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Intensive Induction Chemotherapy Followed by Early High-Dose Therapy and Hematopoietic Stem Cell Transplantation Results in Improved Outcome for Patients with Hepatosplenic T-Cell Lymphoma: A Single Institution Experience

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Abstract

Hepatosplenic T-cell lymphoma is a rare form of non-Hodgkin lymphoma, which carries a poor prognosis. We report our single-institution experience in the management of hepatosplenic T-cell lymphoma (HSTCL)- in 14 patients (pts) among whom 7 who remain alive (50%) and in remission at a median follow-up of 66 months. More frequent long-term survival was seen in those treated with a non-CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) induction and consolidative stem cell transplant (SCT).

Introduction—Hepatosplenic T-cell lymphoma is a rare form of extranodal non-Hodgkin lymphoma, first recognized as a distinct entity in the Revised European-American Lymphoma classification. Typical presentation includes lymphomatous infiltration of spleen and liver, and peripheral lymphadenopathy is rarely seen. The prognosis is almost uniformly poor, and there are no prospective studies of treatment of HSTCL.

Patients and Methods—For this report, we conducted a retrospective review of all pts who underwent treatment for HSTCL at our institution. Individual chart review was performed to report clinical presentation, management, and outcome.

Results—We identified 14 pts with HSTCL managed at our center, 7 of which remain alive with median follow-up of 65.6 months. Six of 7 received alternative induction chemotherapy regimens such as ICE (ifosfamide, carboplatin, etoposide) or IVAC (ifosfamide, etoposide, high-dose cytarabine) as opposed to CHOP and all surviving pts had proceeded to undergo either autologous or allogeneic SCT.

Conclusion—Our results suggest that use of non-CHOP induction regimen and early use of high dose therapy and SCT consolidation may translate to improved survival for pts with HSTCL.

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Keywords

Peripheral; TCR gamma-delta

Introduction

Described first by Farcet et al in 1990,[1] hepatosplenic T-cell lymphoma (HSTCL) is a distinct lymphoma entity with unique clinicopathologic features and poor clinical outcome, which has been recognized in the revised European-American Lymphoma classification in 1994[2] and in the subsequent World Health Organization classifications.[3–7]

Hepatosplenic T-cell lymphoma can occur at any age but is most often seen in teenagers or young adults, with a strong male predominance. [1,8–12] It is an extremely rare lymphoma making up <5% of peripheral T-cell lymphomas.[5,12] Immunocompromised patients are overrepresented, with reports of HSTCL developing during long-term immunosuppression after solid-organ transplant[13–15] and in the setting of other immune dysregulation including malignancy and infection.[16,17] The importance of iatrogenic immunosuppression as a contributor to lymphomagenesis has become particularly relevant in light of increased incidence of HSTCL in patients with chronic inflammatory diseases after treatment with immunosuppressants, specifically agents blocking tumor necrosis factor (TNF)-α and/or thiopurine agents.[18–24]

Occurrence is predominant in young male adults, who typically present with hepatosplenomegaly and peripheral blood cytopenias, especially thrombocytopenia. B-symptoms are common, whereas peripheral lymphadenopathy is usually absent. Patients are most frequently diagnosed after splenectomy and/or liver biopsy, although bone marrow biopsy with an appropriate immunophenotype in this clinical setting might be sufficient to make the diagnosis.[4,25] On pathologic review, neoplastic cells are commonly found in the red pulp of the spleen and show a preference to infiltrate the splenic, hepatic, and bone marrow sinusoids.[11,26] The immunophenotype typically is a $CD4^-/CD8^-$ T-cell with $CD2^+$ and $CD3^+$ expression. Other markers such as CD5, CD25, TIA-1, and granzyme B are usually absent. NK cell markers, such as CD56 and CD16 might be expressed.[4,5,12,25,26] The malignant cells most often express a $\gamma\delta$ T-cell phenotype as can be demonstrated by flow cytometry, and as such βF-1 staining is not found.[5,11] Reports have described similar clinical presentations with tumor cells expressing an $\alpha\beta$-phenotype,[27,28] and are considered an immunophenotypic variant of the same disease entity in the World Health Organization classification. The T-cell receptor (TCR) γ gene is always clonally rearranged[4,5,12,25,26]; the T-cell β gene might be rearranged as well.[4] Cytogenetic evaluation frequently demonstrates isochromosome 7q although this is not specific for this disease.[29–32]

