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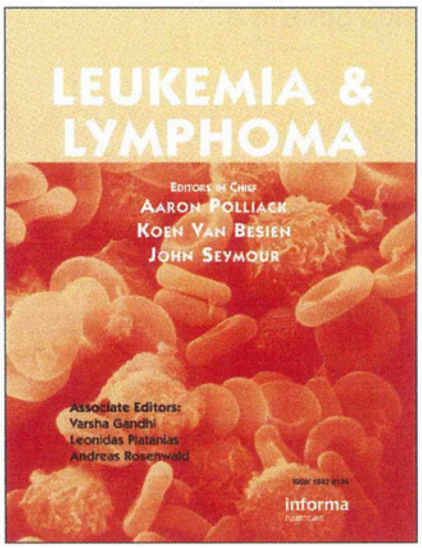

Quantitative PCR detection of CEP110-FGFR1 fusion gene in a patient with 8p11 syndrome

Shohei Yamamoto, Yasuhiro Ebihara, Shinji Mochizuki, Toshiro Kawakita, Seiko Kato, Jun Ooi, Satoshi Takahashi, Arinobu Tojo, Nozomi Yusa, Yoichi Furukawa, Naoki Oyaizu, Junichi Watanabe, Ken Sato, Fumihiko Kimura, Kohichiro Tsuji

doi:10.3109/10428194.2013.767455

Letter to the Editor

Quantitative PCR detection of CEP110-FGFR1 fusion gene in a patient with 8p11 syndrome

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The 8p11 myeloproliferative syndrome (EMS) is an aggressive chronic myeloproliferative disorder (MPD) which frequently accompanies with T or B lymphoblastic lymphoma (LBL), and rapidly transforms into acute myeloid leukemia (AML) [1,2]. The hallmark of this disease is the reciprocal translocation of fibroblast growth factor receptor 1 (FGFR1) gene on chromosome 8p11 and different gene partners [2]. Most common gene partner is ZNF198 at chromosome 13q12. CEP110 at chromosome 9p33 is also one of the partner genes, and only 13 cases have been reported until now [3-11]. The prognosis of EMS is poor despite aggressive chemotherapy, and a few patients can be cured with hematopoietic stem cell transplantation (HSCT) [2]. We describe here a case of EMS with t(8;9) (p12;q33)/CEP110-FGFR1 fusion transcript who never achieved molecular remission even by allogeneic HSCT, and developed an early relapse after the HSCT. We sequentially carried out real-time quantitative polymerase chain reaction (RQ-PCR) analysis for chimeric CEP110-FGFR1 fusion transcript, and demonstrated its usefulness to monitor minimal residual disease (MRD) since the results of RQ-PCR analysis were correlated with the disease status.

A 17-year-old male was admitted to previous hospital because of leukocytosis and lymphoadenopathy. Physical examination showed multiple lymphadenopathy and hepatosplenomegaly. Haemogram findings were as following: white blood cell count, 335 × 10^9 /L (neutrophils 7.5%, lymphocytes 2%, monocytes 3%, basophils 0.5%, eosinophils 1.5%, myelocytes 6% and myeloblasts 79.5%); hemoglobin concentration, 79g/L; and platelet count, 66 × 10^9 /L. LDH value was 907 IU/L. Bone marrow (BM) examination revealed marked hypercellularity with dysplasia and 76.2% of blasts, which were positive for CD2, CD7, CD19, CD13, CD33, CD117, CD34 and TdT, but negative for CD3, CD10, CD14 and myeloperoxidase. Chromosomal analysis of BM cells revealed 46, XY, t(8;9) (p12;q33) [20/20]. Based on these data, he was diagnosed as acute myeloid leukemia (AML-M0) with EMS, and received idarubicin/ cytarabine as an induction therapy. However, he did not achieve complete remission (CR), and was referred to our hospital for further treatment. Multiple lymphoadenopathy and hepatosplenomegaly were found on admission. BM examination showed 56.4% of myeloblasts (Figure 1). Biopsy of an inguinal lymph node (LN) showed diffuse infiltration by lymphoblasts positive for CD2, CD3, CD4, CD5, CD7, CD8 and TdT, consistent with T-LBL. Chromosome analyses of the BM and LN cells revealed

46, XY, t(8;9) (p12;q33) [20/20]. Reverse transcription-PCR analysis detected chimeric CEP110-FGFR1 fusion transcript in both BM and LN. RQ-PCR analysis of BM and LN showed $5.1x10^5$ and $9.4x10^5$ copies / microgram RNA of CEP110-FGFR1 fusion transcript, respectively. The gene rearrangement of BCR/ABL (major and minor), JAK2 V617F, FLT3-ITD and T-cell receptor were negative. The patient was treated by four courses of intensive chemotherapy, which resulted in the reduction of blasts in BM and the improvement of lymphadenopathy and hepatosplenomegaly, but the value of chimeric CEP110-FGFR1 fusion transcript of BM was still high ($1.8x10^5$ copies / microgram RNA). Because of the absence of HLA-matched related or unrelated donor, we chose allogeneic bone marrow transplantation (BMT) from HLA-DR 1 locus mismatched unrelated female donor. Unfortunately, blasts rapidly increased in peripheral blood and BM just before the allogeneic BMT. Cytogenetics examination showed that about half of the blasts had the t(8;9) translocation with additional abnormalities including trisomy of chromosome 21 [9/20]. Therefore, he received continuous low dose of cytarabine and etoposide for 8 days to reduce tumor burden, followed by the conditioning regimen using total body irradiation (12Gy), etoposide 60mg/kg and cyclophosphamide 120mg/kg. Total 2.01×10^8 nucleated cells / kg of BM cells from the donor were infused. Graft-versus-host disease (GVHD) prophylaxis included tacrolimus and short-term methotrexate. On day 16, Grade III acute GVHD (skin, stage 3; liver, stage 0; gut, stage 2) developed. Then, the patient received daily intravenous administration of prednisolone. The engraftment of neutrophil was observed on day 22. Hematological CR and complete chimera without chromosomal abnormality in BM were obtained on day 31, but since chimeric CEP110-FGFR1 fusion transcript still remained (1.6×10^2 copies / microgram RNA), immunosuppressants were tapered. However, BM examination on day 68 showed the relapse with 68.2% blasts, which had t(8;9) (p12;q33) and chimeric CEP110-FGFR1 fusion transcript at 4.6×10^5 copies / microgram RNA. The patient's general condition did not improve, and he died of progression disease 3 months after BMT.

