline hybrid chemotherapy protocol with chlorambucil, vinblastine, prednisolone, procarbazine (ChlVPP) alternating with doxorubicin, bleomycin, vincristine, dacarbazine (ABVD) followed by involved field radiation (IFRT) for those who had residual disease by conventional radiological criteria. The remaining 10(23%) patients were treated with initial 2 courses of vincristine, etoposide, prednisolone and doxorubicin (OEPA) followed by cyclophosphamide, vincristine, prednisolone and procarbazine (COPP). The number of COPP courses was determined by the initial disease stage.

The most commonly used standard dose chemotherapy (SDCT) regimen was EPIC given to 31(72%) patients. Etoposide 100 mg/m^2/day intravenous (IV) infusion was given over 60 minutes for days 1–4, prednisolone 60 mg/m^2/d orally for 5 days, ifosfamide 1g/m^2/day IV infusion over 60 minutes for days 1–5 with mesna hydration, and cisplatin 60mg/m^2, 24-hour continuous infusion on day 10. Chemotherapy cycles were administered every 3 weeks as an inpatient on count recovery with normal liver function test (LFT) and renal functions. Initially, 6 cycles of chemotherapy were planned for every patient, but it was cut short in some cases depending upon their disease responsiveness and clinical condition. In the remaining

Table: Patient characteristics.

	n (%)
Gender	
Males	31 (72.1)
Females	12 (28.9)
Pathology	
Nodular Sclerosis	11 (26)
Mixed cellularity	32 (74)
Primary stage	
Stage 2	12 (28)
Stage 3	18 (42)
Stage 4	13 (30)
Relapse stage	
Stage 1	2 (5)
Stage 2	12 (28)
Stage 3	13 (30)
Stage 4	16 (37)
B-symptoms at relapse	13 (30)
Mediastinal disease at relapse	23 (53)
Anaemia at relapse	33 (77)
Timing of relapse	
3- 12 months	8 (19)
13-24 months	16 (37)
>24 months	19 (44)

13(28%) patients, different regimens were used, including gemcitabine, vinorelbine (Gem/Vino), dexamethasone, high-dose cytarabine and cisplatin (DHAP), ifosfamide, carboplatin and etoposide (ICE) and dexamethasone, high-dose cytarabine and carboplatin (DHAC). IFRT) was administrated to all sites of nodal recurrence in 21(48%) patients after completion of chemotherapy. Those who had received radiotherapy during their first-line treatment and relapsed at the same site were not offered further radiation therapy.

Two (4.65%) patients died before any evaluation due to chemotherapy-related toxicities. Three (7%) patients with disease progression during second-line chemotherapy were considered for HDCT and ASCT. All of them died; 2(66.6%) because of disease refractoriness, and 1(33.3%) because of treatment-related toxicities. Also, 1(2.32%) death was reported as a result of secondary malignancy acute myeloid leukaemia 8 months after the completion of salvage chemotherapy for first relapse.

OS at 2, 5 and 10 years were 32(75%), 24(57%) and 23(54%) respectively with median OS of 54 months (IQR: 0-170 months). EFS at 2, 5 and 10 years was 19(45%), 15(35%) and 15(35%) respectively (Figure 1a-b) with median EFS of 13 months (IQR: 0-170 months). On univariate analysis, stage 4 at initial disease (Figure 2a, p=0.021) and at relapse (Figure 2b, p=0.003), treatment protocol (Figure 2c, p=0.005), treatment responsiveness at initial two cycles of salvage chemotherapy (Figure 2d, p=0.002) and at the end-of-treatment assessment (Figure 2e, p=0.0009) were statistically significant factors. Gender (p=0.89), B-

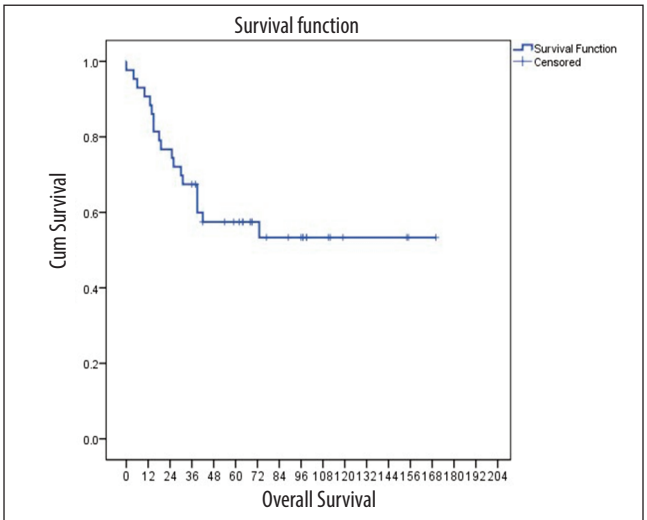

Figure-1a: Overall survival (OS) curves.

