analyses were performed using STATA 8.1 (STATACORP LP, College Station, TX, USA).

RESULTS

Patient Characteristics

Thirty-three patients with AIDS-BL were enrolled. The distributions of clinical characteristics of patients are listed in Table 1. Twenty cases underwent analysis of the *myc* gene, and *myc* rearrangements were detected in 14 patients. The median age was 41 (range 26–70) years, and 97% of the patients were male. Ten (30.3%) had a history of AIDS. The median CD4 + lymphocyte count and HIV viral load at diagnosis of AIDS-BL were 205/mm^3 (range 3–488/mm^3) and 13 700 copies/ml (range 0–12 000 000 copies/ml), respectively. Twenty-nine (87.9%) patients were diagnosed in the advanced stage (III/IV), with BM involvement in 17 (51.5%) patients and CNS infiltration in seven (21.2%) patients. Ten (30.3%) were treated with cART at diagnosis, and their median CD4 + lymphocyte count and HIV viral load at diagnosis of AIDS-BL were 316/mm^3 (range 3–488/mm^3) and 100 copies/ml (range 0–15,000 copies/ml), respectively. Viral load values were not available in two cases. Finally, cART was administered to 90.9% of the patients. For chemotherapy, six (18.2%) patients were treated with CODOX-M/IVAC, 23 (69.7%) patients were treated with hyper-CVAD/MA, two (6.1%) patients were treated with EPOCH and two (6.1%) patients were treated with CHOP.

Patient Outcomes

Response at the end of treatment among 32 assessable patients was as follows: ORR, 26 (78.8%) patients; CR, 24 (72.7%) patients; PR, two (6.1%) patients; SD, one (3.0%) patient and PD, five (15.2%) patients. The overall median follow-up period was 20.0 months (range 0.5–92.7 months). Figure 1 shows the Kaplan–Meier curves for PFS and OS in all patients. The estimated 2-year PFS and OS rates were 59.7 and 68.1%, respectively. At the time of analysis, 10 of 33 patients (30.3%) died, and nine (27.3%) experienced recurrence. There was one treatment-related death.

Impact of Rituximab and Chemotherapy Regimens

Twenty (60.6%) patients were treated with rituximab-containing regimens (rituximab group) and 13 (39.4%) patients were not (non-rituximab group). Of the 20 patients of the rituximab group, none were treated with CODOX-M/IVAC. Fifteen (75.0%) patients in the rituximab group and nine (69.2%) patients in the non-rituximab group achieved CR. The median follow-up in the rituximab group was 17.6 months (range 0.5–73.3 months) and that in the non-rituximab group was 34.1 months (range 1.3–92.7 months). The estimated 2-year PFS rates were 53.3% in the rituximab group and 69.2% in the non-rituximab group; the estimated

Table 1. Patient characteristics

	n	Percentage
Median age, years (range)	41 (26–70)	
≤30	3	9.1
31–40	12	36.4
41–50	10	30.3
51–60	6	18.2
≥61	2	6.1
Male sex	32	97.0
ECOG performance status		
0–1	11	33.3
≥2	22	66.7
Previous AIDS before AIDS-BL	10	30.3
Prior cART before AIDS-BL	10	30.3
Opportunistic disease at diagnosis of AIDS-BL	17	51.5
CD4 + lymphocyte count at diagnosis of AIDS-BL (/mm^3)		
<50	2	6.1
50–100	3	9.1
100–200	10	30.3
>200	18	54.5
Median HIV viral load, copies/ml (range)	13 700 (0–12 000 000)	
Ann Arbor stage		
I–II	4	12.1
III	2	6.1
IV	27	81.8
Bone marrow involvement	17	51.5
CNS infiltration	7	21.2
Extranodal disease	30	90.9
Serum LDH > upper limit of normal	27	81.8
Chemotherapy regimen		
CODOX-M/IVAC	6	18.2
Hyper-CVAD/MA	23	69.7
EPOCH	2	6.1
CHOP	2	6.1
Rituximab		
Yes	20	60.6
No	13	39.4

n, number of patients; ECOG, Eastern Cooperative Oncology Group; AIDS, acquired immunodeficiency syndrome; AIDS-BL, AIDS-related Burkitt lymphoma; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; CNS, central nervous system; LDH, lactate dehydrogenase; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, dexamethasone, etoposide, ifosfamide and cytarabine; hyper-CVAD/MA, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone

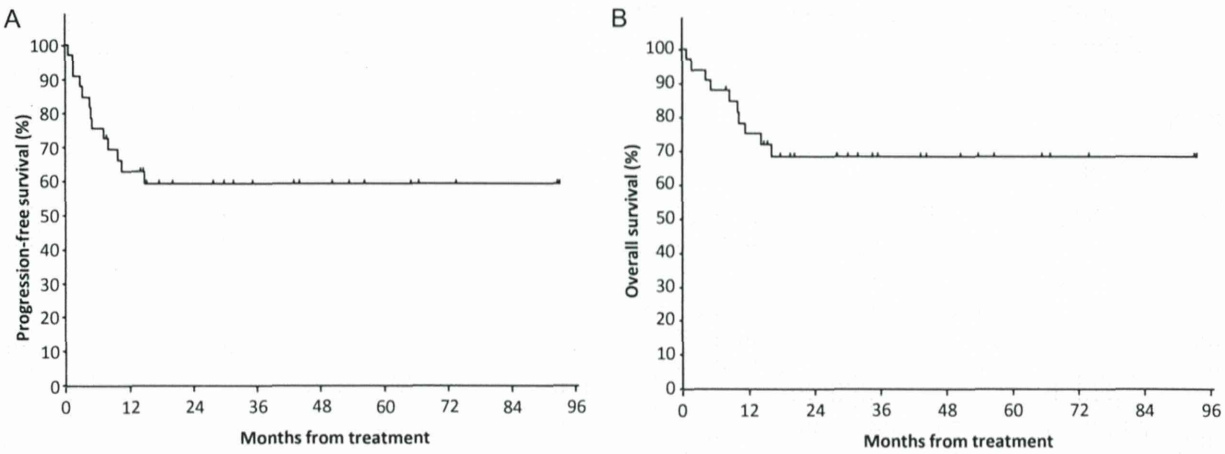


Figure 1. Kaplan–Meier curve of progression-free survival (PFS) (A) and overall survival (OS) (B) in patients with acquired immunodeficiency syndrome-Burkitt lymphoma.

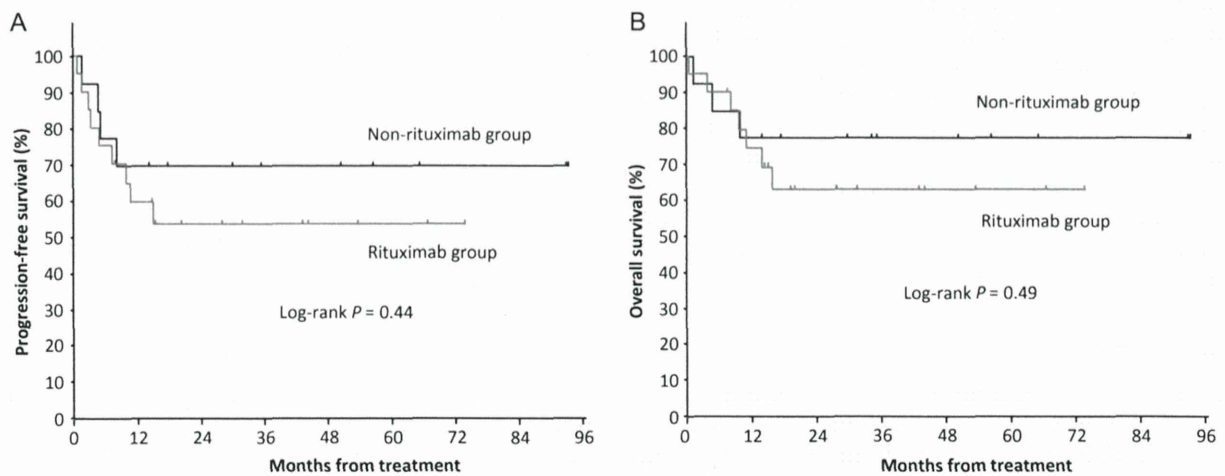


Figure 2. Kaplan–Meier curve of PFS (A) and OS (B) in patients with acquired immunodeficiency syndrome-Burkitt lymphoma treated by rituximab -containing chemotherapy (rituximab group: gray line) and by chemotherapy alone (non-rituximab group: black line).

2-year OS rates were 62.6 and 76.9%, respectively. There was no significant difference in PFS and OS between chemotherapy regimens with rituximab and without rituximab ($P = 0.44$ and $P = 0.49$, respectively) (Fig. 2).

Six (18.2%) patients received CODOX-M/IVAC and 22 (66.7%) patients received hyper-CVAD/MA. The patients receiving rituximab was none in the CODOX-M/IVAC group and 18 (81.8%) in the hyper-CVAD/MA group. Age, PS, clinical stage and LDH were similar among the CODOX-M/IVAC and hyper-CVAD/MA groups. We also compared the PFS and the OS between patients receiving CODOX-M/IVAC and patients receiving hyper-CVAD/MA. The median follow-up in patients receiving CODOX-M/IVAC was 21.9 months (range 1.3–92.7 months) and that in patients receiving hyper-CVAD/MA was 27.7 months (range 0.5–73.3 months). The 2-year PFS rate was 66.7% for patients receiving CODOX-M/IVAC, compared with 64.2% for patients receiving hyper-CVAD/MA ($P = 0.35$) (Fig. 3). The 2-year OS rate was 66.7% for patients receiving CODOX-M/IVAC, compared with 72.6% for patients receiving hyper-CVAD/MA ($P = 0.72$).