EMS is a rare hematopoietic neoplasm characterized by a constellation of pathologic features and genetic alterations involving the FGFR1 located at 8p11[1]. Jackson et al. recently searched the literature for cases of EMS, and showed only 65 cases have been reported [2]. The majority of the EMS patients had myeloid hyperplasia, hyperleukocytosis, marked eosinophilia, monocytosis

and lymphoid organ involvement at diagnosis. In more than two thirds of EMS cases, T-LBL was present at diagnosis. 16% of EMS patients had acute leukemia at diagnosis. To our knowledge, only 13 EMS cases with t(8;9) (p11~12;q32~34) have been reported in the literature [3-11]. All patients had marked leukocytosis, and 10 cases showed eosinophilia and monocytosis. Concurrent T-LBL was described in four patients [3-6]. Two patients were diagnosed as *de novo* AML (myelomonocytic and biophenotypic) [7,8]. Six patients had a transformation of MPD, which progressed to AML (monocytic or myelomonocytic) [3,4,5,9,10,11]. Our patient had *de novo* AML accompanied with T-LBL. His myeloblasts showed the phenotype of marked immature myeloblasts coexpressing B cell lineage markers, which is of interest for considering the origin of ancestor cells which developed into AML and T-LBL.

Vizmanos et al. reported a patient with NIN-PDGFRB fusion transcript, in which they evaluated MRD by reverse transcription-PCR after treatment with imatinib[12].

In the present case, we sequentially performed RQ-PCR analysis for chimeric CEP110-FGFR1 fusion transcript to assess the therapeutic response during the treatment for the first time. The values of chimeric CEP110-FGFR1 fusion transcript before allogeneic BMT were kept at high levels in spite of intensive chemotherapy, showing our patient was refractory and chemotherapy-resistant. Notably, chimeric CEP110-FGFR1 fusion transcript was still detected after allogeneic BMT despite cytogenetical complete remission. This finding indicated that the MRD was present even though complete chimera without chromosomal abnormality was achieved by the BMT. Soon after, indeed, his disease cytogenetically relapsed with the increasing chimeric CEP110-FGFR1 fusion transcript. These results demonstrated that the values of chimeric CEP110-FGFR1 fusion transcript in RQ-PCR analysis were correlated with the disease status, and could be useful to monitor MRD in EMS patients with t(8;9) (p12;q33). In this context, it is of interest that Vizmanos et al. reported a patient with another fusion transcript of platelet-derived growth factor (PDGF) receptor and NIN, a gene encoding a CEP110-like centrosomal protein, who resulted in similar elevated transcript levels six months after treatment [12].

Conflict of interest

The authors declare no conflict of interest.

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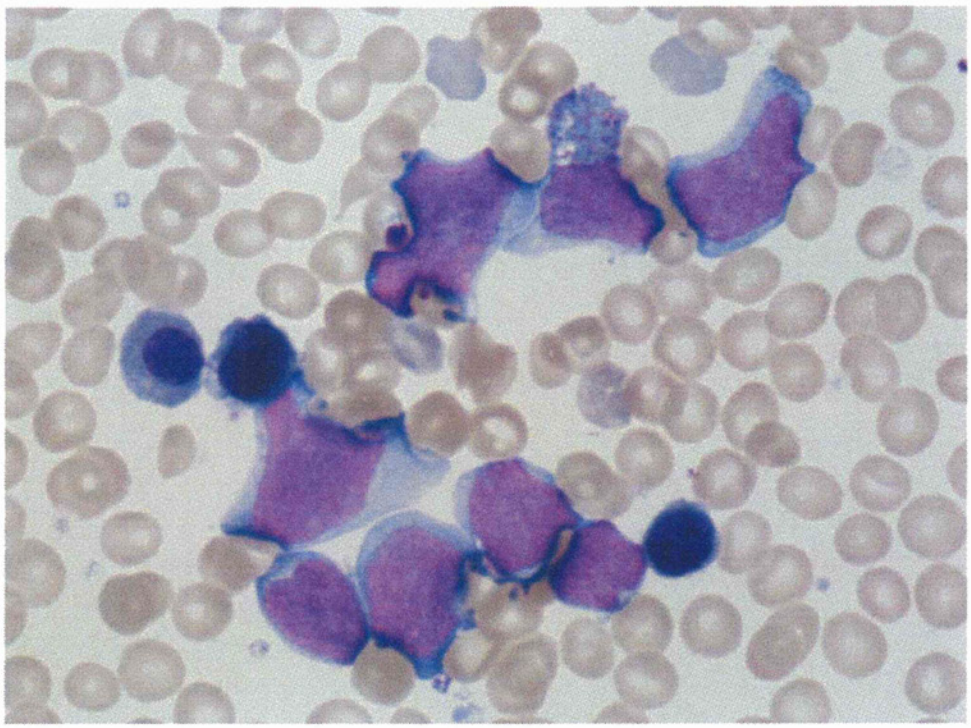
Figure legend

Figure 1

Bone marrow aspiration revealed markedly increased abnormal myeloblasts (May-Giemsa stain. ×1,000)



Transplant Infectious Disease, ISSN 1398-2273

Acute kidney injury after myeloablative cord blood transplantation in adults: the efficacy of strict monitoring of vancomycin serum trough concentrations

H. Mae, J. Ooi, S. Takahashi, S. Kato, T. Kawakita, Y. Ebihara, K. Tsuji, F. Nagamura, H. Echizen, A. Tojo. Acute kidney injury after myeloablative cord blood transplantation in adults: the efficacy of strict monitoring of vancomycin serum trough concentrations. Transpl Infect Dis 2012. All rights reserved

Abstract: *Background.* Acute kidney injury (AKI) is a common medical complication after myeloablative allogeneic stem cell transplantation (SCT). We have previously performed a retrospective analysis of AKI after cord blood transplantation (CBT) in adults, and found that the maximum of vancomycin (VCM) trough levels were significantly higher in patients with AKI. Following these results, we have monitored VCM serum trough concentrations more strictly, to not exceed 10.0 mg/L, since 2008.
Methods. In this report, we performed an analysis of AKI in a new group of 38 adult patients with hematological malignancies treated with unrelated CBT after myeloablative conditioning between January 2008 and July 2011.
Results. Cumulative incidence of AKI at day 100 after CBT was 34% (95% confidence interval 19–50). The median of the maximum value of VCM trough was 8.8 (4.5–12.2) mg/L. In multivariate analysis, no factor was associated with the incidence of AKI. No transplant-related mortality was observed. The probability of disease-free survival at 2 years was 83%.
Conclusion. These findings suggest that strict monitoring of VCM serum trough concentrations has a beneficial effect on outcomes of CBT.

