Table 3. Clinical trials of the interim PET-adapted strategy in patients with newly diagnosed limited- or advanced-stage Hodgkin lymphoma

Trial code	Clinical Trials.gov identifier	Study group	Study design and patients	PET-adapted interventions
Limited stage				
H10	NCT00433433	EORTC/GELA	PIII Both favorable and unfavorable	Standard arm: two courses of ABVD followed by one (favorable) or two (unfavorable) courses of ABVD and consolidative RTx, irrespective of PET2 result Experimental arm: two courses of ABVD followed by one (favorable) or two (unfavorable) courses of ABVD, then PET2 PET2 negative: no radiotherapy (favorable and unfavorable) PET2 positive: two courses of BEACOPP esc. and consolidative RTx (favorable and unfavorable)
HD16	NCT 00736320	GHSG	PIII Favorable	Standard arm: two courses of ABVD followed consolidative RTx irrespective of PET2 result Experimental arm: two courses of ABVD, then PET2 PET2 negative: no consolidative RTx PET2 positive, consolidative RTx
HD17	NCT 01356680	GHSG	PIII Unfavorable	Standard arm: two courses of BEACOPP esc. and two courses of ABVD followed consolidative RTx, irrespective of PET result after chemotherapy Experimental arm: two courses of BEACOPP esc. and two courses of ABVD, then PET PET negative: no consolidative RTx PET positive: consolidative RTx
RAPID	NCT 00943423	CR-UK	PIII No mediastinal bulk	Three courses of ABVD, then PET3 PET3 positive: another ABVD and consolidative RTx PET3 negative: randomization Consolidative RTx or not
Advanced stage				
HD18	NCT 00515554	GHSG	PIII	Two courses of BEACOPP esc., then PET2 PET2 positive: randomization Six courses of BEACOPP esc. or six courses of BEACOPP esc and rituximab PET2 negative: then randomization Six courses of BEACOPP esc. or two courses of BEACOPP esc.
S0816	NCT 00822120	SWOG	PII	Two courses of ABVD, then PET2 PET2 positive: six course of BEACOPP esc. PET2 negative: two courses of ABVD

Continued

Downloaded from http://jjco.oxfordjournals.org/ by guest on December 10, 2014

Table 3. Continued

Trial code	Clinical Trials.gov identifier	Study group	Study design and patients	PET-adapted interventions
HD0607	NCT 00795613	GITIL	PIII	Two courses of ABVD, then PET2 PET2 positive: randomization Eight courses of BEACOPP esc. or eight courses of BEACOPP esc. and rituximab PET2 negative: four courses of AVBD then randomization Consolidative RTx or not
HD0801	NCT 00784537	FIL	PIII	Two courses of ABVD, then PET2 PET2 positive: followed by salvage high-dose chemotherapy PET2 negative: four more courses of AVBD then randomization Consolidative RTx or not
RATHAL	NCT 00678327	CR-UK	PIII	Two courses of ABVD, then PET2 PET2 positive: then randomization Three courses of BEACOPP esc. or four courses of BEACOPP 14 PET2 negative: then randomization Four courses of ABVD or AVD
AHL2011	NCT 01358747	LYSA	PIII	Standard arm: four courses of BEACOPP esc., then PET4 PET4 positive: salvage therapy as induction failure PET4 negative: two courses of BEACOPP esc. Experimental arm: two courses of BEACOPP esc., then PET2 PET2 positive: four courses of BEACOPP esc. PET2 negative: four courses of ABVD

SWOG, Southwestern Oncology Group; GITIL, Gruppo Italiano Terapie Innovative nei Linformi; FIL, Fondazinone Italiana Linformi; CR-UK, Cancer Research UK; LYSA, Lymphoma Study Association; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, predonisone, procarbazine; BEACOPP esc., escalated-dose BEACOPP; PET, positron emission tomography; RTx, radiation therapy; PET2, interim PET after two courses of chemotherapy; PET3, interim PET after three courses of chemotherapy PET4, interim PET after four courses of chemotherapy.

Downloaded from http://jjco.oxfordjournals.org/ by guest on December 10, 2014

regimen, followed by interim PET. If the interim PET is negative, the patients will be treated with four more courses of ABVD. In the interim PET is positive, treatment will be altered to six courses of dose-escalated BEACOPP. This will be a multicenter clinical trial and will require the infrastructure for real-time central review of PET results as well as quality control of the PET technology at each local site. The results of this trial might facilitate establishment of a more patient-tailored treatment strategy for Japanese patients with HL.

Molecularly targeted therapy: antibody therapeutic agents

Brentuximab vedotin

Brentuximab vedotin (BV) is an antibody–drug conjugate created by using a linker to bind a potent tubulin inhibitor, monomethyl auristatin E (MMAE), to anti-CD30 monoclonal antibodies. BV targets CD30, which is located on the surface of Hodgkin and Reed–Sternberg cells. After binding to CD30, BV is quickly incorporated into the cell and transported to lysosomes, where the linker is selectively cleaved. The MMAE that is released inside the cell binds to tubulin and causes apoptosis by inhibiting the G2/M phases of the cell cycle. Monotherapy with BV showed a promising anti-tumor effect in a Phase I trial of recurrent and treatment-resistant CD30-positive lymphoma (41). Subsequently, a Phase II trial was conducted in 102 patients with recurrent and treatment-resistant CD30-positive HL following autologous hematopoietic stem cell transplantation and concurrent high-dose chemotherapy, and BV monotherapy resulted in an excellent anti-tumor effect (42). The response rate was 75% (complete remission rate, 34%), and the median duration of the response in the patients with complete remission was 20.5 months. The most common AEs were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%) and neutropenia (19%), but incidence of Grade 3 or 4 events were limited (14% of neutropenia, 8% of peripheral sensory neuropathy and 2% of fatigue). In Japan, a Phase II clinical trial for treatment of CD30-positive HL and anaplastic large cell lymphoma has been completed (43), and BV was granted health insurance coverage in April 2014. In Europe and the USA, several ongoing clinical trials are investigating the safety and efficacy of BV when used in combination with chemotherapy to treat primary cases of CD30-positive HL A Phase I clinical trial (44) showed that the combined use of the ABVD regimen and BV was associated with a high incidence of lung disorders. No lung disorders were reported when bleomycin was omitted from the chemotherapy [i.e. when BV was administered concurrently with AVD (doxorubicin, vinblastine and dacarbazine)]. Based on these results, a Phase III clinical trial is now in progress to compare the ABVD regimen and the combination of BV and AVD regimen for the treatment of primary HL. In addition, the administration of BV has been investigated as maintenance therapy following autologous transplantation and in combination with the BEACOPP regimen (Table 4).

Rituximab

Rituximab is not approved for treatment of HL, either in Japan or in other countries. However, the use of rituximab to treat NLPHL in Europe and the USA has been explored (45–47). In addition, there are numerous clinical trials in Europe and the USA that have incorporated rituximab into the treatment regimen for CHL (48,49). At present, a large-scale Phase III clinical trial in progress in Germany and Italy is investigating the utility of regimens that include rituximab for treatment of advanced-stage HL with poor prognosis (patients with positive interim PET findings, etc.).

Molecularly targeted therapy: small-molecule drugs

Small-molecule drugs are being developed as molecularly targeted drugs for HL. They include histone deacetylase inhibitors (HDACI) and mammalian target of rapamycin (mTOR) inhibitors.

HDACIs

Based on the results of preclinical studies, HDACI are expected to be effective for HL. A Phase II clinical trial showed that the efficacy of vorinostat for the treatment of HL was limited (SWOG S0517) (50). Clinical trials have also been reported for other HDACI, including mocetinostat (51) and panobinostat (52). Panobinostat is an orally administered pan-HDACI that inhibits Class I and Class II HDACs. It was studied in 129 patients with recurrent HL after high-dose chemotherapy; 41% of those patients had become resistant to the most recent administered chemotherapeutic agents. Panobinostat was orally administered (40 mg three times/week), and 27% of the patients responded (52).

Table 4. Clinical trials targeting CD30 of Hodgkin lymphoma (newly diagnosed and relapsed cases)

Trial code	Clinical Trials.gov identifier	Sponsor	Study design and patients	Intervention
AETHERA	NCT 00433433	Seattle Genetics	PIII Relapsed HL who have received ASCT in 45 days	For consolidation, randomize to placebo q3W (16 courses) or brentuximab vedotin q3W (16 courses)
Targeted BEACOPP	NCT 01569204	University of Cologne	PII Newly diagnosed advanced HL	Randomized to ECAPP-B (brentuximab vedotin) or ECADD-B (brentuximab vedotin)
C250037	NCT 01712490	Millennium Pharmaceuticals	PIII Newly diagnosed advanced HL	Randomized to ABVD or A(Adcetris)-AVD
NCI-2013-01273	NCT 01902160	NCI	PI Relapsed	Brentuximab vedotin combined with temsirolimus
NCI-2013-01275	NCT 01896999	NCI	PI Relapsed	Brentuximab vedotin combined with ipilimumab

HL, Hodgkin lymphoma; ASCT, autologous stem cell transplantation; NCI, National Cancer Institute; ECAPP, etoposide, cyclophosphamide, doxorubicin, predonisone, procarbazine; ECADD, etoposide, cyclophosphamide, doxorubicin, dexamethasone, dacarbazine.

Downloaded from http://jjco.oxfordjournals.org/ by guest on December 10, 2014

mTOR inhibitor

Everolimus, an mTOR inhibitor, is anticipated to show anti-tumor effects against various carcinomas. A small-scale Phase II clinical trial was performed in HL patients (53). The patients had previously undergone a median of six treatment regimens, and 84% had received high-dose chemotherapy. The complete response rate to everolimus was 47%.

Conclusion

The ABVD regimen was reported as the standard treatment for HL in 1992. Numerous clinical trials have been performed since then, but they have not led to any change in the status of the ABVD regimen as the standard treatment for HL. Escalated-dose BEACOPP regimens show superior tumor control, but they are associated with a higher incidence of AEs. For optimization of treatment methods for HL, it will be necessary to develop a comprehensive treatment algorithm that takes into account clinical and biological prognostic factors. The incorporation of interim PET might help to improve the management algorithm for patients with HL In addition, molecularly targeted therapies, such as BV, could lead to a paradigm shift in treatment strategies for HL.

Funding

This work was supported by the National Cancer Center Research and Development Fund (26-A-4).

Conflict of interest statement

Hirokazu Nagai has received honoraria from Chugai Pharmaceuticals.

References

1. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630–6.
2. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol* 2004;22: 2835–41.
3. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol* 2006;24:3128–35.
4. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003;21:3601–8.
5. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005;23:4634–42.
6. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010; 363:640–52.
7. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 2010;28:4199–206.
8. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol* 2012;30:907–13.
9. DeVita VT Jr, Simon RM, Hubbard SM, et al. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. *Ann Intern Med* 1980;92:587–95.
10. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478–84.
11. Boivin JF, Hutchison GB, Zauber AG, et al. Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst* 1995;87:732–41.
12. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J Clin Oncol* 2013;3:592–8.
13. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. *Eur J Cancer Clin Oncol* 1985; 21:601–5.
14. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH. Gonadal function following ABVD therapy for Hodgkin's disease. *Am J Clin Oncol* 1997;20:354–7.
15. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003;21:607–14.
16. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. *J Clin Oncol* 2005;23:9198–207.
17. Johnson PW, Radford JA, Cullen MH, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). *J Clin Oncol* 2005;23:9208–18.
18. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* 2009;27:805–11.
19. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* 2011;365:203–12.
20. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003;348:2386–95.
21. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol* 2009;27:4548–54.
22. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012;379:1791–9.
23. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998;339:1506–14.
24. Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. *Ann Oncol* 2005;16:1160–8.
25. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 2006;107:52–9.
26. Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. *Haematologica* 2006;91:475–81.
27. Zinzani PL, Tani M, Fanti S, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. *Ann Oncol* 2006;17:1296–300.