Prognostic Factors for Survival in Patients with AIDS-BL

Significant clinical variables that affected PFS or OS were identified using univariate Cox regression analyses. Factors predicting poor PFS in univariate analyses were CNS infiltration, extranodal disease (≥ 2), IPI score (3–4) and CR to chemotherapy ($P = 0.030$, $P = 0.039$, $P = 0.013$ and $P = 0.023$, respectively). There was no significant prognostic factor for OS in univariate analyses.

The clinical outcomes were compared between MYC positive cases ($n = 14$) and negative cases ($n = 6$). There was no significant difference in OS and PFS between the abnormalities and non-abnormalities of MYC ($P = 0.16$ and $P = 0.19$, respectively).

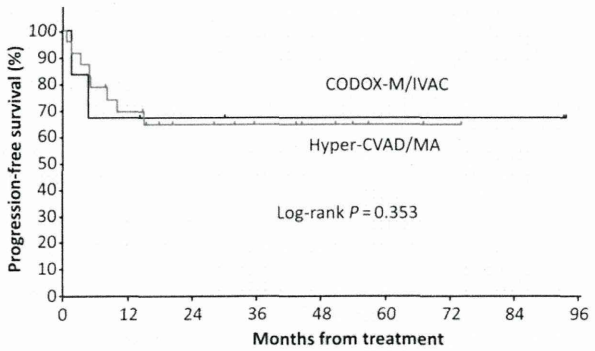


Figure 3. Kaplan–Meier curve of PFS in patients with acquired immunodeficiency syndrome-Burkitt lymphoma treated by hyper-CVAD/MA (gray line) and by CODOX-M/IVAC (black line).

DISCUSSION

We retrospectively evaluated the clinical outcomes of patients with AIDS-BL who received chemotherapy. We identified 33 patients who were treated at regional hospitals for HIV/AIDS in Japan. The ORR and CR rates for all patients were 79 and 73%, respectively. The estimated 2-year PFS and OS rates of all patients were 59.7 and 68.1%, respectively. Mead et al. (23) conducted a clinical trial of highly intensive regimens for non-HIV BL and AIDS-BL, and reported that the estimated 2-year PFS and OS rates of all patients were 60 and 63%, respectively. Thus, favorable overall outcomes were shown for patients with AIDS-BL in this study. There was no significant difference in the OS and the PFS between chemotherapy regimens with/without rituximab ($P = 0.49$ and $P = 0.44$, respectively). In addition, there were no differences in the OS and the PFS when comparing CODOX-M/IVAC and hyper-CVAD/MA groups ($P = 0.72$ and $P = 0.35$, respectively).

The institution of cART has transformed HIV infection into a chronic disease in developed countries and has decreased the incidence of ADCs (26–28). cART consists of two or three antiretroviral agents including reverse transcriptase inhibitors (nucleoside/nucleotide, non-nucleoside), protease inhibitors and integrase strand transfer inhibitor. The application of cART and the cautious management of infections (including prevention) have significantly improved the prognosis of the HIV-infected population, mostly by reducing opportunistic infections. However, the incidence of BL and cervical cancer has not declined in this population (9, 26). AIDS-BL tended to occur in patients with relatively higher CD4 + lymphocyte counts when compared with other lymphomas (3, 5–10). Chronic antigenic stimulation of B-cell by chronic HIV viremia may be the pathogenetic mechanism of AIDS-BL, and patients with chronic HIV viremia have a higher incidence of ARL than those with undetectable viral loads (28, 29). In the present study, 10 (30.3%) patients had been treated with cART at the time of AIDS-BL diagnosis, and the viral loads of these patients tended to be low. Two patients had undetectable viral loads. Therefore, even with the widespread use of cART, AIDS-BL remains an important disease among ADCs.