In the literature, the prognosis of HSTCL is almost uniformly poor, and no prospective trials investigating treatment approaches are reported. Most of the published data consists of case reports and series, with 2 larger single-institution series focused on treatment outcome, demonstrating exceedingly poor long-term therapeutic results with a CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)-based regimen.[25,33]Anecdotal activity of several other chemotherapy regimens has been reported in form of case

reports.[34–39] Several authors have published experiences with high-dose therapy (HDT) autologous or allogeneic stem cell transplantation (SCT),[11,12,25,33,40–46] and a 2007 collection of published case reports of HSTCL treated with allogeneic stem cell transplantation suggests a better outcome for that approach.[47]

Patients and Methods

To investigate our center's experience in the management of HSTCL, we conducted a search using our T-cell lymphoma and bone marrow transplant databases. Included in this report were all patients treated at Memorial Sloan-Kettering Cancer Center with a diagnosis of HSTCL, for whom follow-up information was available. This report summarizes our single-center experience with 14 consecutive patients treated between the years of 1994 and 2012. We reviewed each patient's records for characteristics of initial clinical presentation, the immunohistochemistry of lymphomatous cells, treatment regimen, and responses. Sufficient data to calculate an International Prognostic Index (IPI)[48] and prognostic index for peripheral T-cell lymphoma (PIT)[49] were available for 12 of 14 subjects with 2 patients missing lactate dehydrogenase (LDH) values at time of diagnosis. Kaplan–Meier curves were calculated to determine overall survival (OS) and progression-free survival (PFS). Log-rank χ^2 test was used to compare the effect of clinical variables on survival.

Results

Patient Characteristics

All patients were male with a median age of 36 years (range, 12–59 years, see also Table 1). All subjects had stage IV disease with hepatomegaly and/or splenomegaly. Ten of 14 cases (71%) had documented bone marrow involvement, 10 of 12 patients (91%) had elevated LDH, and all but 1 had B symptoms. Thrombocytopenia was present at diagnosis in 9 of 14 patients (64%), anemia in 12 of 14 patients (86%), and leukopenia in 6 of 14 patients (43%). Transaminases and/or alkaline phosphatase were elevated in 10 of 14 patients (71%). Eight of 14 cases (57%) had previous autoimmune disease: 2 with ulcerative colitis, 4 with Crohn's disease, and 2 with juvenile rheumatoid arthritis. Three patients had received both anti-TNFα therapy (2, infliximab; 1, adalimumab) and 6-mercaptopurine (6-MP); 3 had been treated only with 6-MP. Risk stratification per IPI and PIT are summarized in Table 2.

Clinical Outcomes

Responses to induction regimens were CHOP (complete remission [CR], 1; partial response [PR], 2; progression of disease [POD], l), ICE (ifosfamide, carboplatin, etoposide)/IVAC (ifosfamide, etoposide, high-dose cytarabine) (CR, 4; PR, 2; POD, 2), and pentostatin/2-CDA (POD, 2). Three patients induced with CHOP received ICE as second-line therapy, 2 of 3 achieved a CR. One patient received ICE as consolidation after obtaining a CR to CHOP before proceeding to SCT. Eleven of 14 patients achieved at least a PR and proceeded to HDT-SCT. Four patients received an autologous SCT, and 8 patients an allogeneic SCT (1 as a second graft after relapse from autologous SCT). At the time of this report, 7 of 14 patients are alive, 3–149 months from the time of diagnosis; the 7 surviving patients all underwent HDT-SCT. Six of these remain in remission, 1 relapsed <1 year after