Downloaded from http://jjco.oxfordjournals.org/ by guest on December 10, 2014

28. Zinzani PL, Rigacci L, Stefoni V, et al. Early interim 18F-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients. *Eur J Nucl Med Mol Imaging* 2012;39:4–12.
29. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian–Danish study. *J Clin Oncol* 2007;25:3746–52.
30. Cerci JJ, Pracchia LF, Linardi CC, et al. 18F-FDG PET after 2 cycles of ABVD predicts event-free survival in early and advanced Hodgkin lymphoma. *J Nucl Med* 2010;51:1337–43.
31. Terasawa T, Lau J, Bardet S, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. *J Clin Oncol* 2009;27:1906–14.
32. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007;25:571–8.
33. Juweid ME, Wiseman GA, Vose JM, et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 2005;23:4652–61.
34. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–86.
35. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging* 2010;37:1824–33.
36. Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma* 2009;50:1257–60.
37. Gallamini A, Barrington SF, Biggi A, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. *Haematologica* 2014;99:1107–13.
38. Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nucl Med* 2013;54:683–90.
39. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014;32:1188–94.
40. Gallamini A, Patti C, Viviani S, et al. Early chemotherapy intensification with BEACOPP in advanced-stage Hodgkin lymphoma patients with a interim-PET positive after two ABVD courses. *Br J Haematol* 2011;152:551–60.
41. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010;363:1812–21.
42. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012;30:2183–9.
43. Ogura M, Tobinai K, Hatake K, et al. Phase I/II study of brentuximab vedotin in Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma. *Cancer Sci* 2014;105:840–6.
44. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol* 2013; 14:1348–56.
45. Rehwald U, Schulz H, Reiser M, et al. Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: results of a phase 2 trial of the German Hodgkin Lymphoma Study Group. *Blood* 2003;101:420–4.
46. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood* 2008;111:109–11.
47. Unal A, Sari I, Deniz K, et al. Familial nodular lymphocyte predominant Hodgkin lymphoma: successful treatment with CHOP plus rituximab. *Leuk Lymphoma* 2005;46:1613–7.
48. Younes A, Oki Y, McLaughlin P, et al. Phase 2 study of rituximab plus ABVD in patients with newly diagnosed classical Hodgkin lymphoma. *Blood* 2012;119:4123–8.
49. Kasamon YL, Jacene HA, Gocke CD, Swinnen LJ, et al. Phase 2 study of rituximab-ABVD in classical Hodgkin lymphoma. *Blood* 2012; 119:4129–32.
50. Kirschbaum MH, Goldman BH, Zain JM, et al. A phase 2 study of vorinostat for treatment of relapsed or refractory Hodgkin lymphoma: Southwest Oncology Group Study S0517. *Leuk Lymphoma* 2012;53:259–62.
51. Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial. *Lancet Oncol* 2011;12:1222–8.
52. Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. *J Clin Oncol* 2012;30: 2197–203.
53. Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. *Am J Hematol* 2010;85:320–4.

Downloaded from http://jjco.oxfordjournals.org/ by guest on December 10, 2014

Pediatr Blood Cancer 2015;62:279–284

Statistical Analysis of Relation Between Plasma Methotrexate Concentration and Toxicity in High-Dose Methotrexate Therapy of Childhood NonHodgkin Lymphoma

Masahito Tsurusawa, MD,[1]* Masahiko Gosho, PhD,[1] Tetsuya Mori, MD,[2] Tetsuo Mitsui, MD,[3] Shosuke Sunami, MD,[4] Ryoji Kobayashi, MD,[5] Reiji Fukano, MD,[6] Fumiko Tanaka, MD,[7] Naoto Fujita, MD,[8] Hiroko Inada, MD,[9] Katsuyoshi Koh, MD,[10] Tetsuya Takimoto, MD,[11] Akiko Saito, MD, PhD,[12] Junichiro Fujimoto, MD,[11] Atsuko Nakazawa, MD,[13] Keizo Horibe, MD,[12] and for the lymphoma committee of the Japanese Pediatric Leukemia/lymphoma Study Group

Background. Plasma monitoring of Methotrexate (MTX) levels is a standard approach to predict MTX-related toxicities in a high-dose (HD) MTX monotherapy for childhood acute lymphoblastic leukemia. However, it is uncertain whether plasma MTX levels can predict MTX-related toxicity in the HDMTX plus additional chemotherapy for childhood B-cell nonHodgkin lymphoma (B-NHL). ***Procedures.*** To statistically analyze the relationship between MTX pharmacokinetic parameters and MTX-related toxicities, we collected data from patients with delayed MTX elimination ($\geq$1 μM at 48 hr and/or $\geq$0.5 μM at 72 hr) in the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) BNHL 03 study. Blood MTX levels were measured at 24, 48, and 72 hr after 3 or 5 g/m^2 HD-MTX administration for 24 hr. ***Results.*** Three hundred and four patients received 2–4 courses of the HDMTX plus additional chemotherapy, and delayed MTX elimination was observed in 165 courses of 127 patients. In those, nephrotoxicity was significantly correlated with plasma MTX levels for each patient ($P=0.03$), and also for each course ($P=0.009$), but no other toxicities were correlated. Another analysis according to HDMTX courses showed no significant correlation between the first high plasma MTX levels and subsequent MTX levels in later course. It also showed that incidence of liver and gastrointestinal toxicities was most frequent in the first HDMTX course, and then sharply decreased in later courses ($P<0.001$). ***Conclusions.*** Our results suggest that plasma MTX level is not a reliable predictor for adverse events except for nephrotoxicity in multiple HDMTX therapy courses in childhood B-NHL. Pediatr Blood Cancer 2015;62:279–284. © 2014 Wiley Periodicals, Inc.

Key words: childhood; HDMTX; nonHodgkin lymphoma; toxicity

INTRODUCTION

In the past two decades, treatment outcome of childhood B-cell nonHodgkin Lymphoma (B-NHL) has been greatly improved by using a short intensive multiagent regimen including high-dose methotrexate (HDMTX), intermediate-dose cyclophosphamide (CPA) and anthracycline [1–4]. Since this treatment rationale is based on rapid elimination of tumor cells with short cell cycle time by subsequent administration of multiple anticancer agents, imprudent prolongation of treatment intervals or dose reduction according to drug toxicity may increase the risk of treatment failure [5–8]. Therefore, the balance between efficacy and adverse events is one of the major clinical challenge to achieve a high cure rate of the disease. Among the multiple drugs, MTX-related toxicity may possibly be predicted based on plasma MTX levels in childhood acute lymphoblastic leukemia (ALL), because HDMTX is used as monotherapy in intensification and maintenance phases [9,10]. However, it might be difficult to predict what kinds of toxicities are associated with plasma MTX levels in a HDMTX plus additional chemotherapy for childhood BNHL, because CPA and anthracycline which are concomitantly used with HDMTX, also induce various toxicities similar to MTX toxicities. In addition, it is unknown whether high plasma MTX level is associated to a particular patient, in other words, the first high MTX level is likely to repeat in later HDMTX courses in a particular patient.

In this study, to answer those clinical issues, we statistically analyzed the relationship between MTX pharmacokinetic parameters and MTX-related toxicities in patients with B-NHL treated by the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) B-NHL03 protocol study [4].

© 2014 Wiley Periodicals, Inc.
DOI 10.1002/pbc.25305
Published online 30 October 2014 in Wiley Online Library (wileyonlinelibrary.com).

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

[1]The Advanced Medical Research Center, Aichi Medical University, Aichi, Japan; [2]Division of Pediatric Oncology, National Center for Child Health and Development, Tokyo, Japan; [3]Department of Pediatrics, Yamagata University Hospital, Yamagata, Japan; [4]Department of Pediatrics, Japanese Red Cross Narita Hospital, Chiba, Japan; [5]Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan; [6]Department of Pediatrics, Kushu Cancer Center, Fukuoka, Japan; [7]Department of Pediatrics, Saiseikai Yokohama Nanbu Hospital, Kanagawa, Japan; [8]Department of Pediatrics, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan; [9]Department of Pediatrics, Kurume University Hospital, Kurume, Japan; [10]Department of Hematology-Oncology, Saitama Children's Medical Center, Saitama, Japan; [11]Clinical Research Center, National Center for Child Health and Development, Tokyo, Japan; [12]Clinical Research Center, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [13]Department of Pathology, National Center for Child Health and Development, Tokyo, Japan

Grant sponsor: Ministry of Health, Labor and Welfare of Japan; Grant numbers: H14-Koka(Gan)-031; H15-Koka(Gan)-024; H16-GanRinsho-004; H17-GanRinsho-004; H20-GanRinsho-Ippan-017; H23-GanRinsho-Ippan-014

Conflict of interest: Nothing to declare.

*Correspondence to: Masahito Tsurusawa, MD, Advanced Research Center, Aichi Medical University, Nagakute, Aichi 480-11, Japan.
E-mail: mtsuru@aichi-med-u.ac.jp

Received 22 May 2014; Accepted 15 September 2014

PATIENTS AND METHODS

Patients and Protocol Treatment

The protocol was conducted in 112 hospitals of the Japanese Pediatric Leukemia/Lymphoma Study group (JPLSG) after approval by each institution's review board, and written informed consent was provided by patients or legal guardians before treatment. A total of 346 untreated B-NHL patients under 18 years of age, were registered to participate in the JPLSG B-NHL03 study (University hospital Medical Information Network Japan, UMIN ID: C000000317) between November 2004 and January 2011. Patients were stratified into four therapy groups (G1, G2, G3, G4) based on Murphy's stage, tumor resectability and BM/CNS involvement. Chemotherapy regimens are shown in supplemental Table SI. HDMTX was administered to patients in regimen A (2A for G2, 3A for G3, and 4A1 and 4A2 for G4). G2 received four courses (2A → 2B, ×2), G3 and G4 received six courses (3A → 3A → 3B, ×2; 4A1 → 4A2 → 4B, ×2) of chemotherapy regimens. Regimen A consisted of HDMTX, dexamethasone, vincristine, intermediate-dose cyclophosphamide (CPA), and pirarubicin (THP-adriamycin, THP). Patients in G2 and G3 received 3 g/m^2 HDMTX and those in G4 received 5 g/m^2 HDMTX. HDMTX was administered for 24 hr and intravenous hydration at a rate of 100 ml/m^2/hr with 4.3% glucose, $NaHCO_3$ 33 mEq/L, L-Lactate 20 mEq/L, NaCl 35 mEq/L, and KCL 20 mEq/L was initiated 12 hr before the MTX infusion and was maintained for 48 hr after the infusion. During this period, acetazolamide (125 mg <5 years old or 250 mg ≥5 years old) was administered every 12 hr. Urine pH was checked with each void and a bolus of $NaHCO_3$ (8.4 mEq in 20 ml) was administered if the pH was <7.0. After 12 hr of MTX infusion, leucovorin (LV) 15 mg/m^2 was given orally every 6 hr for a total of seven doses. When patients showed high plasma MTX levels (≥0.2 μM) at 72 hr, LV rescue was continued until MTX concentration level decreased to less than 0.2 μM.

Measurements of Plasma MTX Concentration

Plasma MTX concentrations were determined by each institute, and the measurements were performed by a monoclonal antibody-based immunoassay (fluorescence polarization immunoassay, FPIA) in 91 institutes, or by an enzyme multiplied immunoassay technique (EMIT) in 21 institutes. Delayed MTX elimination was defined as plasma MTX concentration ≥1 μM at 48 hr and/or ≥0.5 μM at 72 hr after MTX administration. Since only one third of the data of MTX concentrations at 24 hr after MTX administration (the end of 24-hr infusion) was available and there were also no sufficient sampling points between 24 and 48 hr to calculate the pharmacokinetic parameters of MTX, we could not analyze the appropriate pharmacokinetic parameters including systemic clearance (CLSYS) based on the two-compartmental model. We therefore calculated the basic two parameters of MTX (elimination rate constant (ke) and terminal half-life ($t_{1/2}$)). The terminal slope of MTX concentration (C) versus time (t), which represents ke, was calculated as $ke = [\ln(C1) \cdot \ln(C2)]/(t2 \cdot t1)$, where C1 and C2 were concentrations at t1 (48 hr) and t2 (72 hr), respectively. The $t_{1/2}$ was calculated by dividing 0.693 by ke.