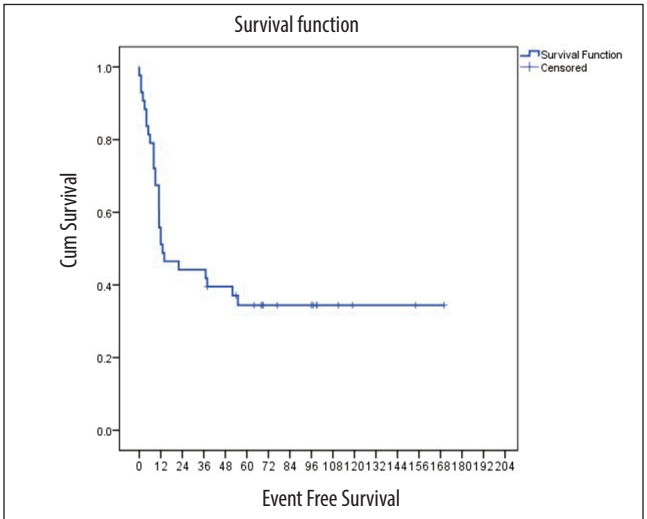

Figure-1b: Event-free survival (EFS).

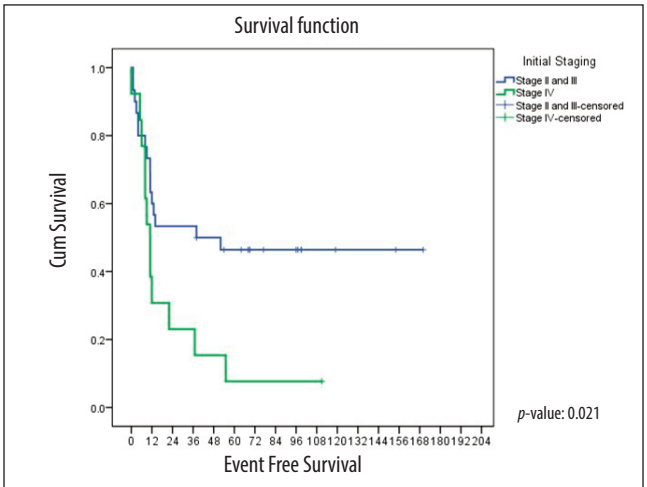

Figure-2a: Univariate analyses showing event free survival (EFS) based on initial staging.

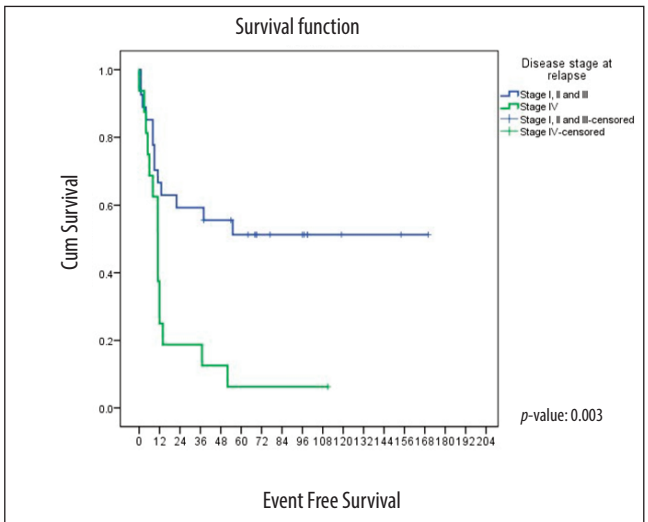

Figure-2b: Event-free survival (EFS) based on stage at relapse.

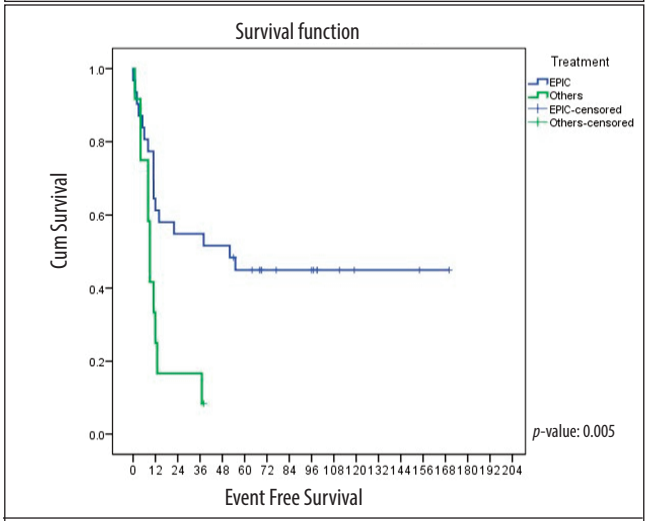

Figure-2c: Event-free survival (EFS) based on chemotherapy regimen.