allogeneic SCT, had been re-treated successfully with donor leukocyte infusions, but has since again relapsed. A total of 8 patients received ICE or IVAC as part of initial therapy and 5 of 8 are alive. Only 2 of 6 patients remain alive among those treated with other initial regimens and both surviving patients received ICE as part of consolidation before HDT-SCT. After autologous-SCT, 2 of 4 patients relapsed at 5 and 35 months. Moreover, after allogeneic-SCT 2 of 7 patients relapsed at 3 and 6 months. Two of 8 patients undergoing allo-SCT died of treatment-related toxicities. With a median follow-up time of 66 months, median PFS and OS for the entire cohort are 13.3 months (range, 2.4–148) and 59 months (range, 4–150 months), respectively (Figure 1).

Complete information to calculate respective prognostic indexes (IPI or PIT) were available for 12 of 14 patients. A correlation with outcome could not be found for either of the 2. Three of 4 patients with an IPI of low to low-intermediate risk (0–2 factors) remain alive compared with 3 of 8 patients with IPI high-intermediate to high-risk disease (≥3 factors) (P = .267) (Figure 2). For the PIT, all 12 patients had at least 1 risk factor: 6 of 10 patients with a PIT of 1–2 are alive versus 0 of 2 patients for PIT of ≥3 (P = .117).

Discussion

Management of HSTCL is challenging, and historically, outcome has almost uniformly been poor. There are no prospective trials to provide guidance for the treatment of this disease, and most of the current literature consists of case reports or case review series. Chemotherapy regimens employed in other series include CHOP and CHOP-like regimen,[25] alemtuzumab/cladribine,[34] hyperCVAD,[35] fludarabine/alemtuzumab,[36] IEV (ifosfamide, epirubicin, and etoposide),[37] and pentostatin.[38,39] Several authors suggest superior outcome with the addition of HDT-SCT, and a number of reports include cases treated successfully with autologous and allogeneic SCT.[11,12,25,33,40–47] There are only 2 reports of larger single-center experiences in the literature thus far. The first was published by Belhadj and colleagues in 2003 and includes data from 21 patients with HSTCL diagnosed between 1981 and 2001.[25] In their report, most patients (90.5%) received induction treatment with CHOP or CHOP-like regimens, and 2 of 21 subjects (9.5%) were induced using platinum cytarabine-based therapy. Seven of 21 patients (33.3%) failed to respond to induction, all died within 16 months. Nine of 21 patients (43%) achieved a CR, 5 of 21 patients (24%) a good PR, the latter including patients induced with non-CHOP regimen. Nine of 21 patients (43%) went on to either allogeneic bone marrow transplantation (3 of 21 patients—2 died of treatment-related disease, 1 with POD) or autologous bone marrow transplantation (6 of 21 patients (28.6%), 4 of which died within 13–33 months). Despite response to induction treatment in two-thirds of the treated patients, long-term therapeutic results were poor with a median survival of 16 months. At the time of report only 2 of 21 patients (9.5%) were alive; both had received induction treatment with platinum/cytarabine with PR and gone on to autologous bone marrow transplant. More recently, Falchook and colleagues published their single-center experience on 14 patients with HSTCL treated at M.D. Anderson Cancer Center between 1997 and 2007.[33] Despite CR rates of 50% with various induction regimens, the duration was short-lived in most cases, and median survival was 8 months. Similar to other reports, all patients treated with CHOP-like regimen (6 of 14) did poorly. The 4 patients (29%) that were alive at the time of report (11–36 months) had been induced with