Statistics

Plasma MTX levels and toxicity data were prospectively collected for each treatment phase and toxicity severity was graded according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0. Continuous variables were summarized as the mean ± standard deviation (SD) or median (minimum, maximum) and categorical variables were presented as numbers and percentages. Correlation between the two variables was estimated by Spearman's correlation coefficient. The plasma MTX concentrations in patients with an adverse event (AE) were compared to those in patients without the AE by using Wilcoxon's rank sum test. In this analysis, one observation for each patient was taken into account. The observation with the AE and the highest concentration at 48 hr was preferentially used if a patient received more than one course and had more than one observation. Furthermore, log-transformed MTX concentrations were compared between patients with and without AE using generalized estimating equations (GEE) method [11] including AE (yes vs. no) and course as factors, in order to take into account repeated measures of the same patient. The presence (≥grade 3) of toxicity (hepatic toxicity, stomatitis, and infection) were analyzed using the GEE with repeated-measures logistic regression model including nephrotoxicity (yes vs. no) and course as factors. We assumed an exchangeable covariance matrix for the repeated-measures in the GEE analyses. All tests were two-sided, and p values less than 0.05 were considered to indicate statistical significance. Statistical analyses were carried out using SAS 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Pharmacokinetic Parameters

One hundred twenty seven patients out of a total of 304 patients who received HDMTX therapy showed delayed MTX elimination. MTX concentrations in patients with delayed MTX elimination are summarized in Table I. Percentages of patients with delayed MTX elimination by treatment groups were 26.2% in G2, 40.5% in G3, and 62.2% in G4, respectively. The male to female ratio in patients with delayed MTX elimination was more than double than patients without delayed MTX elimination (107/20 = 5.35 vs. 123/54 = 2.27,

TABLE I. Summary of High Plasma MTX Concentrations at 48 and 72 hr After MTX Dosing*

			MTX concentration at 48 hr		MTX concentration at 72 hr	
Group	No. of patients	No. of courses	Mean ± SD	Median (Min, Max)	Mean ± SD	Median (Min, Max)
2	26	27	2.63 ± 2.25	1.86 (0.99, 11.00)	0.66 ± 0.52	0.61 (0.08, 1.90)
3	45	53	3.41 ± 5.19	1.77 (0.80, 29.70)	1.02 ± 1.55	0.44 (0.17, 8.23)
4	56	85	3.80 ± 6.29	1.82 (0.93, 48.00)	1.06 ± 1.79	0.54 (0.05, 11.00)

*≥1 μM at 48 hr and/or ≥0.5 μM at 72 hr after MTX administration.

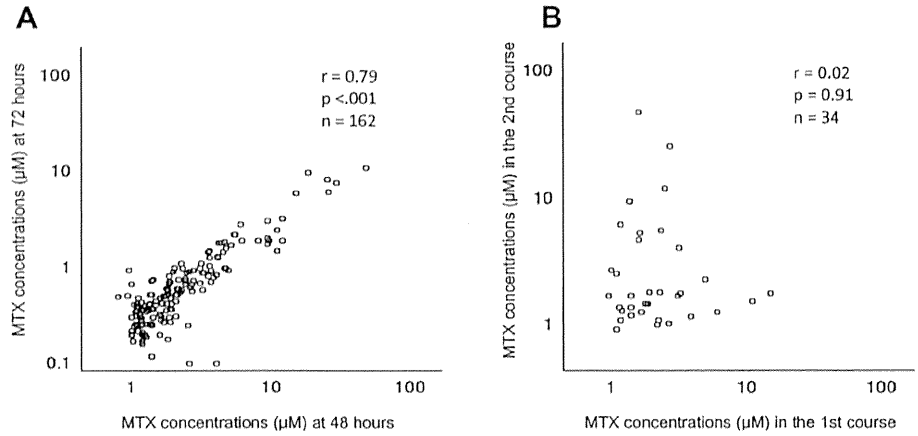

Fig. 1. Correlation between blood MTX concentrations at 48 and 72 hr in patients with delayed MTX clearance (**A**). Correlation between blood MTX concentrations in first and second courses at 48 hr (**B**). r denotes Spearman's rank correlation coefficient.

$P = 0.004$ by Fisher's exact test), and the ratios according to treatment group were 5.5 in G2, 10.2 in G3, and 3.6 in G4. Thus, males with G3 showed the highest risk of delayed MTX elimination. However, there was no significant difference in age between the two groups (mean of years 8.8 vs. 8.8). MTX concentrations were widely variable between patients at either dosage. MTX concentrations at 48 hr ranged from 0.99 to 29.7 μM in the 3 g/m^2 HDMTX group, and 0.93 to 48 μM in the 5 g/m^2 HDMTX group. There was a significantly positive correlation between MTX concentrations at 48 and 72 hr in each patient (Fig. 1A). On the other hand, there was no significant

TABLE II. Relationship Between Plasma MTX Pharmacokinetics (MTX Concentration and MTX Half-Life) and Adverse Events

	Adverse event (number of patients base)			Adverse event (number of courses base)		
	No, n = 118	Yes, n = 9	P^a	No, n = 156	Yes, n = 9	P^b
Nephrotoxicity ≥grade 2[c]						
48 hr	1.93 (0.80, 25.50)	6.17 (0.99, 48.00)	0.0307	1.81 (0.80, 25.50)	6.17 (0.99, 48.00)	0.009
72 hr	0.53 (0.08, 9.89)	1.82 (0.35, 11.00)	0.0023	0.50 (0.05, 9.89)	1.82 (0.35, 11.00)	<0.001
$t_{1/2}$ (hr)	12.3 (4.5, 35.4)	14.1 (9.9, 42.6)	0.373	12.7 (4.5, 1571.7)	14.1 (9.9, 42.6)	0.318
	Adverse event (number of patients base)			Adverse event (number of courses base)		
	No, n = 84	Yes, n = 42	P^a	No, n = 120	Yes, n = 44	P^b
Hepatic toxicity ≥grade 3/4[c]						
MTX 48 hr	1.98 (0.80, 48.00)	1.91 (0.95, 15.00)	0.65	1.82 (0.80, 48.00)	1.82 (0.95, 15.00)	0.95
MTX 72 hr	0.58 (0.08, 11.00)	0.59 (0.16, 6.00)	0.96	0.51 (0.05, 11.00)	0.53 (0.16, 6.00)	0.58
$t_{1/2}$ (hr)	12.6 (4.5, 35.4)	13.0 (8.0, 1,571.7)	1.00	12.8 (4.5, 35.4)	12.9 (8.0, 1,571.7)	0.26
	Adverse event (number of patients base)			Adverse event (number of courses base)		
	No, n = 68	Yes, n = 58	P^a	No, n = 98	Yes, n = 66	P^b
Oral mucositis ≥grade 3/4[c]						
MTX 48 hr	1.86 (0.80, 48.00)	2.28 (0.95, 25.50)	0.38	1.69 (0.80, 48.00)	2.23 (0.95, 25.50)	0.25
MTX72 hr	0.49 (0.08, 11.00)	0.60 (0.10, 9.89)	0.35	0.45 (0.05, 11.00)	0.59 (0.10, 9.89)	0.23
$t_{1/2}$ (hr)	12.9 (5.7, 35.4)	12.6 (4.5, 1,571.7)	0.83	12.8 (5.4, 35.4)	12.7 (4.5, 1,571.7)	0.23
	Adverse event (number of patients base)			Adverse event (number of courses base)		
	No, n = 23	Yes, n = 103	P^a	No, n = 37	Yes, n = 127	P^b
Infection ≥grade 3/4[c]						
MTX 48 hr	2.03 (0.80, 48.00)	1.90 (0.93, 29.70)	0.49	1.90 (0.80, 48.00)	1.81 (0.93, 29.70)	0.56
MTX 72 hr	0.70 (0.22, 11.00)	0.56 (0.08, 9.89)	0.31	0.50 (0.22, 11.00)	0.52 (0.05, 9.89)	0.25
$t_{1/2}$ (hr)	13.0 (10.0, 35.4)	12.4 (4.5, 27.7)	0.48	12.9 (8.5, 35.4)	12.6 (4.5, 1,571.7)	0.74

Data are presented as median (min, max). n: number of patients or courses. [a]Wilcoxon's rank sum test. [b]Generalized estimating equations method for repeated log-transformed MTX concentrations. [c]NCI-CTC version 2.0.

correlation between MTX concentrations at 48 hr in the first and next HDMTX courses in each patient (Fig. 1B).

Toxicities

In order to clarify what kinds of MTX toxicities are closely associated with MTX pharmacokinetic parameters, we statistically analyzed the correlation between the parameters (plasma MTX levels and half-life ($t_{1/2}$)) and MTX-related toxicities (stomatitis, nephrotoxicity, hepatic toxicity, and infection). In this study, we excluded hematological toxicity and CNS toxicity from the analysis, because neutropenia ≥grade 3 was observed in almost all (>98%) patients regardless of MTX levels, and CNS toxicity ≥grade 3 occurred in only one case. In general, adverse events (AEs) ≥grade 3 were collected for analysis, but serum creatinine and proteinuria ≥grade 2 were used for nephrotoxicity because the number of nephrotoxic AEs ≥grade 3 was very few (n = 4) and proteinuria has been shown to be a HDMTX-related nephrotoxicity [12]. The number of patients with nephrotoxicity ≥grade 2 was nine: five in grade 2, one in grade 3 and one in grade 4 with high serum creatinine levels, and two in grade 2 with proteinuria. As shown in Table II, only nephrotoxicity was significantly correlated with higher MTX levels for each patient, and also for each course, but other toxicities had no correlations to MTX levels. MTX half-life showed no significant relation to any of the MTX-related toxicities. We also analyzed statistical difference in the frequency of other toxicities, such as hepatic toxicity, stomatitis and infection between patients with nephrotoxicity and patients without (Table III). These results showed that patients with nephrotoxicity tended to have higher frequencies of hepatic toxicity, although the difference did not reach significant levels.

Lastly, we studied the difference in incidences of severe toxicities according to HDMTX courses in all patients of group 3 and group 4 (Fig. 2). Incidences of hematological toxicities did not vary widely during the four courses. However, incidences of non-hematological toxicities such as liver and gastrointestinal toxicities showed a large variation during the courses: the incidence was the greatest in the first course, and then sharply decreased in later courses in both groups ($P < 0.001$). In addition, the incidences seemed to be unrelated with plasma MTX levels.

Modification of Protocol Treatments

In our study, treatment modifications according to delayed MTX elimination were reported in 15 patients (2 in group 2, 4 in group 3, and 9 in group 4). Eleven of which had suffered from MTX-induced nephrotoxicity with high creatinine levels (6 in grade 1, 3 in grade 3, 1 in grade 3 and 1 in grade 4). The modifications were as follows: dose reduction or prolongation of treatment intervals of CPA and THP in 8, withdrawal of CPA and THP in 2, reduction of HDMTX dose (from 5 to 3 g/m^2) in the next HDMTX course in 3 (2 between 1st and 2nd course, one between 2nd and 3rd course), and exchanging course 4A with course 4B without HDMTX in 2. Of the 15 patients, 14 patients except one, who had CNS involvement, survived without diseases.

TABLE III. Incidence of MTX-Related Toxicities According to Nephrotoxicity

		Nephrotoxicity ≥grade 2		
Group		No	Yes	P^a
Hepatic toxicity				
Total	Grade 3	36 (23.2)	3 (33.3)	
	Grade 4	2 (1.3)	2 (22.2)	
	≥grade 3/4	38 (24.5)	5 (55.6)	0.051
2	Grade 3	5 (20.0)	1 (50.0)	
	Grade 4	0 (0.0)	0 (0.0)	
	≥grade 3/4	5 (20.0)	1 (50.0)	0.34
3	Grade 3	10 (20.4)	0 (0.0)	
	Grade 4	1 (2.0)	1 (33.3)	
	≥grade 3/4	11 (22.4)	1 (33.3)	0.79
4	Grade 3	21 (25.9)	2 (50.0)	
	Grade 4	1 (1.2)	1 (25.0)	
	≥grade 3/4	22 (27.2)	3 (75.0)	0.10
Oral mucositis				
Total	Grade 3	57 (36.8)	3 (33.3)	
	Grade 4	5 (3.2)	1 (11.1)	
	≥grade 3/4	62 (40.0)	4 (44.4)	0.84
2	Grade 3	5 (20.0)	1 (50.0)	
	Grade 4	1 (4.0)	0 (0.0)	
	≥grade 3/4	6 (24.0)	1 (50.0)	0.42
3	Grade 3	20 (40.8)	1 (33.3)	
	Grade 4	0 (0.0)	1 (33.3)	
	≥grade 3/4	20 (40.8)	2 (66.7)	0.46
4	Grade 3	32 (39.5)	1 (25.0)	
	Grade 4	4 (4.9)	0 (0.0)	
	≥grade 3/4	36 (44.4)	1 (25.0)	0.39
Infection				
Total	Grade 3	119 (76.8)	7 (77.8)	
	Grade 4	1 (0.6)	0 (0.0)	
	≥grade 3/4	120 (77.4)	7 (77.8)	0.87
2	Grade 3	20 (80.0)	1 (50.0)	
	Grade 4	0 (0.0)	0 (0.0)	
	≥grade 3/4	20 (80.0)	1 (50.0)	0.28
3	Grade 3	38 (77.6)	3 (100.0)	
	Grade 4	0 (0.0)	0 (0.0)	
	≥grade 3/4	38 (77.6)	3 (100.0)	NC
4	Grade 3	61 (75.3)	3 (75.0)	
	Grade 4	1 (1.2)	0 (0.0)	
	≥grade 3/4	62 (76.5)	3 (75.0)	0.75

[a]Generalized estimating equations method for repeated adverse event (≥grade 3/4). NC: not calculated. Data are n (%).