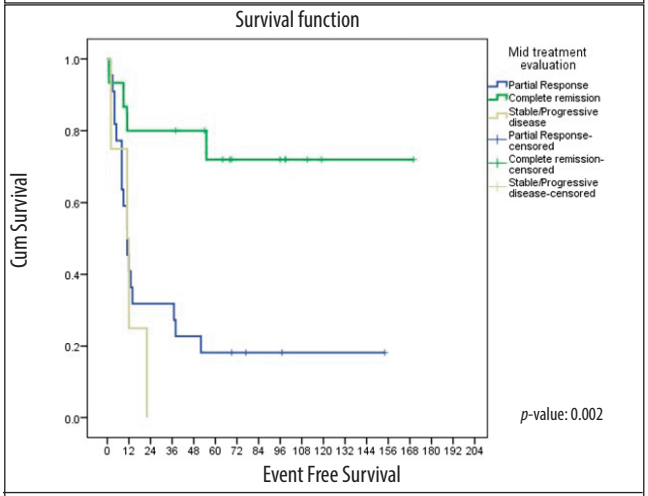

Figure-2d: Event-free survival (EFS) based on treatment response after initial 2 courses of chemotherapy.

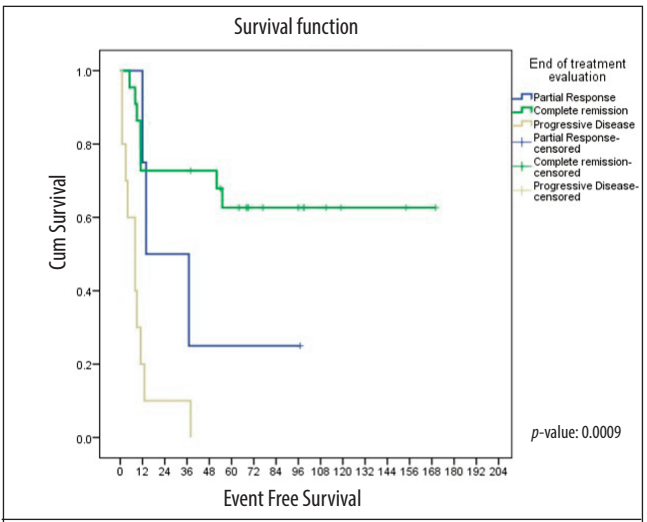

Figure-2e: Event-free survival (EFS) based on end-of-treatment evaluation.

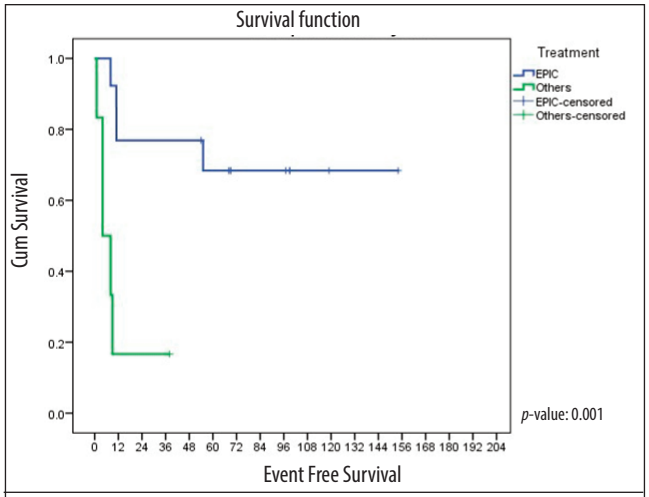

Figure-3: Event-free survival (EFS) based on chemotherapy regimen for relapse after 2 years.

symptoms at relapse (p=0.11), anaemia at relapse (p=0.43), mediastinal disease (p=0.91), histopathology (p=0.789) and DFI (p=0.135) were not found to be significant prognostic factors. Multivariate cox regression analysis revealed disease stage at relapse (p=0.004), chemotherapy regimen (p=0.025) and end-of-treatment disease response (p=0.005) as significant variables.

Further, 8(18.6%) patients relapsed at 3-12 months, 16(37.2%) at 13-24 months and 19(44.2%) after 24 months. The treatment regimen was not a significant factor for the patients with DFI 3-24 months (p=0.25). There were 2(6.45%) treatment-related deaths in patients treated with EPIC regimen. Patients with DFI >24 months and treated with EPIC regimen had median EFS 69 months from first relapse compared to only 6 months in those who received other regimens. Of the 13 patients with DFI>24 months treated with EPIC), 11(84.6%) were long-term survivors

(Figure 3, p=0.001), while 1(7.7%) patient had disease progression and 1(7.7%) suffered from disease recurrence; both of them subsequently abandoned the treatment. Of the 6(31.5%) patients with DFI >24 months who were treated with regimens other than EPIC, 5(83.3%) had disease progression as second event, and 1(16.6%) abandoned the treatment.