more intense regimen, 3 of 4 survivors had been consolidated with allogeneic SCT. From these data the authors attempted to identify possible clinical characteristics to help predict outcome. Sex was the only factor conferring a statistically different survival (median OS 25 months in female vs. 8 months in male patients). There were trends suggesting better survival in patients with TCR rearrangements in the γ chain with all 4 patients with such rearrangement achieving CR and still alive in remission, though statistically nonsignificant trends toward worse survival were seen with liver involvement at diagnosis (median OS 7.5 vs. 13 months without liver involvement) and history of prior immunocompromise (median OS 6 vs. 11 months without prior immunocompromise). No trends in OS were seen for age, presence of B-symptoms, or cytopenias at presentation, TCR status, or cytogenetics.

Our single-institution experience further supports the notion that use of non-CHOP induction chemotherapy regimens such as ICE or IVAC and early HDT-SCT consolidation might improve the outcome for patients with HSTCL compared with reported results with CHOP or CHOP-like regimens alone. At the time of this report, 7 of 14 patients (50%) remain alive, 5 of which were initially treated with non-CHOP regimen. All 7 surviving patients had preceded to HDT-SCT, 5 receiving an allogeneic, and 2 an autologous graft. Both patients treated with autologous SCT were in CR at the time of transplant, while 2 of 5 recipients of allogeneic grafts received transplant in PR. The 3 patients that did not undergo SCT as part of their management did poorly (see also Figure 1).

When applying the prognostic factors suggested by Falchook and colleagues, our data do not confirm a trend toward worse OS in patients with liver involvement at the time of diagnosis ($P = .382$), nor improved OS in patients with γTCR rearrangements ($P = .919$) or previous history of immunosuppression ($P = .455$). Formally established scoring models used to assess prognosis in peripheral T-cell lymphoma include the IPI[48] and the PIT.[49] These systems might not be as useful for stratifying patients with HSTCL because those affected are almost universally young with stage IV disease. As noted above, we were unable to show correlation with outcome for either of the 2 prognostic models, bearing in mind the limitations of our sample size. Notably, for patients who are not estimated among the highest risk at initial presentation (PIT < 3; IPI < 3) our data show long-term survivors among those consolidated with autologous as well as allogeneic SCT.

Serial reports of HSTCL in patients receiving immunosuppressive therapy with agents blocking TNF-α have prompted a safety alert through the US FDA, originally issued in 2009 and recently updated.[50]An increase in incidence has also been reported with other immunosuppressants such as azathioprine, or 6-MP.[24,51–53] The contribution of the underlying autoimmune disease itself is less well established for inflammatory bowel diseases[54] than for autoimmune arthritis.[55] In our series, 8 of 14 patients carried a diagnosis of autoimmune disease, 6 of which were treated with systemic immunosuppressants other than corticosteroids. Only 3 had received previous TNF-α blockade, which was given sequentially or in combination with 6-MP. The other 3 patients had been treated with 6-MP alone. Two patients with a previous diagnosis of autoimmune disease had no documented history of such immunosuppression, but for 1 of them previous treatment records for juvenile arthritis were unavailable to our review.

Conclusion

Our choice of transplant approach has largely been guided by the availability of a suitable donor. Though our series is clearly too small to draw definitive conclusions our preference is for allogeneic SCT. However, our experience suggests HDT and consolidation with autologous SCT represents a reasonable alternative for those who can achieve a CR to their initial chemotherapy. Certainly for patients without a suitable allogeneic donor, this is our preferred approach.

As a case series, this study's principal limitations are the small number of subjects and its retrospective nature. It certainly cannot dissect the relative importance of the individual components of therapy (non-CHOP induction vs. HDT consolidation). In the absence of prospective trials for this very rare disease, it might however provide guidance in the treatment of these young patients with no established standard of care.