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Key words: vancomycin; myeloablative conditioning; cord blood transplantation; acute kidney injury

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Received 14 May 2012, revised 17 July 2012, 13 August 2012, accepted for publication 18 August 2012

DOI: 10.1111/tid.12038
Transpl Infect Dis 2012: **0:** 1–6

Acute kidney injury (AKI) is a common medical complication early after myeloablative allogeneic stem cell transplantation (SCT). The incidence of AKI, defined as a 2-fold rise in serum creatinine (sCr) concentration from baseline, has been reported ranging from 36% to 72% in SCT in a myeloablative setting (1–7), and about 20% required hemodialysis. We have previously reported a retrospective analysis of AKI in a group of 54 adult patients with hematological malignancies who received unrelated cord blood transplantation (CBT) after myeloablative conditioning between 2004 and 2007 (8). A statistically significant decrement of renal function from baseline was observed between days 11 and 20. Among the 54 patients, AKI occurred in 27.8% and was associated with a high mortality rate. Although no difference was seen in maximum cyclosporine (CYA) trough levels, the maximum vancomycin (VCM) trough levels were significantly higher in patients with AKI (8). Following these results, we have monitored VCM serum trough concentrations more strictly. In this report, we performed an analysis of AKI in a new group of 38 adult patients with hematological malignancies treated with unrelated CBT after myeloablative conditioning between January 2008 and

July 2011. The main purpose of this retrospective single-center study was to confirm the efficacy of strict monitoring of VCM serum trough concentrations, as well as to identify factors related to the incidence of AKI.

Patients and methods

Patients

This was a retrospective single-center analysis. Between January 2008 and July 2011, 39 consecutive adult patients with hematological malignancies were treated with unrelated CBT at The Institute of Medical Science, University of Tokyo. We excluded 1 patient who experienced primary engraftment failure. A total of 38 patients were analyzed. Patients qualified as standard risk if they were in first or second complete remission, had chronic-phase chronic myelogenous leukemia or refractory anemia of myelodysplastic syndrome, or had no high-risk cytogenetics. Patients in third complete remission, in relapse, or in refractory disease, with chronic myelogenous leukemia beyond chronic phase, or with high-risk cytogenetics were classified as high risk. Analyses of data were performed in December 2011. Written informed consent for treatment was obtained from all patients.

Conditioning

All patients received 4 fractionated 12 Gy total body irradiation on days −8 and −7, in addition to cytosine arabinoside (Ara-C) and cyclophosphamide. Ara-C was administered intravenously (IV) over 2 h at a dose of 3 g/m^2 every 12 h on day −5 and −4 (total dose 12 g/m^2). In patients with myeloid malignancies, recombinant human granulocyte colony-stimulating factor (G-CSF) was combined with Ara-C. G-CSF was administered by continuous infusion at a dose of 5 μg/kg/day. Infusion of G-CSF was started 12 h before the first dose of Ara-C and stopped at the completion of the last dose. Cyclophosphamide was administered IV over 2 h at a dose of 60 mg/kg once daily on days −3 and −2 (total dose 120 mg/kg). Two days after the completion of conditioning, patients received a CBT.

Graft-versus-host disease (GVHD) prophylaxis

All patients received standard CYA and methotrexate as GVHD prophylaxis. CYA was given IV every day starting on day −1 at a dose of 3 mg/kg/day. Methotrexate (15 mg/m^2 IV) was given on day 1, and 10 mg/m^2 on day 3 and 6. Once oral intake could be tolerated, patients were administered oral CYA at a dose of 1:2, in 2 divided doses per day, based on the last intravenous dose. CYA was reduced when sCr levels rose above 1.5 times baseline, or other serious agent-associated toxicities occurred. Physicians could freely modify the CYA dose for patients experiencing severe acute GVHD (aGVHD) or risk of disease relapse. Corticosteroid-based treatment was considered when grade II or higher severe aGVHD occurred (0.5–2 mg/kg).

Supportive care

All patients received G-CSF by intravenous infusion starting on day 1 until durable granulocyte recovery was achieved. The supportive care regimen, including prophylaxis for infection was the same as previously reported (8, 9).

Monitoring

All patients were monitored retrospectively 10 days before, and after the first 100 days, of CBT. Daily laboratory data collecting and the detecting method of VCM and CYA trough concentration were the same as previously reported (8). Therapeutic drug monitoring for VCM by assessing serum trough concentration was done twice in weekly, and modified to not exceed 10.0 mg/L.

End-points and definitions

AKI was defined as 2-fold rise in sCr concentration on daily laboratory results from the baseline (the average of days −10 to 0). Myeloid engraftment was defined as the first of 3 consecutive days, during which the absolute neutrophil count was at least 0.5 × 10^9/L. Platelet recovery time was achieved on the first of 3 days when the platelet count was higher than 50 × 10^9/L without transfusion support. The aGVHD was graded according to previously published criteria (10). Transplant-related mortality was defined as death from any cause except relapse. Relapse was defined by morphologic evidence of disease in peripheral blood, bone marrow, or extramedullary sites. Disease-free survival was defined as the time from CBT to relapse, death, or the last observation.

Statistical analysis

Continuous variables are expressed as median and their range. For dichotomous variables, the frequencies of positive occurrence are given along with their corresponding percentages. Continuous variables were divided into high or low with their median values, and a single VCM trough concentration of 10.0 mg/L was defined as a threshold level for analysis. Cumulative incidence of AKI was estimated with competing risk setting, of which death and relapse were defined as competing risk events. Variables considered in univariate analysis were body weight, age, recipient gender, recipient cytomegalovirus serology, disease status at transplant (standard or high risk), total nucleated cell dose, CD34+ cell dose, baseline sCr levels, VCM use, VCM trough levels, CYA trough levels, foscarnet use, aminoglycosides use, days of neutrophil engraftment, aGVHD grade 3–4, and positive blood culture result. Variables with a *P*-value <0.1 for cumulative incidence of AKI were tested in multivariate analysis using Cox proportional hazards models, and *P*-values <0.05 were considered to be statistically significant. The probability of disease-free survival was estimated from the time of CBT according to the Kaplan–Meier method. Endpoints were calculated at the last contact, the date of the last follow-up being December 1, 2011. Statistical software R, version 2.12.2, was used for analysis.