Discussion

To the best of our knowledge, this is the first comprehensive study from Pakistan addressing outcome of first relapse of HL and predictive value of various risk factors in children and adolescents at the time of relapse. Also, this is among the few paediatric series in which majority of patients were treated uniformly at diagnosis, as well as at relapse.

Results confirmed the prognostic significance of chemo-responsiveness in relapse setting. Relapsed HL patients whose disease was unresponsive to salvage chemotherapy had an inferior outcome despite additional intensive salvage regimens and ASCT. On the other hand, the outcome of patients with adequate response to salvage chemotherapy was excellent with OS of 72%. None of these patients were treated with HDCT and ASCT, and there were only 9 events in this subgroup. This is an important finding for resource-poor countries, where access to intensive HDCT and ASCT is limited and expensive.

Poor response to re-induction chemotherapy had unfavourable impact on the survival outcome of rHL. EFS for patients with inadequate response after initial 2 courses of salvage chemotherapy was 20% (p=0.002). Our findings are in agreement with another paediatric series which reported superior outcome (>70%) in patients with good response to salvage therapy compared to patients with progression or poor response (10%). Similarly, a study reported 100% second CR in patients who had adequate response (CR/PR) to retrieval chemotherapy with low and intermediate risk disease at the time of relapse. The cohort was treated with non-myeloablative combined modality therapy and none of them died of the disease.[13,19]

In the current study, there was a trend towards poorer survival for patients with high-stage disease at initial diagnosis and at the time of first relapse. Children who presented with stage 4 at the time of upfront treatment had 5-year EFS of 10% compared to 46% (p=0.021) for those who had stage 1-3. Similar trends with stage 4 disease were observed at the time of recurrence (p=0.003). Also, majority of patients with stage 4 disease at diagnosis had stage 4 disease at the time of relapse even after acquiring complete radiological remission at the end of treatment. This finding is in line with other international studies emphasising that disease burden at diagnosis is a critical predictor of treatment resistance in patients with advanced stage HL.[20]

The cumulative incidence of rHL is approximately 10% and its management remains clinically important and challenging. The backbone of salvage regimens is based on new drugs combination with and without radiation and HDCT and ASCT.[21] In paediatric series, there is paucity of randomised trials to define the best salvage regimen for rHL, but a wide range is available with overall response rate of 70-90% and complete response rate of 20-55%.[22] A study reported EPIC as an effective regimen with response rate of 58% and low treatment-related morbidity and mortality.[23] In our study, EPIC chemotherapy appeared to be an effective regimen with overall response rate of 74%. It was well tolerated by most patients. Patients who were treated with EPIC had 45% EFS compared to <20% for those having received other regimens (p=0.005). This EFS difference was more pronounced in children who relapsed after 24 months (70% vs 18%, p=0.001). There is also limited data comparison of conventional chemotherapy versus ASCT among children with rHL. Currently, there is increasing data suggesting that low-risk relapse can be successfully treated with conventional chemotherapy and or radiation.[24]

A retrospective study revealed no survival difference among children who were treated with ASCT compared to those who received standard dose chemotherapy at relapse (p=0.4). Comparable outcome with standard dose chemotherapy with or without ASCT has also been reported.[25]

At present, there is no consensus on a standard model for risk stratification for rHL, which might in turn define the risk-adapted treatment strategies. Among the known prognostic factors, time to treatment failure has been reported as a strong predictor of outcome in literature.[18,24] In our cohort, time to relapse (3-12 months: p= 0.12, 13-24 months=0.073 and >24 months: p=0.57) was not a significant factor. Our results may be confounded due to small number of patients in the early relapse (3-12 months) group.

In HL survivors, second malignant neoplasms are extensively reported in the literature partly due to reliance on alkylator-based chemotherapy and radiotherapy and partly due to the long-term data available for HL survivors.[26] In our series, one patient developed acute myeloid leukaemia 8 months after completion of salvage treatment.

The current study has potential limitations that are inherent in all retrospective studies. A significant number of our patients had CT scan-based assessment to re-induction chemotherapy which is especially problematic

in the interpretation of residual fibrosis in HL.

Conclusion

First relapse HL is potentially salvageable with standard dose chemotherapy with/without radiation. The patients with early stage at relapse and those with chemo-responsiveness can be effectively treated without high-dose chemotherapy and ASCT. The outcome was better with EPIC regimen for patients who had DFI >2 years.

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