DISCUSSION

Recent pharmacokinetic and pharmacogenetic studies of HDMTX treatment in childhood lymphoid malignancies have shown significant relations between polymorphisms in genes coding for enzymes involved in folate metabolisms and MTX-related toxicities. However, individual prediction of MTX toxicity and dose adjustment of HDMTX based on pretreatment genotyping do not reach a practical use [13–15] and routine monitoring of plasma MTX concentrations still has an important role to predict MTX toxicities in clinical practice.

In the present study, we analyzed the relation between MTX pharmacokinetics and MTX-related toxicities in the HDMTX plus additional chemotherapy for childhood B-NHL. We found that plasma MTX levels were significantly correlated with nephrotoxicity (creatinine and/or proteinuria ≥grade 2), but not other toxicities. MTX half-life was not associated with any toxicity. These results suggest that MTX-induced nephrotoxicity could be

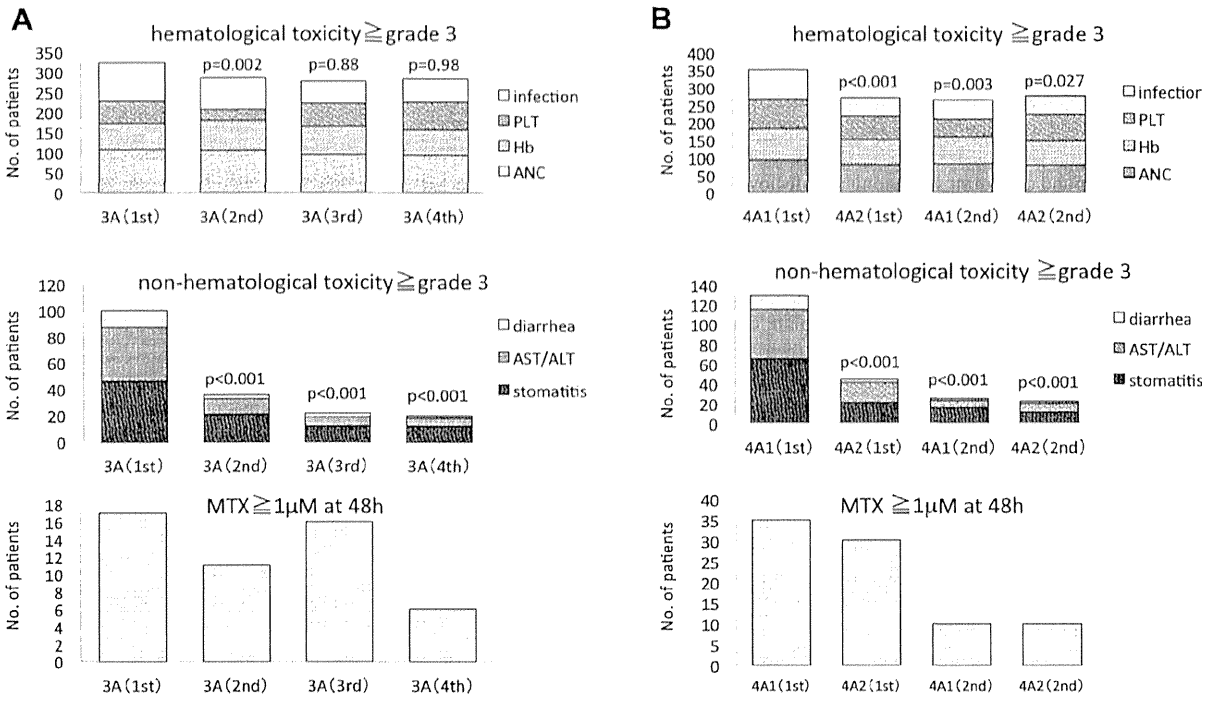

Fig. 2. Incidence of MTX-related toxicities and delayed MTX elimination according to HDMTX course. Left panel (**A**) for group 3; Right panel (**B**) for group 4. Number in vertical axis shows number of patients with hematological toxicities (**upper panel**), non-hematological toxicities (**middle panel**), and delayed MTX elimination (≥1 μM at 48 hr) (**lower panel**). Number of patients who received HDMTX therapy of each course was 108 in 1st 3A1, 106 in 2nd 3A1, 95 in 3rd 3A1, and 94 in 4th 3A1 in group 3, and 94 in 1st 4A1, 83 in 1st 4A2, 79 in 2nd 4A1, and 78 in 2nd 4A2 in group 4, respectively. *P* values reported from Dunnett's test based on the generalized estimating equation method comparing the toxicity count by course (reference group is 3A (1st) or 4 A1 (1st)).

caused by the long-time exposure to high plasma MTX levels during 48–72 hr, but is not related with MTX half-life determined in the elimination phase in our study.

Very few studies have been reported on nephrotoxicity of HDMTX in lymphoma patients [12,16]. May et al. [16] retrospectively studied the incidence of nephrotoxicity in adults with lymphoma, and reported a 21% (37/179 courses) incidence of nephrotoxicity with creatinine ≥grade 2 in patients associated with delayed MTX elimination. This was five times higher than 4% (7/165 courses) incidence of nephrotoxicity in our study. This discrepancy may be due to the difference in age of patients between the two studies. They also suggested that renal toxicity was not related to delayed MTX elimination, because the ratio (20%) of nephrotoxicity of patients who do not have was the almost same as patients with delayed MTX elimination. However, this is not consistent with our findings, because the incidence of nephrotoxicity ≥grade 2 in patients without delayed MTX elimination was 0% in our study (data not shown). Lack of correlation between delayed MTX elimination and other toxicities was rather unexpected. This finding suggests that MTX-related toxicities such as stomatitis, hepatic toxicity and infection are affected by CPA and THP as well as MTX in the HDMTX courses in childhood B-NHL treatment.

In our study, delayed MTX elimination was significantly associated with male sex. This finding is inconsistent with some HDMTX studies in childhood ALL, in which female sex has been reported to be associated with high MTX concentrations or low MTX clearance [17,18], whereas other studies have shown that gender is not significantly associated with MTX concentrations or pharmacokinetic polymorphism in childhood ALL [19,20]. Thus, the role of gender in MTX pharmacokinetics still remains to be elucidated in childhood ALL. In childhood NHL, our results may provide actionable observation that male sex has two times higher risk than female to suffer delayed elimination of MTX in HDMTX therapy, although male sex was not an unfavorable prognostic factor in outcome [4].

There was no significant relation between the first high plasma MTX levels and subsequent MTX levels in the later HDMTX course. This finding showed that there was a wide intra-individual variability of blood MTX levels as previously described by others [21]. Since MTX is primarily eliminated by kidney, creatinine clearance may reflect blood MTX levels. However, there have been controversial studies for relation between creatinine concentrations and plasma MTX levels. One study of children who received 3 or 5 g/m^2 of HDMTX has shown a positive correlation between serum creatinine concentrations and blood MTX levels [22] whereas, another study for children who received 1 or 2 g/m^2 failed to show the positive association [21]. Although creatinine clearance is not steady, it is unlikely that creatinine clearance may change during administration of HDMTX, since all patients were strictly monitored and maintained a high urine output and urinary alkalization during HDMTX administration in our study. From the point of view of clinical practice, we

infer that the first episode of delayed MTX elimination does not predict subsequent high MTX levels in later HDMTX courses. This is also supported by the study of Hempel et al., in which they showed that glomerular toxicity at the end of HDMTX can be completely reversed until the next HDMTX course [12].

The last finding was that the first HDMTX courses had a great incidence of liver and gastrointestinal toxicities followed by a sharp reduction of the incidence in later courses. These results may be explained by the plasma folate concentrations in HDMTX courses. Valik et al. [23] reported a severe encephalopathy occurred at the first HDMTX course but not the second course in a male with acute leukemia, where pretreatment plasma folate concentrations were low before the first HDMTX course and then 10-fold higher before the second course. In addition, Sterba et al. [24] showed the plasma folate concentrations increase significantly with increasing number of HDMTX courses in children with ALL and NHL, and they suggested that the increasing folate baseline concentration could be caused by repetitive LV administration. Similar result was reported in osteosarcoma patients [25]. Consequently, low frequencies of gastrointestinal and liver toxicity in later HDMTX courses in our study may be explained by the difference of pretreatment folate levels according to HDMTX courses, although plasma folate levels were not available in our study. In contrast to the non-hematological toxicities, incidence of hematological toxicity showed few changes by the HDMTX courses and plasma MTX levels, suggesting that hematological toxicity was more affected by CPA and THP than HDMTX. This finding shows the need of prophylaxis and countermeasure for patients with neutropenia to prevent developing severe infections throughout the HDMTX courses.

In this study we employed a 24-hr infusion of HDMTX. However, recent studies have shown the efficacy of 4-hr infusion of HDMTX for childhood B-NHL. Woessmann et al. [26] compared the 4-hr infusion and 24-hr infusion of HDMTX in the NHL-BFM95 study and concluded that a 4-hr infusion is not inferior to, but less toxic than, a 24-hr infusion for low- and intermediate-risk patients. In addition, Cairo et al. [27] have reported that a 4-hr infusion of HDMTX resulted in a favorable outcome for high-risk BNHL patients in the FAB/LMB96 study. Consequently, 4-hr infusion of HDMTX should be considered in our next studies.

In summary, we did not find evidence for relation between plasma MTX levels and MTX-related toxicities except nephrotoxicity. This suggests that when high blood MTX levels are associated with nephrotoxicity, the occurrence of other developing toxicities should be taken into consideration. In addition, the first HDMTX administration was associated with a great incidence of gastrointestinal and liver toxicities followed by a reduction of the incidence in later courses. Hence, these findings suggest that the first episode of severe non-hematological toxicity does not predict the recurrence of severe toxicities in later courses.

ACKNOWLEDGEMENTS

We thank the patients who enrolled in the B-NHL03 study and their families, and Dr. T. Hasegawa for measurements of MTX pharamacokinetic parameters. This study was supported by Grants for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan; H14-Koka(Gan)-031, H15-Koka(Gan)-024, H16-GanRinsho-004, H17-GanRinsho-004, H20-GanRinsho-Ippan-017, H23-GanRinsho-Ippan-014.