Results

Characteristics of patients and cord blood units

The characteristics of 38 patients and cord blood units are shown in Table 1. Among the patients, the median age was 41.5 years (range, 18–52 years), the median weight was 59.5 kg (range, 39–76 kg), the median number of cryopreserved nucleated cells was 2.8×10^7/kg (range, $1.7–5.7 \times 10^7$/kg), and the median number of cryopreserved CD34+ cells was 0.9×10^5/kg (range, $0.4–2.6 \times 10^5$/kg). All patients received a single and human leukocyte antigen-mismatched cord blood unit.

Time courses of changing renal function

No patient had confirmed renal dysfunction before transplantation. The changes of renal function as variations (%) of sCr from baseline levels observed on days 11–20 were greatest and significant (+15.8%,

Characteristics and clinical course

Characteristics	
Patients, *n*	38
Male/Female, *n*	25/13
Median age, years (range)	41.5 (18–52)
Median weight, kg (range)	59.5 (39–76)
Median number of cryopreserved nucleated cells, $\times 10^7$/kg (range)	2.8 (1.7–5.7)
Median number of cryopreserved CD34+ cells, $\times 10^5$/kg (range)	0.9 (0.4–2.6)
Recipient CMV status, Positive/Negative, *n*	32/6
Diagnosis	
AML, *n*	12
MDS-related secondary AML, *n*	6
RAEB, *n*	3
RA, *n*	2
CML, *n*	3
ALL, *n*	11
NHL, *n*	1
Disease status at transplant	
Standard risk, *n*	10
High risk, *n*	28
Conditioning regimen	
TBI + Ara-C/G-CSF + CY, *n*	26
TBI + Ara-C + CY, *n*	12
GVHD prophylaxis	
CYA + MTX, *n*	38
Baseline sCr, mg/dL (range)	0.62 (0.33–0.87)
Neutrophil >0.5 $\times 10^9$/L, days (range)	21 (17–30)
Patients with positive blood culture, *n* (%)	6 (16)
Patients taking aminoglycosides, *n* (%)	32 (84)
Patients taking foscarnet, *n* (%)	10 (26)
Patients taking liposomal amphotericin, *n* (%)	16 (42)
Maximum CYA trough value, μg/L (range)	258.5 (40–453)
Patients taking VCM, *n* (%)	32 (84)
Duration of VCM therapy, days (range)	54 (6–100)
Maximum VCM trough value, mg/L (range)	8.8 (5.2–12.2)
Patients with maximum VCM trough value, >10.0 mg/L, *n* (%)	9 (24)
Patient requiring hemodialysis, *n* (%)	0 (0)

CMV, cytomegalovirus; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; RA, refractory anemia; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; TBI, total body irradiation; Ara-C, cytosine arabinoside; G-CSF, recombinant human granulocyte colony-stimulating factor; CY, cyclophosphamide; GVHD, graft-versus-host disease; CYA, cyclosporine; MTX, methotrexate; sCr, serum creatinine; VCM, vancomycin.

Table 1

0.57 ± 0.18 mg/dL to 0.71 ± 0.24 mg/dL, $P < 0.001$). No obvious recovery occurred of declined renal function, which remained until day 100.

Incidence and risk factors of AKI

Cumulative incidence of AKI at day 100 after CBT was 34% (95% CI 19–50) (Fig. 1). The median of the maximum value of VCM trough was 8.8 (4.5–12.2) mg/L. In univariate analysis, baseline sCr levels and foscarnet use were associated with the incidence of AKI (Table 2). In multivariate analysis, no factor was associated with the incidence of AKI (Table 2).

Transplant outcomes

All patients had myeloid reconstitution, and the median time to >0.5 × 10^9/L absolute neutrophil count was 21 days (range, 17–30 days). A self-sustained platelet count >50 × 10^9/L was achieved in 37 patients at a median time of 45.5 days (range, 34–127 days). In 37 of 38 evaluable patients, aGVHD occurred. The grading of aGVHD was grade I in 7 patients, grade II in 25, grade III in 4, and grade IV in 1. No one experienced hepatic veno-occlusive disease. Six of 38 patients (16%) had positive blood culture; however, no one had confirmed hypotension, indicated with decrease in systolic blood pressure >10 mmHg to <90 mmHg. Of 6 patients with positive blood cultures, 4 patients were not administered VCM. The total number of positive blood cultures was 13 of 998 specimens. Ten of 13 bacterial pathogens from blood cultures were gram-positive cocci (Table 3). Vancomycin-resistant *Enterococci* were detected in 1 patient from blood culture, however, this had been continuously detected from stool specimens since admission. No patients required hemodialysis. Among the 38 patients, no patient died of transplant-related causes (transplant-related mortality 0%). Six patients relapsed. Of these 6 patients, 5 patients died of relapse. A total of 32 of 38 patients are alive and free of disease at between 139 and 1400 days (median: 634 days) after CBT. The probability of disease-free survival at 2 years was 83% and 77% at 3 years (Fig. 2).

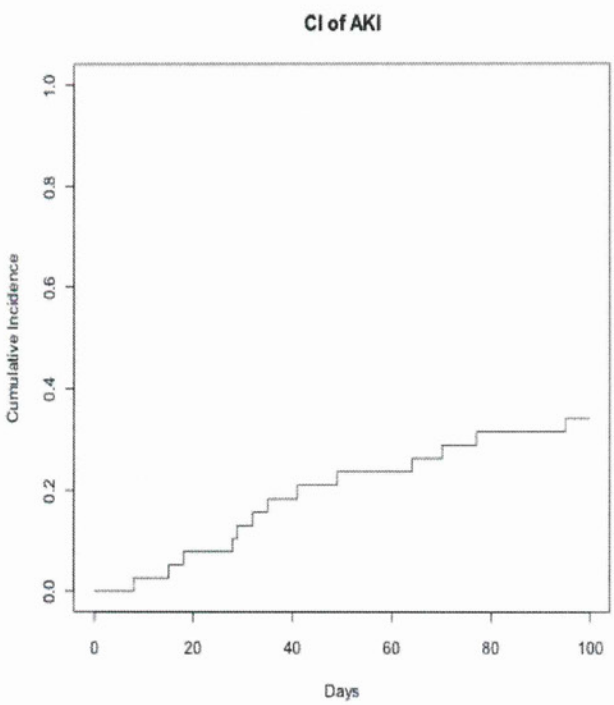

Fig. 1. Cumulative incidence (CI) of acute kidney injury (AKI).