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Clinical Practice Points

- Hepatosplenic T-cell lymphoma typically presents with infiltration of spleen and liver and rarely involves nodal regions.
- A history of inflammatory bowel disease might predispose patients to the development of HSTCL; the use of TNF-α antagonist or 6-MP analogs might also increase this risk.
- Of the 14 patients in our study, 7 remain alive; 6 received non–CHOP-based induction therapies (ICE or IVAC).
- All patients who remained without evidence of disease underwent consolidative transplantation.
- In our experience, consideration of a non–CHOP-based induction therapy with intent to consolidate with an allogeneic SCT in first CR appears to be a necessity considering the high propensity of primary refractory or short interval relapse associated with HSTCL.

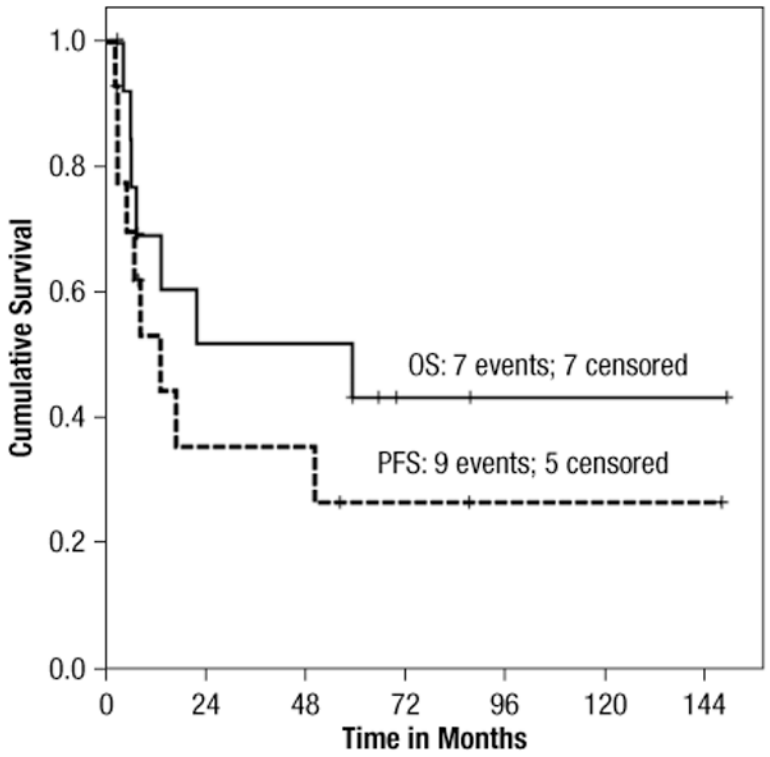

Figure 1.

Progression-Free Survival and Overall Survival. Kaplan-Meier Curve of Progression-Free Survival and Overall Survival in Our Cohort