REFERENCES

1. Reiter A, Schrappe M, Tiemann M, Ludwig WD, Yakisan E, Zimmermann M, Woessmann W, Mann G, Chott A, Ebell W, Klingebiel T, Graf N, Kremens B, Muller-Weihrich S, Oluss HJ, Zintl F, Henze G, Riehm H. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: Reports of the Berlin–Frankfurt–Münster Group trial NHL–BFM 90. Blood 1999;94:3294–3306.
2. Patte C, Auperin A, Michon J, Behrendt H, Leverrger G, Frappaz D, Lutz P, Coze C, Perel Y, Rahael M, Terriel-Lacombe MJ. The Société Française d'Oncologie Pédiatrique LMB89 protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370–3379.
3. Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, Weston C, Raphael M, Perkins SL, McCarthy K, Cairo MS. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents. It is possible to reduce treatment for the early responding patients. Blood 2007;109:2773–2780.
4. Tsurusawa M, Mori T, Kikuchi A, Mitsui T, Sunami S, Kobayashi R, Takimoto T, Saito A, Watanabe T, Fujimoto J, Nakazawa A, Ohshima K, Horibe K. Improved treatment results of children with B-cell non-Hodgkin lymphoma: A report from the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 Study. Pediatr Blood Cancer 2014;61:1215–1221.
5. Iversen O, Iversen U, Ziegler J, Bluming A. Cell kinetics in Burkitt lymphoma. Eur J Cancer 1974;10:155–163.
6. Murphy SB, Melvin SL, Mauer AM. Correlation of tumor cell kinetics studies with surface marker results in childhood non-Hodgkin's lymphoma. Cancer Res 1979;39:1534–1538.
7. Reiter A, Schrappe M, Ludwig WD, Lampert F, Harbott F, Henze G, Niemeyer CM, Gadner H, Muller-Weihrich S, Ritter J, Odenwald E, Riehm H. Favorable outcome of B-cell acute lymphoblastic leukemia in childhood: A report of three consecutive studies of the BFM group. Blood 1992;80:2471–2478.
8. Tsurusawa M, Aoyama M, Saeki K, Fujimoto T. Cell cycle kinetics in childhood acute leukemia studied with in vitro bromodeoxyuridine labeling Ki67-reactivity, and flow cytometry. Leukemia 1995;11:1921–1925.
9. Evans WE, Pratt CB, Taylor RH, Barker LF, Crom WR. Pharmacokinetic monitoring of high-dose methotrexate. Early recognition of high-risk patients. Cancer Chemother Pharmacol 1979;3:161–166.
10. Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med 1977;297:630–634.
11. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
12. Hempel L, Misselwitz J, Fleck C, Kentouche K, Leder C, Appenroth D, Rost M, Zintl F. Influence of high-dose methotrexate (HD-MTX) on glomerular and tubular kidney function. Med Pediatr Oncol 2003;40:348–354.
13. Kodidela S, Chandra PS, Dubashi B. Pharmacogenetics of methotrexate in acute lymphoblastic leukemia: Why still at the bench level. Eur J Clin Pharmacol 2014;70:253–260.
14. Kishi S, Cheng C, French D, Pei D, Das S, Cook EH, Hijiya N, Rizzari C, Rosner GL, Frudakis T, Pui CH, Evans WE, Relling MV. Ancestry and pharmacogenetics of antileukemic dug toxicity. Blood 2007;109:4151–4157.
15. Schmiegelow K. Advances in individual prediction of methotrexate toxicity: A review. Br J Haematol 2009;146:489–503.
16. May J, Carson KR, Butler S, Liu W, Bartlett N, Wagner-Johnston ND. High incidence of methotorexate associated renal toxicity in patients with lymphoma: A retrospective analysis. Leuk Lymphoma 2014;55:1345–1349.
17. Mary V, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui CH, Evans WE. Patients characteristics associated with high-risk methotrexate concentrations and toxicity. J Clin Oncol 1994;12:1667–1672.
18. Rau T, Erney B, Gores R, Eschenhagen T, Beck J, Langer T. High-dose methotrexate in pediatric acute lymphoblastic leukemia: Impact of ABCC2 polymorphism on plasma concentrations. Clin Pharmacol 2006;80:468–476.
19. Ramsey LB, Panetta JC, Smith C, yang W, Fan Y, Winick NJ, Matin PL, Cheng C, Devidas M, Pui CH, Evans WE, Hunger SP, Loh M, Relling MV. Genome-wide study of methotrexate clearance replicates SLCO1B1. Blood 2012;121:898–904.
20. Noha M, Sahar M, Manal A, EEN Ebid. Study of the pharmacokinetic and pharmacogenetic contribution of the toxicity of high-dose methotrexate in children with acute lymphoblastic leukemia. Med Oncol 2012;29:2053–2062.
21. Joannon P, Oviedo I, Cambell M, Tordeccila J. High-dose methotrexate therapy of childhood acute lymphoblastic leukemias: Lack of relation between serum methotrexate concentration and creatinine clearance. Pediatr Blood Cancer 2004;43:17–22.
22. Mao J, Zhang L, Shen H, Tang Y, Song H, Zhao F, Xu W. Creatinine clearance rate and serum concentration are related to delayed methotrexate elimination in children with lymphoblastic malignancies. Neoplasma 2014;61:77–82.
23. Valik D, Sterba J, Bajciova V, Demlova R. Severe encephalopathy induced by the first but not the second course of high-dose methotrexate mirrored by plasma homocysteine elevations and preceded by extreme differences in pretreatment plasma folate. Oncology 2005;69:269–272.
24. Sterba J, Dusek L, Demlova R, Valik D. Pretreatment plasma folate modulates the pharmacodynamics effect of high-dose methotrexate in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma: 'folate overrescue' concept revisited. Clin Chem 2006;52:692–700.
25. Holmboe L, Andersen AM, Morkid L, Slordal L, Hall KS. High dose methotrexate chemotherapy: Pharmacokinetics, folate and toxicity in osteosarcoma patients. Br J Clin Pharmacol 2011;73:106–114.
26. Woessmann W1, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, Ludwig WD, Klingebiel T, Graf N, Gruhn B, Juergens H, Niggli, F, Parwaresch R, Gadner H, Riehm H, Schrrape M, Reiter R. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: A report of the BFM Group Study NHL-BFM95. Blood 2005;105:948–958.
27. Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton R, Michon J, Weston C, Gerrard M, Perkins SL, Raphael M, McCarthy K, Patte C. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736–2743.

bjh research paper

Haematopoietic stem cell transplantation for relapsed or refractory anaplastic large cell lymphoma: a study of children and adolescents in Japan

Reiji Fukano,[1] Tetsuya Mori,[2] Ryoji Kobayashi,[3] Tetsuo Mitsui,[4] Naoto Fujita,[5] Fuminori Iwasaki,[6] Junji Suzumiya,[7] Motoaki Chin,[8] Hiroaki Goto,[6] Yoshiyuki Takahashi,[9] Junichi Hara,[10] Yong-Dong Park,[11] Masami Inoue,[12] Yuhki Koga,[13] Jiro Inagaki,[1] Hisashi Sakamaki,[14] Souichi Adachi,[15] Keisei Kawa,[16] Koji Kato[17] and Ritsuro Suzuki[18]

[1]Department of Paediatrics, National Kyushu Cancer Centre, Fukuoka, [2]Division of Paediatric Oncology, National Centre for Child Health and Development, Tokyo, [3]Department of Paediatrics, Sapporo Hokuyu Hospital, Sapporo, [4]Department of Paediatrics, Yamagata University Hospital, Yamagata, [5]Department of Paediatrics, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, [6]Division of Haemato-oncology/Regenerative Medicine, Kanagawa Children's Medical Centre, Yokohama, [7]Department of Oncology/Haematology, Shimane University Hospital Cancer Centre, Izumo, [8]Department of Paediatrics and Child Health, Nihon University Itabashi Hospital, Tokyo, [9]Department of Paediatrics, Nagoya University Graduate School of Medicine, Nagoya, [10]Department of Paediatric Haematology/Oncology, Osaka City General Hospital, [11]Department of Paediatrics, Osaka Red Cross Hospital, [12]Department of Haematology/Oncology, Osaka Medical Centre and Research Institute for Maternal and Child Health, Osaka, [13]Department of Paediatrics, Kyushu University Hospital, Fukuoka, [14]Division of Haematology, Tokyo Metropolitan Cancer and Infectious Diseases Centre Komagome Hospital, Tokyo, [15]Human Health Sciences, Kyoto University, Kyoto, [16]Japanese Red Cross Kinki Block Blood Centre, Osaka, [17]Department of Haematology and Oncology, Children's Medical Centre, Japanese Red Cross Nagoya First Hospital, and [18]Department of HSCT Data Management and Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan

Received 30 June 2014; accepted for publication 4 September 2014

Correspondence: Reiji Fukano, MD, Department of Paediatrics, National Kyushu Cancer Centre, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan.
E-mail: fukano.r@nk-cc.go.jp

Summary

To evaluate haematopoietic stem cell transplantation (HSCT) in children and adolescents, we reviewed the records of 47 patients who were ≤18 years, had relapsed or refractory anaplastic large cell lymphoma, and received HSCT between 1990 and 2010. At HSCT, complete remission (CR) was less common in allogeneic HSCT recipients ($n = 24$) than in autologous HSCT recipients ($n = 23$) ($P = 0{\cdot}01$). The autologous and allogeneic HSCT groups differed in terms of 5-year event-free survival (EFS) (38% vs. 50%, $P = 0{\cdot}63$), cumulative incidence of progress or relapse (49% vs. 28%, $P = 0{\cdot}25$), and treatment-related mortality (12% vs. 25%, $P = 0{\cdot}40$). However, these differences were not significant. Patients with non-CR at autologous HSCT had a significantly lower EFS rate (14% vs. 48%, $P = 0{\cdot}03$). Conversely, although those with non-CR at allogeneic HSCT had a lower EFS rate, this was not significant (44% vs. 63%, $P = 0{\cdot}26$). Reduced-intensity conditioning regimens were used for three of the 16 allogeneic HSCTs received by patients with non-CR. These three patients achieved CR, surviving 32–65 months after HSCT. These results demonstrated that allogeneic HSCT might be a treatment option for patients who do not achieve CR through conventional chemotherapy.

Keywords: anaplastic large cell lymphoma, children, adolescents, haematopoietic stem cell transplantation, reduced-intensity conditioning.

© 2014 John Wiley & Sons Ltd
British Journal of Haematology, 2015, **168**, 557–563
First published online 14 October 2014
doi:10.1111/bjh.13167

Anaplastic large cell lymphoma (ALCL) is rare in children, accounting for 10–15% of childhood non-Hodgkin lymphoma cases (Murphy, 1994). The event-free survival (EFS) rate is 65–75% in children and adolescents receiving a first-line strategy based on short-pulse chemotherapy over a period of 3–6 months (Brugières *et al*, 1998, 2009a; Seidemann *et al*, 2001; Le Deley *et al*, 2010). Accordingly, the relapse rate is approximately 30% in most study series. The treatment of relapsed and refractory ALCL remains a matter of debate. Patients with relapsed ALCL have a 30–60% chance of survival under current treatment strategies, which include high-dose chemotherapy with haematopoietic stem cell transplantation (HSCT) and long-term treatment with vinblastine (Brugières *et al*, 2000, 2009b; Williams *et al*, 2002; Mori *et al*, 2006; Woessmann *et al*, 2006; Stockklausner *et al*, 2008; Gross *et al*, 2010). In contrast, patients who experience ALCL progression during first-line chemotherapy have extremely poor outcomes (Woessmann *et al*, 2006) and autologous or allogeneic HSCT is required as the most appropriate therapy.

Some evidence is available regarding the roles of autologous and allogeneic HSCT in paediatric ALCL. However, data are limited to several HSCT case series and case reports. In particular, few reports have been published regarding allogeneic HSCT for paediatric ALCL. We previously reported a retrospective analysis of 26 paediatric patients with recurrent ALCL in Japan (Mori *et al*, 2006). In that study, only three of the eight patients who received autologous HSCT while in their second complete remission (CR) survived without further relapse. In contrast, all six patients who received allogeneic HSCT while in their second CR survived without further relapse. However, our previous study included too few patients for us to discuss the efficacy of HSCT for relapsed or refractory childhood ALCL.

In the present study, we sought to evaluate the efficacy of HSCT for relapsed or refractory ALCL in children and adolescents. We performed a further retrospective analysis of 47 patients who received autologous or allogeneic HSCT for relapsed or refractory ALCL between 1990 and 2010.

Patients and methods

Patients and transplantations

This study was approved by the institutional ethics committee of National Kyushu Cancer Centre. Data on patients who had undergone HSCT were collected from the registries belonging to the Transplant Registry Unified Management Program system of the Japan Society for Hematopoietic Cell Transplantation. The study included 47 patients who had a diagnosis of relapsed or refractory ALCL and received HSCT at age ≤18 years between March 1990 and September 2010. Twenty-three patients received autologous HSCT and 24 patients received allogeneic HSCT. Refractory disease was defined as progression during fist-line treatment. Reduced-intensity conditioning (RIC) regimens were defined as (a) total body irradiation of ≤500 cGy as a single fraction or ≤800 cGy if fractionated, (b) <9 mg/kg of busulfan, (c) ≤180 mg/m^2 of melphalan, (d) <10 mg/kg of thiotepa, or (e) the BEAM regimen (carmustine, etoposide, cytarabine and melphalan), according to previous reports (Yaniv & Stein, 2008; Giralt *et al*, 2009; Ohta *et al*, 2010; Luger *et al*, 2012). All other conditioning regimens were defined as myeloablative conditioning (MAC) regimens.