Discussion

In this study, similar trends were observed in the time course of renal function changes as previously reported (8). However, the elevation in sCr was lower in this study, especially in days 11–20 (from 35.0% [8] to 15.8% in this study). Cumulative incidence of AKI was 34%; however, this was not assessed in our previous study (8). When we assessed the incidence of AKI with an identical definition to the previous

Univariate and multivariate analysis of factors associated with acute kidney injury

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Baseline sCr, mg/dL				
>0.62	0.27 (0.08–0.98)	0.047	0.33 (0.08–1.32)	0.12
<0.62	1		1	
Foscarnet				
(+)	3.11 (1.07–9.05)	0.037	2.45 (0.71–8.42)	0.15
(−)	1		1	
VCM trough, >10.0 mg/L				
(+)	2.68 (0.89–8.09)	0.081	2.64 (0.76–9.19)	0.13
(−)	1		1	

CI, confidence interval; sCr, serum creatinine; VCM, vancomycin.

Table 2

Isolated bacterial pathogens from blood cultures

Pathogens	*n*
Enterococcus faecalis	3
Vancomycin-resistant *Enterococcus faecium*	3
Methicillin-resistant *Staphylococcus* species	1
Methicillin-resistant *Staphylococcus epidermidis*	3
Stenotrophomonas maltophilia	1
Bacillus species	1
Bacillus cereus	1

Table 3

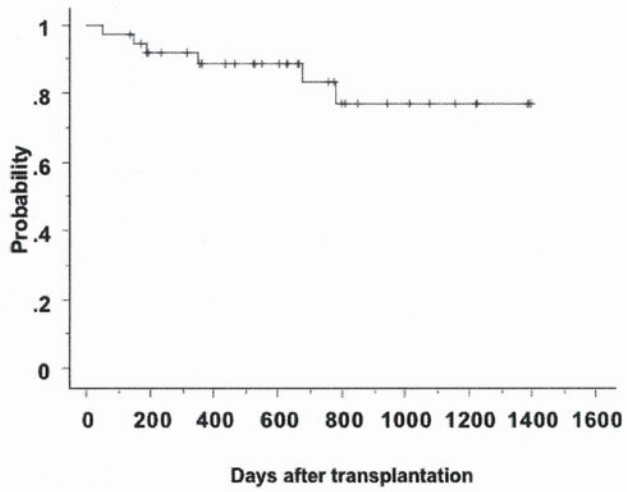

Fig. 2. Probability of disease-free survival after cord blood transplantation.

study, defined as just a 2-fold rise in sCr of 10 days average before and after transplantation, the incidence of AKI decreased to 11% in this study. In our previous study, the maximum VCM trough levels were significantly higher in patients with AKI (8); therefore, we have monitored VCM serum trough concentrations more strictly to not exceed 10.0 mg/L since 2008 in this study period. The average maximum value of VCM trough levels was lowered to 8.7 ± 2.1 mg/L from 12.2 ± 4.6 mg/L in the previous study, and proportion of patients with trough levels >10.0 mg/L was also decreased from 57% to 24%. Although baseline sCr levels and foscarnet use were associated with the incidence of AKI, VCM trough levels were not associated with AKI in univariate analysis. No factor was associated with AKI in multivariate analysis. Parikh et al. (11) reported AKI significantly affects survival after myeloablative allogeneic SCT in their meta-analysis, and more recently, Kagoya et al. (7) as well as Gooley et al. (12) reported the association of severity of AKI classification and non-relapse mortality within 100 days after transplantation. Although cumulative incidence of AKI was 34% in this study, no patients required hemodialysis or died of transplant-related causes. Recently, Yazaki et al. (13) reported the association of overall mortality and early bacterial infection of CBT in adults. They reported that cumulative incidence of early bacterial infection at day 100 was 21%, early bacterial infection had a negative effect on survival for adults, and the median day of development was 10 days after transplant, suggesting that prevention of bacterial infection in the very early post-CBT phase is important. Recently, a shift has occurred in the type of infecting organisms that cause bacteremia from predominantly gram-negative organisms to gram-positive cocci. The same trend is confirmed in the CBT (13, 14). VCM has an important role for infection control of gram-positive bacteremia, and was given to almost all the patients in this study. The reduced susceptibility of staphylococci for VCM has been reported since the mid 1990s, and prolonged exposure to lower VCM concentration has been associated with resistance (15). Although very few studies about pharmacokinetics and pharmacodynamics of VCM are available, several studies revealed area under the curve/minimum inhibitory concentration (AUC/MIC) as a preferred parameter, and AUC/MIC >400 associated with successful outcome and prevention of resistance (15, 16). Because of the difficulty of determining multiple concentrations for calculating AUC in the clinical setting, VCM trough concentrations have been recommended as the best surrogate marker for AUC/MIC, and concentrations of 15–20 mg/L – higher than the 5–15 mg/L previously recommended – is recommended as the target range (16). However, because an increased risk of nephrotoxicity with elevated VCM trough concentrations has been reported, and no appropriate pharmacokinetic/pharmacodynamic parameters for VCM have been determined (15, 17, 18), careful assessments are needed for using VCM at high target concentrations. Although we controlled VCM levels to not exceed 10.0 mg/L in this study, no patient died of bacterial infections. Further studies are required to determine the optimal VCM trough concentrations. Few reports are available about monitoring VCM trough concentrations for preventing AKI in allogeneic SCT in adults. Despite the limitations associated with this retrospective review of a small number of patients, our results suggest that strict monitoring of VCM serum trough concentrations has a beneficial effect on outcomes of CBT.

Acknowledgements:

Thanks: The authors would like to thank the physicians and nurses who cared for patients in this study.

Conflict of interest: The authors declare no conflict of interest of this manuscript.

Author contributions: H.M. and J.O. designed the study, analyzed data, and wrote the manuscript; J.O., S.T., S.K., T.K., Y.E., K.T., and A.T. cared for the patients; F.N. performed the statistical analysis; and H.E. and A.T. reviewed the study.