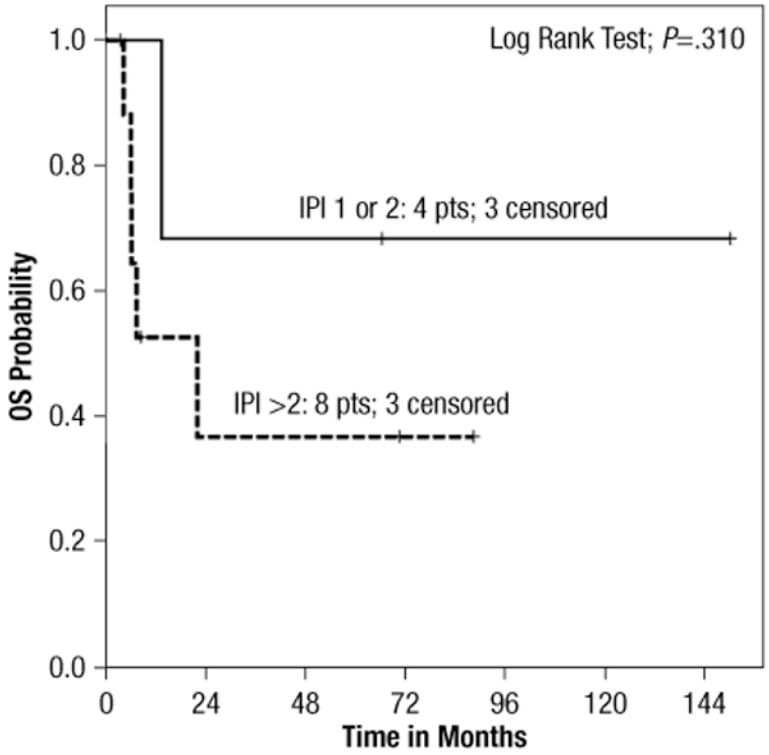

Figure 2.

Survival per IPI. Kaplan-Meyer Curve Stratified in Groups with International Prognostic Index (IPI) 0–2 Versus 3–5 Demonstrating No Significant Difference in Overall Survival

Table 1

Clinical Presentation

Patient Number	Age/Sex	HM	SM	LAN	B-Sx	Hgb	Pltl	WBC	LDH	LFT	BM	EBV	Comorbidities	IS-Therapy
1	46/M	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	None	No
2	34/M	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	UC	6-MP
3	51/M	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	HTN, DM, Emphysema	No
4	23/M	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	jRA	Unclear
5	37/M	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	NA	UC Seminoma	6-MP
6	59/M	Yes	No	Yes	Yes	Yes	No	No	NA	NA	No	NA	PVD	No
7	12/M	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Asthma	No
8	19/M	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	NA	None	No
9	48/M	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NA	jRA	No
10	53/M	No	Yes	Yes	Yes	Yes	No	Yes	NA	NA	Yes	NA	Depression	No
11	50/M	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	CD	Infliximab, 6-MP
12	22/M	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	CD	6-MP
13	27/M	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	CD	Adalimumab, 6-MP
14	18/M	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	NA	CD	Infliximab, 6-MP

Listed for all 14 patients are clinical, laboratory, and pathologic variables at the time of diagnosis, comorbidities, and previous immunosuppressive therapy.

Abbreviations: 6-MP = 6-mercaptopurine; BM = bone marrow involvement; B-Sx = presence of B-symptoms; CD = Crohn's disease; DM = diabetes mellitus; EBV = evidence of Ebstein Barr virus in pathologic specimen; Hgb = decreased hemoglobin; HM = hepatomegaly; HTN = hypertension; IS-Therapy = prior immunosuppressive therapy other than steroids; jRA = juvenile rheumatoid arthritis; LAN = lymphadenopathy; LDH = elevated lactate dehydrogenase; LFT = abnormal liver function tests; M = male; NA = not assessed; Pltl = decreased platelet count; PVD = peripheral vascular disease; SM = splenomegaly; UC = ulcerative colitis; WBC = abnormal leukocyte count.

Table 2

Treatment Summary and Response to Therapy[b]