Statistical analysis

Overall survival (OS), EFS, cumulative incidences of relapse and treatment-related mortality (TRM) were estimated using the Kaplan–Meier method. The Mann–Whitney *U* test, χ^2-test, and Fisher's exact test were used to assess differences in patient characteristics. The level of statistical significance was set at $P < 0{\cdot}05$. All analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Autologous HSCT

The patients' characteristics are shown in Table I. Twenty-three patients received autologous HSCT for relapsed or refractory disease as their first transplantation. The median follow-up duration for survivors after autologous HSCT was 154 (range: 9–224) months. The median age at HSCT was 15 (range: 7–18) years. Sixteen patients had achieved CR at HSCT and seven patients had residual disease. Bone marrow and peripheral blood were the stem cell sources in three and 20 patients, respectively. Engraftment was observed in 23 (100%) cases, occurring at a median of 12 d. The 5-year cumulative incidence of relapse was 49% ± 11% (Fig 1A). Treatment-related death occurred in three of the patients who received autologous HSCT and the 5-year cumulative incidence of TRM was 12% ± 9% (Fig 1B). Two of the three patients died of infectious complications and one patient died of multiple organ failure. The 5-year OS and EFS rates were 51% ± 11% and 38% ± 10%, respectively (Fig 2A, B). We observed 5-year EFS rates of 48% ± 13% and 14% ± 13% for patients with CR and non-CR, respectively, at autologous HSCT (Fig 3A), which constituted a significant difference ($P = 0{\cdot}03$).

Allogeneic HSCT

Twenty-four patients received allogeneic HSCT for relapsed or refractory disease (Table I). The median follow-up duration for survivors after allogeneic HSCT was 68 (range: 32–212) months. The median age at HSCT was 13·5 (range: 3–18) years. Of the 24 patients, four had received previous autologous HSCT. Eight patients had achieved CR at HSCT and 16 patients had residual disease (Table I). The sources of stem cells were bone marrow in 13 patients, cord blood in

© 2014 John Wiley & Sons Ltd

Table I. Characteristics of patients with relapsed or refractory ALCL according to the receipt of autologous or allogeneic HSCT.

	Autologous	Allogeneic	*P*
Patients (*n*)	23	24	
Age at HSCT (years)			
Median	15	13·5	0·27
Range	7–18	3–18	
Sex			
Male	17	21	0·24
Female	6	3	
Stage at diagnosis			
I	1	0	0·36
II	3	4	
III	11	6	
IV	4	8	
Unknown	4	6	
Disease status at HSCT			
CR2/CR≥3	14/2	5/3	0·01
Non-CR	7	16	
Conditioning			
TBI/TLI based	7/1	17/1	0·06
Non-TBI based	15	6	
Stem cell source			
BM	3	13	
PB	20	5	
CB	0	6	
Donor			
MRD	–	7	
MUD	–	2	
MMRD	–	6	
MMUD	–	7	
Unknown	–	2	

HSCT, haematopoietic stem cell transplantation; CR, complete remission; BM, bone marrow; CB, cord blood; PB, peripheral blood; MRD, matched related donor; MUD, matched unrelated donor; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; TBI, total body irradiation; TLI, total lymphoid irradiation.

six patients and peripheral blood in five patients. Seven patients had human leucocyte antigen (HLA)-matched related donors, and two patients received stem cells from HLA-matched unrelated donors. Thirteen patients had HLA-mismatched donors. Engraftment was observed in 21 (88%) cases, occurring at a median of 17 d. Two patients died of infection and one died of disease progression before engraftment. The 5-year cumulative incidence of relapse was 28% ± 10% (Fig 1A). Treatment-related death occurred in five patients; four patients died of infectious complications and one patient died of acute graft-*versus*-host disease (GVHD). The 5-year cumulative incidence of TRM was 25% ± 10% (Fig 1B). Acute GVHD of any grade occurred in 13 patients, nine of whom had grade II–IV GVHD. The 5-year OS and EFS rates were 54% ± 10% and 50% ± 10%, respectively (Fig 2A, B). Seven of 24 patients had multiple relapses before their HSCT; the 5-year EFS rates among patients with and without multiple relapses were 43% ± 19% and 53% ± 12%, respectively ($P = 0·67$). We observed 5-year EFS rates of 63% ± 17% and 44% ± 12% among patients with CR and those with non-CR respectively, at allogeneic HSCT (Fig 3B), which did not constitute a significant difference ($P = 0·13$).

At HSCT, CR was less common among allogeneic HSCT recipients than it was among autologous HSCT recipients ($P = 0·01$). However, there were no significant differences between the autologous and allogeneic HSCT patients in terms of cumulative incidence of relapse ($P = 0·25$), cumulative incidence of TRM ($P = 0·40$), 5-year OS ($P = 0·95$) or 5-year EFS ($P = 0·63$).

RIC regimens

Of the 24 patients in the allogeneic group, four underwent allogeneic HSCT using RIC. Their outcomes are shown in Table II. One of the four patients died of bacterial infection and the other three patients survived in CR without relapse after allogeneic HSCT. Interestingly, none of these three patients were in CR at HSCT.

Discussion

Currently, the efficacy and toxicity of HSCT are poorly defined for childhood cases of relapsed or refractory ALCL. Evidence is especially lacking in regards to the efficacy and toxicity of allogeneic HSCT. The present study included 23 patients who underwent autologous HSCT and 24 patients who underwent allogeneic HSCT. Each of the patients was a child or adolescent who had relapsed or refractory ALCL and underwent HSCT in Japan. This report comprises the largest cohort concerning allogeneic HSCT for relapsed or refractory ALCL in childhood.

The Berlin-Frankfürt-Münster (BFM) cohort had efficacies of autologous HSCT (77% OS and 59% EFS among 39 children with relapsed ALCL) that lie at or above the upper range of previously reported series (Woessmann *et al*, 2011). In national case series from the United Kingdom and France, one of six and nine of 15 patients stayed in continuous CR (Brugières *et al*, 2000; Williams *et al*, 2002; Woessmann *et al*, 2011). The Center for International Blood and Marrow Transplant Research (CIBMTR) has reported another large series of autologous HSCTs that were performed for ALCL, noting an EFS of 35% in 24 patients (Gross *et al*, 2010). Previously, we have reported a retrospective analysis of relapsed ALCL, which included 26 patients in Japan (Mori *et al*, 2006). Three of the eight patients who underwent autologous HSCT survived in continuous CR. In the current study, the 5-year OS rate, EFS rate and cumulative incidence of relapse among the 23 patients who underwent autologous HSCT were 51%, 38% and 49%, respectively. These results are similar to the findings of a previous CIBMTR report (Gross *et al*, 2010). In a study of 64 adult and paediatric cases of autologous HSCT for ALCL, Fanin *et al* (1999) reported that disease status at HSCT

© 2014 John Wiley & Sons Ltd

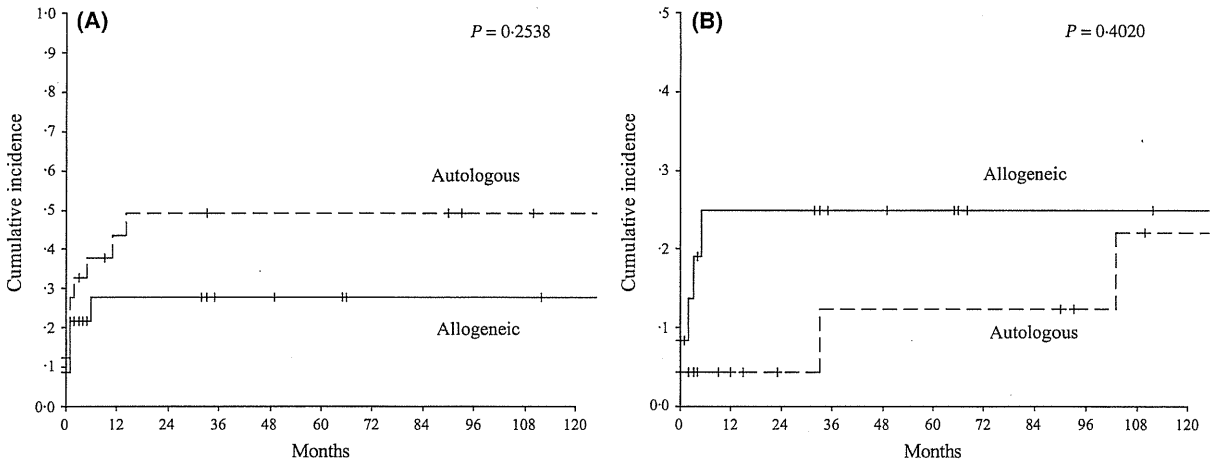

Fig 1. The cumulative incidence of relapse (A) and treatment-related mortality (B) according to autologous and allogeneic haematopoietic stem cell transplantation.

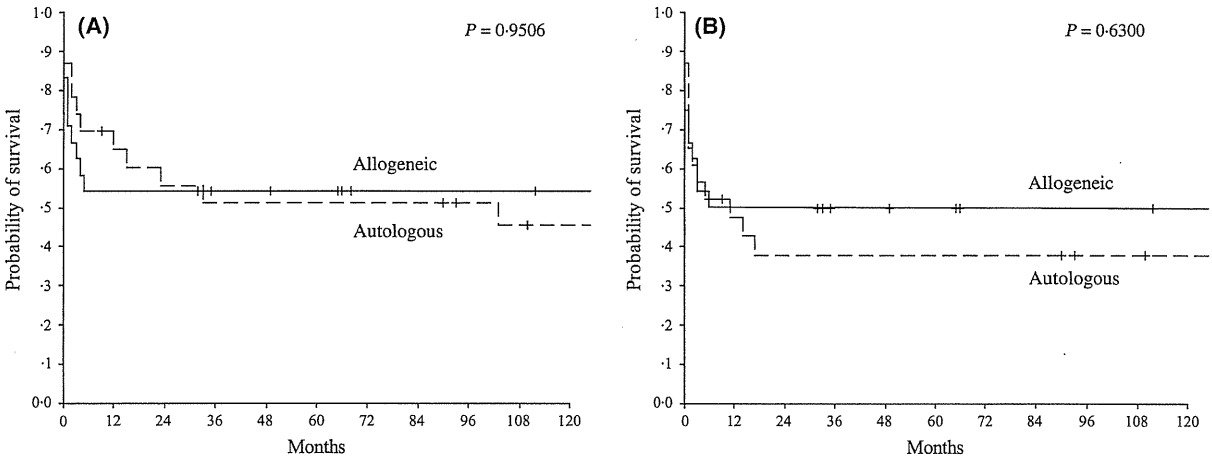

Fig 2. Overall survival (A) and event-free survival (B) according to autologous and allogeneic haematopoietic stem cell transplantation.

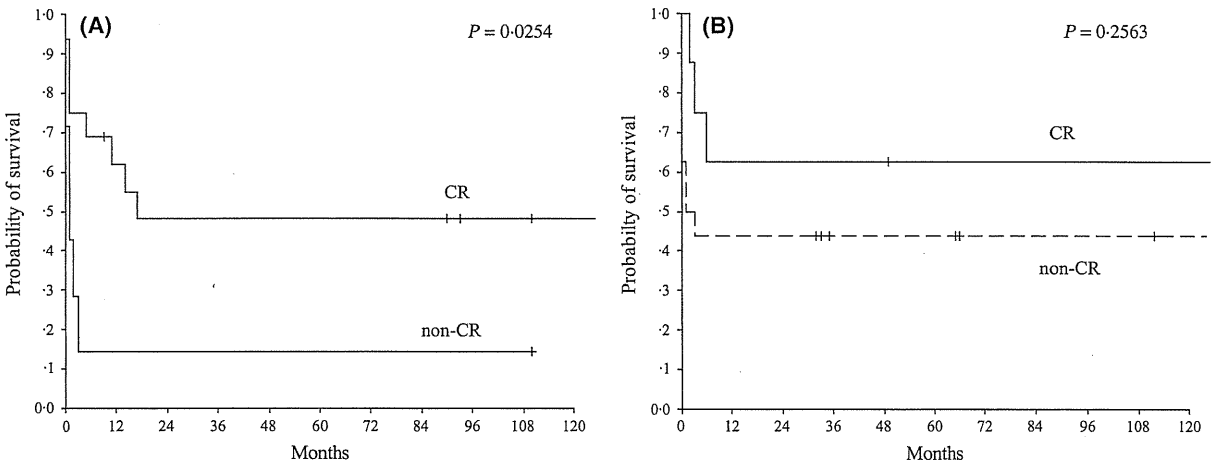

Fig 3. Event-free survival according to disease status at HSCT. (A) Autologous HSCT, (B) allogeneic HSCT. HSCT, haematopoietic stem cell transplantation; CR complete remission.