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Int J Hematol (2013) 97:103–108
DOI 10.1007/s12185-012-1245-0

ORIGINAL ARTICLE

Therapeutic outcome of multifocal Langerhans cell histiocytosis in adults treated with the Special C regimen formulated by the Japan LCH Study Group

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Received: 24 August 2012 / Revised: 4 December 2012 / Accepted: 4 December 2012 / Published online: 16 December 2012

Abstract Little information is available regarding effective systemic therapies for adult Langerhans cell histiocytosis (LCH). The Japan LCH Study Group has formulated an ambulatory treatment regimen for adult patients with LCH. In total, 14 patients (median age 43 years, range 20–70 years) with multifocal LCH with biopsy-confirmed histology were enrolled. None had received cytoreductive agents for LCH previously. Four had single system (SS) and ten had multi system (MS) disease. All were treated with the Special C regimen, which consists of vinblastine/prednisolone and methotrexate with daily 6-mercaptopurine for 36 weeks. At the end of the therapeutic regimen, all SS patients achieved no active disease (NAD), and six of the ten MS patients showed a response (NAD in two, partial response in four). At the last follow-up (median 34 months), 11 patients were alive (NAD in eight and active disease in three). Of the three deceased, one died of hemorrhage during the Special C treatment, and two of infections during subsequent therapy. Although this study is limited by the small sample size, this ambulatory regimen shows signs of efficacy for adult LCH. This was particularly evident for patients with multifocal SS disease, but half of those with MS disease also benefited.

Keywords Langerhans cell histiocytosis · Adult · Chemotherapy

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease that is characterized by the infiltration of clonal CD1a-positive

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dendritic cells. It mostly develops in infancy or early childhood with a childhood incidence of 2.2–8.9 cases per million; in adults, the incidence is one-third of the childhood incidence (1–2 cases per million) [1, 2]. LCH is categorized as a single system (SS) disease with multifocal or single/localized lesion(s) and as a multi system (MS) disease with or without risk organ (hematopoietic system, lung, liver, or spleen) involvement [3]. Children with multifocal SS or MS LCH are required to undergo systemic chemotherapy, but no such therapy is recommended for those with localized SS LCH [3]. Also in adults, systemic chemotherapy is required for multifocal SS or MS LCH lesions [1, 5], although adult-specific, smoking-related solitary pulmonary LCH lesions are treated differently [4]. While recent prospective, large-scale, multi-institutional trials have improved the therapeutic outcomes of multifocal childhood LCH [6, 7], only a few therapeutic trials involving a small number of cases have been performed for adult LCH [8–10].

A major obstacle in treating adult LCH patients is that they are often reluctant to take a leave of absence from their jobs for hospitalization, which can limit the provision of sufficient chemotherapy. Considering this adult-specific situation, the Japan LCH Study Group (JLSG) formulated Special C regimen for adult LCH patients in giving therapy safely at the outpatient clinic without hospitalization, which consisted of combinations of vinblastine (VBL)/prednisolone (PSL) and methotrexate (MTX) with daily 6-mercaptopurine (6-MP). These drugs were conventional agents and successfully employed as first-line chemotherapy for pediatric LCH patients [11]. The pilot study with the use of this regimen on adult patients with multifocal SS or MS LCH was performed. Results are reported here.

Patients and methods

This multicenter study was planned as a pilot study at the participating facilities of JLSG. The study was approved by the institutional review board (IRB). The study procedure was in accordance with the Helsinki Declaration. Eligible patients signed a detailed written informed consent statement meeting the requirements of the IRB. Patients were eligible for the study when having histologically diagnosed multifocal LCH who were at least 20 years of age. The diagnosis of LCH was confirmed by histopathology of biopsies of affected organs, which were positive for S-100 and/or CD1a antigen. Patients also needed to have adequate performance status and normal hepatic, renal, and cardiac functions. Exclusion criteria included the presence of serious infection and a history receiving cytoreductive chemotherapy for LCH. All patients were treated with the Special C regimen, which consisted of nine cycles of 6 mg/m^2 (max. 6 mg) of VBL on day 1, 2 mg/kg (max. 60 mg) of PSL on days 1–5, 20 mg/m^2 of MTX on day 15, and 1.5 mg/kg of 6-MP on days 1–28, over a period of 36 weeks. The dose of 6-MP was adjusted to white blood cell counts of 2,000–3,000 μ/L. Preventive medication of trimethoprim-sulfamethoxazole combination was recommended. At the end of treatment, the response was categorized as follows: no active disease (NAD) was defined as the disappearance of the signs or symptoms of disease, a partial response was defined as regression of >50 % of the signs or symptoms of disease without organ dysfunction and new lesions, no response was defined as regression of <50 % of the signs or symptoms of disease with or without organ dysfunction and the absence of new lesions, and progressive disease was defined as progression in the signs or symptoms of disease and/or the appearance of new lesions. Disease status at the last follow-up was defined as alive with NAD, alive with disease, or died. Common Terminology Criteria for Adverse Events v3.0 was used to grade adverse events.

Results

Fourteen adult patients with multifocal LCH (nine males and five females) were enrolled in this adult pilot study between 2002 and 2010 (Table 1). Four had a previous history of malignant disease (NK/T cell lymphoblastic lymphoma, renal cancer, diffuse large B cell lymphoma, and uterine cervical cancer). The median age at LCH onset was 34 years (range 16–69 years). In terms of prior medication other than cytoreductive agents for LCH, six patients were treated with PSL alone. Of the 14 patients with multifocal LCH, four had SS disease (skin, $n = 2$; multiple bones, $n = 2$) and ten had MS disease, of whom five had diabetes insipidus (DI) and one had central nervous system degeneration (CNSD) already at the time our treatment was initiated. The median time between disease onset to the initiation of our treatment was 2.4 years (range 0.1–32.7 years). The median age when our treatment was initiated was 40 years (range 20–70 years). Nine, three, and two of the patients were treated in the Departments of Internal Medicine, Dermatology, and Pediatrics, respectively. At the end of therapy, all SS patients attained NAD, while six of the ten MS patients had a response (NAD in two and a partial response in four) (Table 2). In terms of reactivation, two patients with SS disease in the skin had cutaneous reactivation and three patients with MS disease had reactivation in lymph node, bone, and mucosa (one in each patient). All reactivation sites were included in the primary lesions. Four of the five reactivations occurred approximately 1 year after therapy was initiated. In terms of treatment at reactivation, four patients underwent a