Patient Number	Time to Treatment Start (Months)	Removal of Spleen	Induction Regimen	Response Induction	Further Regimen (Pre-Txp)	Auto or Allo	Status at Time of Txp	Conditioning Regimen	$CD34^+$ Dose ($\times 10^6$/kg)	Response to Txp	Relapse, After Txp (Months)	Further Treatment Post Txp	Response to Further Rx	IPI	PIT	OS From Induction (Months)	Status
1	10	Yes	ICE × 3	CR	None	Allo	CR	Melphalan, fludarabine, campath	9.4	CR	6	DLI	CR	3 (HI)	1	50.5	Alive
2	2	No	IVAC × 4	CR	None	Auto	CR	Etoposide, cyclophosphamide, TBI	10	CR	—	—	NA	3 (HI)	2	57.7	Alive
3	6	Yes	IVAC × 4	POD	EPOCH × 2	Allo	CR	TBI, thiotepa, cyclophosphamide	27.4	CR	—	—	NA	3 (HI)	3	9.9	DOT
4	6	Yes	ICE × 3	PR	None	Allo	PR	Bus/mel/flu, splenic XRT, equine ATG	14.3	SD	3	Allo	CR	2 (LI)	1	66.0	Alive
5	4	Yes	CHOP × 2	POD	ICE × 5	Auto	CR	BEAM	2.58	CR	5	CIE	Unclear[a]	3 (HI)	2	21.7	DOD
6	1	Yes	CHOP × 1	PR	ICE × 4	Auto	CR	Cyclophosphamide, carmustine, etoposide	2.8	CR	25	CHOP × 3, Allo	PR	NA[b]	NA[b]	59.2	DOT
7	3	Yes	Pentostatin	POD	NYII–POD; topotecan/vinorelbine/thiotepa	Allo	PR	Thiotepa, cyclophosphamide, TBI, ATG	9.91	CR	3	TLR7 agonist, fludarabin cyclophosphamide, DLI	POD	1 (L)	0	13.1	DOD
8	4	Yes	2CDA × 2	POD	CHOP × 3-POD; ICE × 2	Allo	PR	TBI, cyclophosphamide	Unclear	CR	—	—	NA	1 (L)	2	149.6	Alive
9	2	No	CHOP × 4	PR	ICE-POD; EPOCH × 2	—	NA	NA	NA	NA	NA	NA	NA	4 (H)	3	5.9	DOD
10	4	Yes	CHOP × 6	CR	ICE	Auto	CR	BEAM	4.5	CR	—	—	NA	NA[b]	NA[b]	23	Alive
11	1	No	ICE × 4	PR	EPOCH × 1-POD; pentostatin × 4	—	NA	NA	NA	NA	NA	NA	NA	3 (HI)	2	4	DOD
12	1	No	ICE × 4	POD	None	—	NA	NA	NA	NA	NA	NA	NA	3 (HI)	2	5.7	DOD
13	2	No	IVAC × 4	CR	Campath × 1	Allo	CR	Thiotepa, cyclophosphamide, TBI	8.02	CR	NA	NA	NA	3 (HI)	2	4.7	Alive
14	4	No	Pediatric ALL induction then IVAC × 2	CR	None	Allo	CR	Etoposide, TBI	8.01	NRE	NA	NA	NA	2 (LI)	1	3	Alive

Listed for all 14 patients are initial chemotherapy regimens with response; further management including subsequent chemotherapy and transplant approach; risk stratification per IPI and PIT; overall survival, and vital status at the time of analysis. Time to treatment start indicates time interval between the onset of symptoms and start of induction.

Abbreviations: 2CDA = 2-chlorodeoxyadenosine/cladribine; ALL = acute lymphoblastic leukemia; ATG = antithymocyte globulin; BEAM = carmustine, etoposide, ara-C, melphalan; Bus/mel/flu = busulfan, melphalan, fludarabine; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; CIE = cyclophosphamide, idarubicin, etoposide; CR = complete response; DLI = donor leukocyte infusion; DOD = died of disease; DOT = treatment-related death; EPOCH = etoposide, vincristine, doxorubin, cyclophosphamide, prednisone; H = high; HD = high dose; HI = high intermediate; ICE = ifosfamide, carboplatin, etoposide; IPI = International Prognostic Index; IVAC = ifosfamide, etoposide, high dose cytarabine; L = low; LI = low intermediate; MTX = methotrexate; NRE = no response evaluable; NYII = high dose cytarabinec, daunorubicin, PEG asparaginase, cyclophosphamide, HD MTX, vincristine; OS = overall survival; PEG = pegylated; PIT = index for peripheral T-cell lymphoma; POD = progression of disease; PR = partial response; Rx = treatment; TBI = total body irradiation; TLR7 = toll-like receptor 7; Txp = transplant.

[a] Response unclear, treatment received at outside institution.

[b] Incomplete clinical information to fully determine score.