© 2014 John Wiley & Sons Ltd

Table II. Details and outcomes of patients treated with reduced intensity conditioning and allogeneic HSCT.

Patients	Status at HSCT	Age at HSCT (years)	Donor	Stem cell source	Conditioning regimen	GVHD prophylaxis	aGVHD (Grade)	Extensive cGVHD	Outcome	Follow-up (months)
1	PR	3	UD	CB	TLI 2 Gy, Flu, Mel	Tac, MTX	III	–	CR	32
2	PR	9	UD	CB	Flu, Mel	Tac, MTX	II	–	CR	65
3	CR	18	UD	BM	Flu, Mel, ATG	Tac, MTX	0	NA	TRM	5
4	PR	16	UD	BM	Bu, Flu	Tac, MTX	III	+	CR	33

HSCT, haematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; UD, unrelated donor; BM, bone marrow; CB, cord blood; TLI, total lymphoid irradiation; Bu, busulfan; Flu, fludarabine; Mel, melphalan; ATG, antithymocyte globulin; GVHD, graft-*versus*-host disease; Tac, tacrolimus; MTX, methotrexate; aGVHD, acute GVHD; cGVHD, chronic GVHD; TRM, treatment-related mortality; NA, not applicable.

had predictive value for OS and EFS. In the current study, the EFS of the patients with CR at autologous HSCT was significantly higher than that of the patients with non-CR at autologous HSCT. Brugières *et al* (2000) reported that an interval of <12 months between diagnosis and relapse was associated with a higher risk of failure for the treatment of relapsed ALCL, including autologous HSCT. However, our cohort did not provide sufficient data to compare the risk of failure with the interval between diagnosis and relapse.

The role of allogeneic HSCT has not been defined for cases of childhood ALCL. The currently available evidence is limited to a few reports. The BFM group reported a series of 20 paediatric patients who underwent allogeneic HSCT for relapsed or refractory ALCL, finding a 75% 3-year EFS (Woessmann *et al*, 2006). Twelve of the patients in this study were in CR at HSCT. The CIBMTR has reported another large series of allogeneic HSCTs that were performed for ALCL, observing an EFS of 46% for 12 relapsed or refractory patients (Gross *et al*, 2010). Giulino-Roth *et al* (2013) also reported the cases of 13 paediatric patients with ALCL, eight of whom underwent autologous HSCT and five of whom underwent allogeneic HSCT. The OS and disease-free survival rates were 83% and 77%, respectively. Although our previous study noted that all six patients who underwent allogeneic HSCT during their second CR survived without further relapse (Mori *et al*, 2006), 5-year OS and EFS rates were limited to 54% and 50% in the present study. Patients who underwent allogeneic HSCT while in CR accounted for only eight of the 24 cases. Indeed, the rate of CR at HSCT was lower in the current study than in previous reports of allogeneic HSCT. In the present study, we found no significant difference in EFS according to disease status (CR or non-CR) at allogeneic HSCT. However, the low CR rate at allogeneic HSCT might be associated with the survival rate in the current study, which was lower than the rates noted in previous reports.

In the present study, we observed a 25% TRM rate among patients who underwent allogeneic HSCT for relapsed and refractory disease. Although the cumulative incidence of TRM for allogeneic HSCT was higher than that for autologous HSCT, the difference was not significant ($P = 0{\cdot}40$) (Fig 1B). Several investigations have shown that RIC followed by allogeneic HSCT has the potential to reduce TRM and long-term toxicity in cases of malignant and non-malignant diseases (Carella *et al*, 2000; Dreger *et al*, 2003; Jacobsohn *et al*, 2004; Bradley *et al*, 2007). The BFM cohort of allogeneic HSCTs included one case in which an RIC regimen was administered to a patient with ALCL. The RIC regimen comprised total lymphoid irradiation (2 Gy), fludarabine and melphalan (Brugières *et al*, 2000). Another case in which an RIC regimen [thraco-abdominal irradiation (2 Gy), fludarabine and melphalan] was used has also been reported (Ohta *et al*, 2010). Both of these patients survived in continuous CR following allogeneic HSCT. In the present study, four patients received an RIC regimen followed by allogeneic HSCT. Of these four patients, three were in non-CR at allogeneic HSCT, yet survived in CR for 32–65 months without relapse after HSCT. These results suggest that RIC for relapsed or refractory ALCL may be useful in cases involving allogeneic HSCT, regardless of disease status. However, there are only a few reports of allogeneic HSCT using an RIC regimen for paediatric ALCL. Further evaluations of the efficacy of RIC are necessary and should include larger numbers of patients and a prospective design.

The treatment of relapsed or refractory ALCL remains a matter of debate. Recent studies have reported the efficacies of second-line treatments for relapsed or refractory ALCL, including vinblastine monotherapy, brentuximab vedotin and crizotinib. Brugières *et al* (2009b) studied 36 paediatric patients treated with weekly vinblastine for relapsed or refractory ALCL, finding that this treatment was highly efficacious, with a CR rate of 83%. Furthermore, the 5-year EFS rate was 30%, at which time all but two of the patients had stopped vinblastine for more than 2 years. In adults, a phase II trial of brentuximab vedotin was conducted in patients with relapsed or refractory systemic ALCL. Fifty of 58 patients (86%) achieved an objective response, including 33 patients (57%) in CR (Pro *et al*, 2012). The Children's Oncology Group reported a phase I study of crizotinib for paediatric patients with refractory ALCL, finding that seven of nine children acheived CR following crizotinib monotherapy (Mossé *et al*, 2013). Autologous and allogeneic HSCTs are associated with high rates of toxicities and TRM. Consequently, it will be necessary to speculate about the selection of second-line treatments for relapsed or refractory ALCL in children and adolescents.

© 2014 John Wiley & Sons Ltd

In conclusion, both autologous and allogeneic HSCT can offer the prospect of durable disease-free survival for relapsed and refractory ALCL in childhood and adolescence. Patients with CR at the time of autologous HSCT had significantly greater EFS than patients with non-CR at the time of autologous HSCT. Our results suggest that allogeneic HSCT might provide a better outcome for patients who are resistant to chemotherapy after relapse, and those with non-CR at the time of HSCT. Furthermore, an RIC regimen followed by allogeneic HSCT might even be useful for these patients. However, the small number of patients in our cohort prevented us from investigating the efficacy of allogeneic HSCT with an RIC regimen. In the new era of molecular target drugs, the best candidates for autologous and allogeneic HSCT remain to be clarified by further analyses and prospective studies of relapsed or refractory ALCL in childhood and adolescence.

Acknowledgements

We thank each of the clinicians, hospital administrators and health centre administrators who provided precise data via the registry of the Japan Society for Stem Cell Transplantation.

Author contributions

R Kobayashi, T Mori and R Fukano designed the research study; M Chin, H Goto, Y Takahashi, J Hara, YD Park, M Inoue, Y Koga, J Inagaki, H Sakamaki, S Adachi, K Kawa, K Kato and R Suzuki collected the data; R Fukano analysed the data and wrote the paper. All authors reviewed the manuscript.

Conflict of interest

There are no conflicts of interest to declare.

References

Bradley, M.B., Satwani, P., Baldinger, L., Morris, E., van de Ven, C., Del Toro, G., Garvin, J., George, D., Bhatia, M., Roman, E., Baxter-Lowe, L.A., Schwartz, J., Qualter, E., Hawks, R., Wolownik, K., Foley, S., Militano, O., Leclere, J., Cheung, Y.K. & Cairo, M.S. (2007) Reduced intensity allogeneic umbilical cord blood transplantation in children and adolescent recipients with malignant and non-malignant diseases. *Bone Marrow Transplantation*, **40**, 621–631.

Brugières, L., Deley, M.C., Pacquement, H., Meguerian-Bedoyan, Z., Terrier-Lacombe, M.J., Robert, A., Pondarré, C., Leverger, G., Devalck, C., Rodary, C., Delsol, G. & Hartmann, O. (1998) CD30(+) anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. *Blood*, **92**, 3591–3598.

Brugières, L., Quartier, P., Le Deley, M.C., Pacquement, H., Perel, Y., Bergeron, C., Schmitt, C., Landmann, J., Patte, C., Terrier-Lacombe, M.J., Delsol, G. & Hartmann, O. (2000) Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children—A report from the French Society of Pediatric Oncology. *Annals of Oncology*, **11**, 53–58.

Brugières, L., Le Deley, M.C., Rosolen, A., Williams, D., Horibe, K., Wrobel, G., Mann, G., Zsiros, J., Uyttebroeck, A., Marky, I., Lamant, L. & Reiter, A. (2009a) Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. *Journal of Clinical Oncology*, **27**, 897–903.

Brugières, L., Pacquement, H., Le Deley, M.C., Leverger, G., Lutz, P., Paillard, C., Baruchel, A., Frappaz, D., Nelken, B., Lamant, L. & Patte, C. (2009b) Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology. *Journal of Clinical Oncology*, **27**, 5056–5061.

Carella, A.M., Cavaliere, M., Lerma, E., Ferrara, R., Tedeschi, L., Romanelli, A., Vinci, M., Pinotti, G., Lambelet, P., Loni, C., Verdiani, S., De Stefano, F., Valbonesi, M. & Corsetti, M.T. (2000) Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **18**, 3918–3924.

Dreger, P., Brand, R., Hansz, J., Milligan, D., Corradini, P., Finke, J., Deliliers, G.L., Martino, R., Russell, N., Van Biezen, A., Michallet, M. & Niederwieser, D. (2003) Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. *Leukemia*, **17**, 841–848.

Fanin, R., Ruiz de Elvira, M.C., Sperotto, A., Baccarani, M. & Goldstone, A. (1999) Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation*, **23**, 437–442.

Giralt, S., Ballen, K., Rizzo, D., Bacigalupo, A., Horowitz, M., Pasquini, M. & Sandmaier, B.; Reduced-intensity conditioning regimen workshop: defining the dose spectrum. (2009) Report of a workshop convened by the center for international blood and marrow transplant research. *Biology of Blood and Marrow Transplantation*, **15**, 367–369.

Giulino-Roth, L., Ricafort, R., Kernan, N.A., Small, T.N., Trippett, T.M., Steinherz, P.G., Prockop, S.E., Scaradavou, A., Chiu, M., O'Reilly, R.J. & Boulad, F. (2013) Ten-year follow-up of pediatric patients with non-Hodgkin lymphoma treated with allogeneic or autologous stem cell transplantation. *Pediatric Blood & Cancer*, **60**, 2018–2024.

Gross, T.G., Hale, G.A., He, W., Camitta, B.M., Sanders, J.E., Cairo, M.S., Hayashi, R.J., Termuhlen, A.M., Zhang, M.J., Davies, S.M. & Eapen, M. (2010) Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. *Biology of Blood and Marrow Transplantation*, **16**, 223–230.

Jacobsohn, D.A., Duerst, R., Tse, W. & Kletzel, M. (2004) Reduced intensity haemopoietic stem-cell transplantation for treatment of non-malignant diseases in children. *Lancet*, **364**, 156–162.

Le Deley, M.C., Rosolen, A., Williams, D.M., Horibe, K., Wrobel, G., Attarbaschi, A., Zsiros, J., Uyttebroeck, A., Marky, I.M., Lamant, L., Woessmann, W., Pillon, M., Hobson, R., Mauguen, A., Reiter, A. & Brugières, L. (2010) Vinblastine in children and adolescents with highrisk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *Journal of Clinical Oncology*, **28**, 3987–3993.

Luger, S.M., Ringdén, O., Zhang, M.J., Pérez, W.S., Bishop, M.R., Bornhauser, M., Bredeson, C.N., Cairo, M.S., Copelan, E.A., Gale, R.P., Giralt, S.A., Gulbas, Z., Gupta, V., Hale, G.A., Lazarus, H.M., Lewis, V.A., Lill, M.C., McCarthy, P.L., Weisdorf, D.J. & Pulsipher, M.A. (2012) Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplantation*, **47**, 203–211.

Mori, T., Takimoto, T., Katano, N., Kikuchi, A., Tabuchi, K., Kobayashi, R., Ayukawa, H., Kumagai, M.A., Horibe, K. & Tsurusawa, M. (2006) Recurrent childhood anaplastic large cell lymphoma: a retrospective analysis of registered cases in Japan. *British Journal of Haematology*, **132**, 594–597.