Table 1 Characteristics of 14 Adult LCH patients who participated in the JLSG-02 study

Disease type	UPN	Sex	Preceding malignancy	Onset age (years)	Preceding Tx. for LCH	Organ(s) involved	Interval between onset and regimen C treatment (years)	Age when treated with regimen C (years)
Single system	158	M	NK/T-LBL	29	None	Multi-B	0.3	29
	189	F	None	18	None	Multi-B	1.3	20
	202	M	Renal cancer	69	None	Sk	1.2	70
	E03	F	None	66	PSL	Sk	2.5	69
Multi system	36	M	None	38	PSL	Sk, B, LN, Pit	0.8	39
	95	M	None	40	PSL	Sk, B, ST, H	4.9	45
	120	M	None	19	PSL	Sk, LN, ST, Pit	1.1	20
	173	F	None	26	PSL	Muc, B, Pit	13.7	40
	208	M	None	16	None	B, L, Pit, CNSD	6.5	23
	249	M	DLBCL	62	None	Sk, ST	0.1	63
	295	M	None	18	None	Sk, B, L, Pit	32.7	50
	305	M	None	23	None	Sk, Muc, B, L	2.3	25
	E01	F	UCC	53	None	Sk, LN, Mus	5.0	58
	E02	F	None	54	PSL	B, Mus, Muc	2.8	56

NK/T-LBL NK/T cell lymphoblastic lymphoma, *DLBCL* diffuse large B cell lymphoma, *UCC* uterine cervical cancer, *PSL* prednisolone, *Tx* therapy, *Multi-B* multiple bone, *Sk* skin, *B* bone, *LN* lymph node, *Pit* pituitary, *ST* soft tissue, *H* hematopoietic system, *Muc* mucosa, *L* lung, *CNSD* central nervous system degeneration, *Mus* muscle

Table 2 Outcome of 14 adult LCH patients who were treated with the Special C regimen

Disease type	UPN	Response at the end of Tx.	Adverse effects more than Grade 2	Reactivation (time)	Second-line systemic Tx.	Permanent sequelae	Status at last follow-up (months)
Single system	158	NAD	No	None	No	None	AWND (68)
	189	NAD	Yes	None	No	None	AWND (57)
	202	NAD	No	Skin (28 months)	ND	None	Died (41)
	E03	NAD	No	Skin (14 months)	No	None	AWD (18)
Multi system	36	NR	No	NE	2CdA/HD-CA, HSCT	DI, cGVHD	AWND (107)
	95	NE	Yes	NE	No	NE	Died (0.1)
	120	PR	No	LN (9 months)	AraC/VCR/ PSL, AZP/ MTX	DI, skin scar	AWND (83)
	173	PR	Yes	Bone (14 months)	VBL/MTX/ 6MP	DI, hypothyroidism	AWND (47)
	208	NR	Yes	NE	ND	DI, CNSD	AWD (53)
	249	PD	No	NE	AraC/VCR/PSL	NE	Died (1.3)
	295	PR	No	None	No	DI, honeycomb lung	AWND (21)
	305	PR	No	Mucosa (12 months)	AraC/VCR/PSL	Loss of teeth, honeycomb lung	AWD (16)
	E01	NAD	Yes	None	No	None	AWND (24)
	E02	NAD	No	None	No	Loss of teeth	AWND (27)

NAD no active disease, *PR* partial response, *NR* no response, *PD* progressive disease, *NE* not evaluable, *ND* no data, *2CdA* cladribine, *HD-CA* high dose cytarabine, *HSCT* hematopoietic stem cell transplantation, *AraC* cytarabine, *VCR* vincristine, *PSL* prednisolone, *AZP* azathioprine, *MTX* methotrexate, *6MP* 6-mercaptopurine, *CNSD* CNS degeneration, *DI* diabetes insipidus, *cGVHD* chronic graft versus host disease, *AWND* alive with no active disease, *AWD* alive with disease

Grade 3 neutropenia in UPN E01, grade 4 neutropenia in UPN 189 and UPN 208, grade 3 infection (varicella-zoster virus reactivation) in UPN 173, grade 3 hepatic dysfunction (ALT 283 IU/L and total bilirubin 3.1 mg/dl) in UPN 208 and grade 5 bleeding in UPN 95)

cytarabine-containing regimen and one patient underwent hematopoietic stem cell transplantation. Treatment responses in the four patients (SS, $n = 2$; MS, $n = 2$) who had a history of malignant disease were NAD in three and PD in one. As a total, 3 patients died; one from hemorrhage and 2 from infections as commented later. In terms of eventual outcome, eleven patients were alive (NAD in eight and active disease in three) with a median follow-up duration of 34 months. Of whom, one patient (UPN 36) was a recipient of allogeneic bone marrow transplantation from unrelated donor, which was done because of disease progression, with the conditioning regimen of total body irradiation (8 Gy) and cyclophosphamide and with the graft versus host disease prophylaxis using a short-course MTX/tacrolimus. Eight patients had some sequelae of which association with LCH are well known, namely DI in five, CNSD in one, loss of teeth in two, and honeycomb lung in two. The overall survival and event-free survival rates at 3 years were 85.7 % (95 % confidence interval, 67.3–100 %) and 28.6 % (95 % confidence interval, 0–57.2 %), respectively (Fig. 1).

In terms of adverse events, Grade 3 or more adverse events were observed in 5 of the 14 patients (see footnotes in Table 2). Of the three deceased, two died of infections (pneumonia, sepsis) during subsequent therapy after stopping the Special C regimen (UPN 202 and UPN 249). UPN 95, which had a huge cystic lesion of LCH on his back and within the cyst occasional bleedings had been noted previously, died of fatal hemorrhagic shock due to massive bleeding in the cyst after 2 days of treatment with the Special C regimen.

Discussion

There are a number of issues that hamper the timely and effective treatment of adult LCH. First, it often takes time to correctly diagnose LCH in adults because the disease is not often seen by physicians who are taking care of adult patients, and the clinical features of LCH are quite heterogeneous. A report by the International Registry of the Histiocyte Society indicated that the median latency period between disease onset and diagnosis in adult patients with LCH was 4 months [5]. Second, the various symptoms of this rare disease cause patients to visit a variety of clinics including internal medicine, dermatology, orthopedics, dental surgery, otolaryngology, and neurology clinics. Indeed, more than one-third of our patients with multifocal LCH underwent our regimen at clinics other than the Department of Internal Medicine. Thus, patients with adult LCH are mostly treated in various clinics that apply various therapeutic regimens. Third, it is very common in adult LCH to adopt a "wait and see" strategy after diagnosis, even when it is multifocal LCH, because it is believed that most cases of adult LCH do not progress rapidly. Indeed, the International Registry of the Histiocyte Society report found that 30–40 % of adult patients with multifocal LCH did not receive chemotherapy when they are diagnosed [5]. Further supporting this is that, in our cohort, 50 % of the SS LCH cases and 40 % of the MS LCH cases did not receive any chemotherapy for more than 1 year after the onset of LCH. The reason of this treatment delay seems to be that LCH was not familiar to the treating physicians, and there were only a few evidences about how to treat adult LCH patients. It should be noted that LCH is a disease that causes late sequelae and that, during the "wait and see" period, patients often develop neurological sequelae such as DI, anterior pituitary hormone deficiencies, and CNSD [12]. Indeed, more than half of our patients had DI and one patient had CNSD already at the time our treatment was initiated. The incidence of DI in adult LCH is up to 30 % [5], which seems to be higher than in childhood LCH [13]. Fourth, a considerable proportion of adult LCH patients have a previous history of malignancy [5], which could cause LCH to become chemotherapy-resistant. In fact, four patients in our study had a history of malignant disease; however, numbers were too small to confirm the refractoriness in these cases. Anyway, all of these issues make it difficult to treat adult LCH patients.

To date, only a few attempts have been made to establish an effective systemic therapy for adult patients with LCH [8–10]. Three case series involving a small number of patients have been reported (Table 3). In the case series of Saven et al., 12 patients underwent cladribine (2CdA) monotherapy [8]. Nine responded and six maintained a continuous response with a median follow-up of 3.6 years. Grade 3–4 neutropenia was observed in seven patients. Notably, the response rate in patients who were resistant to other cytoreductive chemotherapies was the same as the response rate of the other patients in their cohort. This

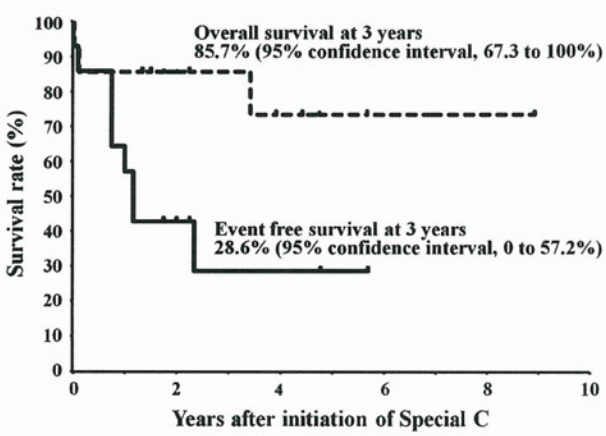

Fig. 1 Survival curve of adult patients treated with the Special C regimen

indicates that 2CdA is highly effective. 2CdA is a promising agent also in children with recurrent LCH, especially those with intracranial mass lesions [14]. 2CdA has also been found to be effective for adult patients with central nervous system LCH lesions [12]. However, this drug is not suitable as a first-line agent because of its high cost, with a risk of severe hematological toxicity [15] and secondary hematologic malignancies [8]. Another case series was that of McClain et al., who reported the responses of seven adult LCH patients in the LCH-A1 study of the International Registry of the Histiocyte Society, where patients were treated with a regimen derived from the pediatric LCH protocol that consists of VBL and PSL [9]. Three patients responded to the therapy, but five developed Grade 3–4 neuropathy, and only two were able to complete the treatment courses. Adult patients with LCH seem to be particularly sensitive to the neuropathic effects of VBL. The third case series of that of Derenzini et al., who recently reported the efficacy of MACOP-B regimen which is an intensive chemotherapy that was originally used for aggressive non-Hodgkin's lymphomas [10]. All seven patients responded and four have maintained a continuous

Table 3 Case series reports of the results of various treatments for adult LCH

Disease type (no. of pts.)	Age at Tx. years (range)	Regimen	Tx response	Adverse effects (≥Grade 3)	Eventual response	Median follow-up (years)	References
SS (3) MS (9)	44 (19–72)	2CdA 0.1 mg/kg, day 1–7, every 4 weeks Total duration: 2–6 months	SS: 2/3 MS: 7/9	Neutropenia 7/12 (58 %)	SS: 1/3 MS: 5/9	3.6	Saven et al. [8]
MS (7)	NA	Induction: VBL 6 mg/m^2, day 1, 8, 15, 22, 29, 36 PSL 1 mg/kg, day 1–28 Maintenance: VBL 6 mg/m^2, day 1 PSL 1 mg/kg, day 1–5 6-MP 30 mg/m^2, day 1–21 Total duration: 6 or 12 months	MS: 3/7	Neuropathy 5/7 (71 %)	MS: 3/7	0.5	McClain et al. [9]
SS (4) MS (3)	27 (18–62)	CY 350 mg/m^2, day 1, 15, 29, 43, 57, 71 ADR 50 mg/m^2, day 1, 15, 29, 43, 57, 71 MTX 400 mg/m^2, day 8, 36, 64 VCR 1.4 mg/m^2, day 8, 22, 36, 50, 64 Bleo 10 mg/m^2, day 22, 50, 78 PSL 40 mg/m^2, day 1–84 Total duration: 3 months	SS: 4/4 MS: 3/3	Neutropenia 2/7 (29 %)	SS: 3/4 MS: 1/3	6.5	Derenzini et al. [10]
SS (4) MS (10)	43 (20–70)	VBL 6 mg/m^2, day 1 PSL 2 mg/kg, day 1–5 MTX 2 mg/day, day 15 6-MP 1.5 mg/kg/day, day 1–28 Total duration: 9 months	SS: 4/4 MS: 6/10	Neutropenia 3/14 (21 %) Bleeding 1/14 (7 %) Infection 1/14 (7 %) Hepatic dysfunction 1/14 (7 %)	SS: 2/4 MS: 3/10	2.8	Present study

Tx treatment, *SS* single system, *MS* multisystem, *2CdA* cladribine, *VBL* vinblastine, *PSL* prednisolone, *6-MP* 6-mercaptopurine, *CY* cyclophosphamide, *ADR* adriamycin, *MTX* methotrexate, *VCR* vincristine, *Bleo* bleomycin