© 2014 John Wiley & Sons Ltd

Mossé, Y.P., Lim, M.S., Voss, S.D., Wilner, K., Ruffner, K., Laliberte, J., Rolland, D., Balis, F.M., Maris, J.M., Weigel, B.J., Ingle, A.M., Ahern, C., Adamson, P.C. & Blaney, S.M. (2013) Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase I consortium study. *Lancet Oncology*, **14**, 472–480.

Murphy, S.B. (1994) Paediatric lymphomas: recent advances and commentary on Ki-1-positive anaplastic large-cell lymphomas of childhood. *Annals of Oncology*, **5**, 31–33.

Ohta, H., Kusuki, S., Yoshida, H., Sato, E., Hashii, Y. & Ozono, K. (2010) Allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning for a child with recurrent anaplastic large cell lymphoma. *International Journal of Hematology*, **92**, 190–193.

Pro, B., Advani, R., Brice, P., Bartlett, N.L., Rosenblatt, J.D., Illidge, T., Matous, J., Ramchandren, R., Fanale, M., Connors, J.M., Yang, Y., Sievers, E.L., Kennedy, D.A. & Shustov, A. (2012) Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *Journal of Clinical Oncology*, **30**, 2190–2196.

Seidemann, K., Tiemann, M., Schrappe, M., Yakisan, E., Simonitsch, I., Janka-Schaub, G., Dörffel, W., Zimmermann, M., Mann, G., Gadner, H., Parwaresch, R., Riehm, H. & Reiter, A. (2001) Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt- Munster Group Trial NHL-BFM 90. *Blood*, **97**, 3699–3706.

Stockklausner, C., Behnisch, W., Mechtersheimer, G., Möller, P. & Kulozik, A.E. (2008) Long-term remission of children with relapsed and secondary anaplastic large cell non-Hodgkin lymphoma (ALCL) following treatment with pulsed dexamethasone and low dose etoposide. *Paediatric Blood & Cancer*, **50**, 126–129.

Williams, D.M., Hobson, R., Imeson, J., Gerrard, M., McCarthy, K. & Pinkerton, C.R. (2002) Anaplastic large cell lymphoma in childhood: analysis of 72 patients treated on The United Kingdom Children's Cancer Study Group chemotherapy regimens. *British Journal of Haematology*, **117**, 812–820.

Woessmann, W., Peters, C., Lenhard, M., Burkhardt, B., Sykora, K.W., Dilloo, D., Kremens, B., Lang, P., Führer, M., Kühne, T., Parwaresch, R., Ebell, W. & Reiter, A. (2006) Allogeneic haematopoietic stem cell transplantation in relapsed or refractory anaplastic large cell lymphoma of children and adolescents: a Berlin- Frankfurt-Munster group report. *British Journal of Haematology*, **133**, 176–182.

Woessmann, W., Zimmermann, M., Lenhard, M., Burkhardt, B., Rossig, C., Kremens, B., Lang, P., Attarbaschi, A., Mann, G., Oschlies, I., Klapper, W. & Reiter, A. (2011) Relapsed or refractory anaplastic large-cell lymphoma in children and adolescents after Berlin-Frankfurt-Muenster (BFM)-type first-line therapy: a BFM-group study. *Journal of Clinical Oncology*, **29**, 3065–3071.

Yaniv, I. & Stein, J. (2008) Reduced-intensity conditioning in children: a reappraisal in 2008. *Bone Marrow Transplantation*, **41** (Suppl 2), S18–S22.

© 2014 John Wiley & Sons Ltd

第76回日本血液学会学術集会
リンパ系腫瘍：ALL/ML
EL-31 疾患

ホジキンリンパ腫の治療

永井宏和

Key words : Hodgkin lymphoma, Combined modality treatment, ABVD, Interim PET

はじめに

ホジキンリンパ腫（Hodgkin lymphoma, HL）は本邦では悪性リンパ腫8～10%程度を占める。病理組織学的に結節性リンパ球優位型ホジキンリンパ腫（nodular lymphocyte predominant Hodgkin lymphoma, NLPHL）と古典ホジキンリンパ腫（classical Hodgkin lymphoma, CHL, 結節硬化型古典ホジキンリンパ腫，リンパ球豊富型古典ホジキンリンパ腫，混合細胞型古典ホジキンリンパ腫，リンパ球減少型古典ホジキンリンパ腫）に分類される。NLPHLとCHLは病理組織学的，臨床病態が異なる。またNLPHLは本邦では極めてまれな疾患である。本稿においてHLは基本的にCHLを指す。HLの標準治療法，HLの治療戦略における治療中間PET（interim PET）の位置づけ，新規薬剤の有用性について概説する。

HLの治療概要

Ann Arbor分類（Cotswolds修正案）[1]の臨床病期I, II期は限局期，III, IV期は進行期に分類される。限局期では化学療法と放射線療法の併用を計画するcombined modality treatment（CMT）が採用される。進行期では化学療法が標準治療であり，症例によって残存部位に放射線療法が追加する場合がある。以下で紹介する臨床試験のほとんどがCHLとNLPHLを区別せずHL全体を対象としている。治療効果判定はPET-CTを用いる[2,3]。

限局期HLの治療

限局期HLは予後因子の評価により予後良好群と予後不良群に分類することができる。種々の臨床研究で予後不良因子とされたものは，巨大腫瘤，病変数，年齢，性別，血沈，臨床症状などである[4]。これら予後不良因子が存在しないもしくは少ない限局期症例が予後良好群，予後不良因子が多く存在する限局期症例が予後不良群と分類できる。予後良好群，予後不良群に関わらず限局期HLの標準療法はCMTである。ABVD（doxorubicin, bleomycin, vinblastine, dacarbazine）療法4コース後に領域照射（involved field radiation threrapy, IFRT）30 Gyを行う[5]。拡大照射野は有害事象が多いため，放射線単独，化学療法との併用のどちらにおいても採用してはならないことが[6]，EORTC/GELAのinter group studyであるH8試験で示された（Fig. 1）。この試験では予後良好群（H8-F）はMOPP-ABV（doxorubicin, bleomycin, vinblastine）3コース＋領域照射のCMTと放射線単独療法（拡大照射野：subtotal irradiation（STLI））の2群にランダム化割付，予後不良群（H8-U）ではMOPP-ABV 4コース＋領域照射，MOPP-ABV 6コース＋領域照射，MOPP-ABV 4コース＋拡大照射の3群にランダム化割付が行われた。H8-F群においては10年の無イベント生存率，全生存率においてMOPP-ABV 3コース＋領域照群が放射線単独療法（拡大照射群）に優った。また，H8-Uにおいも拡大照射併用の有用性は示されなかった。この結果により限局期HLの治療において拡大照射野（単独，CMT）は選択してはならないことが明らかとなった。

以下に予後良好群と予後不良群別の治療研究について概説するが，この層別化治療選択は本邦において経験は少ない。

・予後良好限局期と予後不良限局期の分類

以前は限局期HLの標準治療法として拡大照射野を用いた放射線単独療法がおこなわれていた。この時代では放射線単独治療からの再発を予測する予後因子を明らかにすることが重要であり，縦隔のバルキー病変，年齢な

国立病院機構名古屋医療センター 臨床研究センター

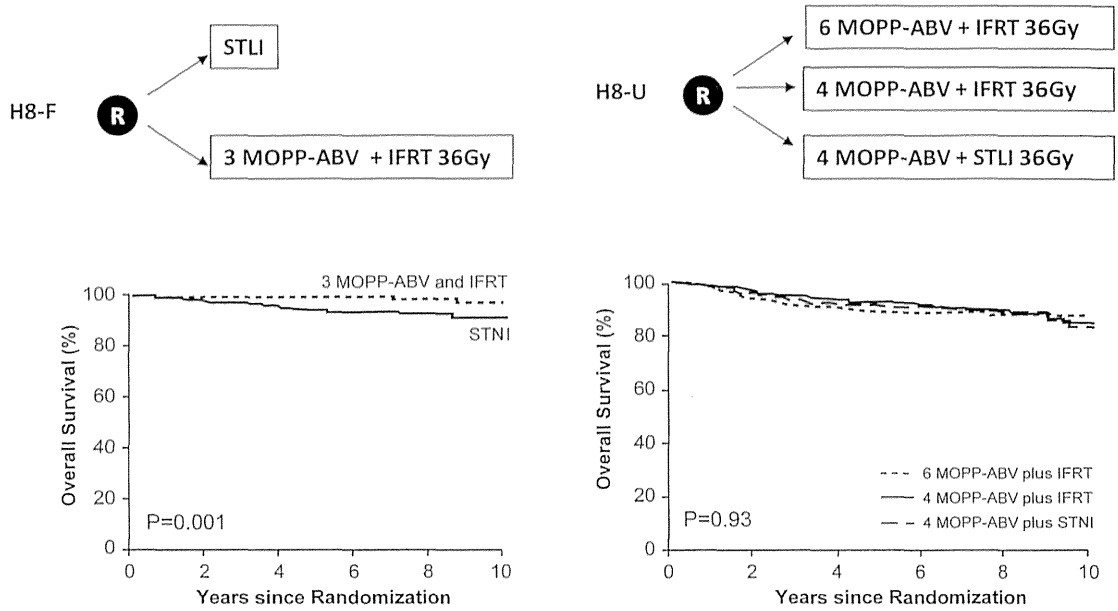

Fig. 1　Schemas and results of H8 trial (EORTC/GELA): limited stage HL
There were not any benefits of extended field radiation both for favorable (H8-F) and unfavorable (H8-U) HL. Favorable patients treated with STNI alone showed poorer overall survival than with combined modality treatment (H8-F). IFRT: involved field irradiation, STNI: subtotal nodal irradiation

どの因子が同定されてきた。これらの因子を中心に限局期HLの予後因子解析が精力的に行われ，予後良好群と予後不良群を区別するシステムが確立していった。Table 1に European Organization for Research and Treatment of cancer (EORTC)/Groupe d'Etude des Lymphomes de l'Adulte (GELA)，German Hodgkin Lymphoma Study Group (GHSG)，National Cancer Institute of Canada (NCIC)/Eastern Cooperative Oncology Group (ECOG) の規準を示す[7~9]。

予後良好群に対する臨床研究（CMT）

GHSGは限局期予後良好HLに対して，ABVD療法2コース対4コースの無作為化，領域照射20 Gy対30 Gyとの無作為化を行う4群比較の臨床第III相試験をおこなった[10]。5年全生存期間および治療成功期間は4群間でほぼ同等であったが，毒性はABVD療法4コース群で急性毒性および急性毒性死亡の発現頻度が高く，30 Gy IFRT群は20 Gy群に比べ急性毒性が多かった。これら毒性を考慮しABVD療法2コース＋領域照射20 Gyが限局期予後良好HLの新たな標準治療となる可能性があることが報告された（Fig. 2）。

予後良好群に関しては治療効果を維持しながらも有害事象が少ない治療法を開発していく方向性であると考えられる。

予後不良群に対する臨床研究（CMT）

GHSGは予後不良群に対してABVD療法4コース対BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, predonisone, procarbazine) 療法4コースの無作為化，その後に領域照射20 Gy対30 Gyの無作為化を行う4群比較の臨床第III相試験を施行した（HD11試験）[11]。治療成功期間がABVD療法4コース＋領域照射20 Gyで短い傾向（有意差は認められず）があり，領域照射30 Gyが施行された場合は化学療法の種類にかかわらず治療成功期間は同等であった。急性毒性はBEACOPP群で有意に多いことも示され，予後不良群においてはABVD療法4コース＋領域照射30 Gyが推奨された。このHD11試験に続きGHSGは同様の対象でABVD療法4コース＋領域照射30 Gyと増量BEACOPP療法2コースに引き続きABVD療法2コースを行い30 Gyの領域照射を行う2群を比較するHD14試験を施行した[12]。治療成功期間は後者が優っていた。EORTC/GELA（H9試験）は予後不良群に対し領域照射と併用する化学療法としてABVD 4コース，ABVD 6コース，BEACOPP 4コースの無作為試験を行っており，CMTにおける最適の化学療法の検索が進行している。

予後不良群に関してはより高い有効性を目指す治療法の開発が進んでいると考えられる。

限局期症例に対する化学療法単独治療法

縦隔バルキー病変が認められない限局期症例に対して