BL is a rapidly proliferating tumor that develops over a matter of days or weeks and that has a propensity for CNS involvement. The prognosis of patients with AIDS-BL is very poor. Lim et al. (11) reported that the addition of cART to CHOP-based chemotherapy resulted in a significant improvement in the outcome of AIDS-related DLBCL, whereas the survival of patients with AIDS-BL remained poor. Similarly, in a Phase II study, the survival of patients with AIDS-BL was significantly worse when compared with patients of AIDS non-BL who were treated with rituximab plus CDE (cyclophosphamide, doxorubicin and etoposide) (30). The reason for these poor outcomes was likely related to the fact that patients received only reduced-dose chemotherapy regimens (13, 14). Wang et al. (31) compared HIV-infected BL patients and non-HIV-infected BL patients treated with CODOX-M/IVAC or less intensive regimens, and reported that the 2-year event-free survival was significantly better in patients treated with CODOX-M/IVAC than in those receiving less intensive chemotherapy. In two retrospective studies, toxicity and outcomes experienced by patients with AIDS-BL were similar to those of patients with non-HIV BL in response to CODOX-M/IVAC or hyper-CVAD/MA (24, 31). Another prospective study clarified that patients with AIDS-BL treated with intensive immunochemotherapy had a higher incidence of severe mucositis and infections than patients with non-HIV-infected BL; however, the survival was similar when comparing those two groups (32). Therefore, in the cART era, more intensive regimens should be considered for patients with AIDS-BL in a manner similar to treatment offered to patients with non-HIV BL. EPOCH would be another promising regimen for ARLs including BL and be less intensive than CODOX-M/IVAC and hyper-CVAD/MA (25, 33). It might be considered a good alternative for frail patients.

Standard chemotherapy regimen for AIDS-BL patients remains controversial. Our study showed that the type of chemotherapy regimen had no significantly different impact on outcomes when comparing CODOX-M/IVAC vs. hyper-CVAD/MA (2-year PFS, 66.7 and 64.2%, respectively; $P = 0.35$, and 2-year OS, 66.7 and 72.6%, respectively; $P = 0.72$). This result suggests that intensive chemotherapy regimens might provide to favorable outcomes to patients with AIDS-BL.

One important question is whether patients with AIDS-BL should be treated with rituximab. The B-cell lineage restricted marker, CD20 is strongly expressed in BL. *In vitro*, rituximab has a proven anti-BL effect (34). One randomized clinical trial of ARL treated with rituximab reported that the addition of rituximab to CHOP was associated with a significantly higher risk of treatment-related death when compared with the use of CHOP alone. This was due to an increase in infection-related deaths in patients receiving rituximab plus chemotherapy, especially in patients with CD4 + lymphocyte counts $<50/mm^3$ (35). Another study showed that the addition of rituximab increased the risk of infections (36). No randomized trial examining the role of rituximab has been performed in patients with

AIDS-BL. In the present study, rituximab-containing chemotherapy was not superior to chemotherapy without rituximab. The reasons for these results were not apparent, but the rituximab-containing highly intensive chemotherapy might contain some defects in treating AIDS-BL patients.

In conclusion, this study demonstrated favorable overall outcomes for patients with AIDS-BL in the cART era. Highly intensive chemotherapy regimens would bring high remission rates and prolonged OS. The addition of rituximab to highly intensive chemotherapy has not shown to be beneficial for patients with AIDS-BL. These data warrant the design of a prospective trial to optimize the treatment for patients with AIDS-BL.

Funding

This study was supported by a Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (grant number: H22-AIDS-002).

Conflict of interest statement

None declared.

References

1. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. *Blood* 2004;104:3009–20.
2. Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. *Lancet* 1991;337:805–9.
3. Straus DJ. Treatment of Burkitt's lymphoma in HIV-positive patients. *Biomed Pharmacother* 1996;50:447–50.
4. Newcom SR. Acquired immunodeficiency syndrome-related lymphoma. *Blood* 1992;80:2944–6.
5. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. *Lancet* 2012;379:1234–44.
6. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* 2001;98:2339–44.
7. Pluda JM, Venzon DJ, Tosato G, et al. Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. *J Clin Oncol* 1993;11:1099–107.
8. Carbone A, Gloghini A, Gaidano G, et al. AIDS-related Burkitt's lymphoma. Morphologic and immunophenotypic study of biopsy specimens. *Am J Clin Pathol* 1995;103:561–7.
9. Mounier N, Spina M, Gabarre J, et al. AIDS-related non-Hodgkin lymphoma: final analysis of 485 patients treated with risk-adapted intensive chemotherapy. *Blood* 2006;107:3832–40.
10. Guech-Ongey M, Simard EP, Anderson WF, et al. AIDS-related Burkitt lymphoma in the United States: what do age and CD4 lymphocyte patterns tell us about etiology and/or biology? *Blood* 2010;116:5600–4.
11. Lim ST, Karim R, Nathwani BN, Tulpule A, Espina B, Levine AM. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. *J Clin Oncol* 2005;23:4430–8.
12. Spina M, Simonelli C, Talamini R, Tirelli U. Patients with HIV with Burkitt's lymphoma have a worse outcome than those with diffuse large-cell lymphoma also in the highly active antiretroviral therapy era. *J Clin Oncol* 2005;23:8132–3; author reply 3–4.
13. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. *N Engl J Med* 2006;354:2431–42.
14. Bishop PC, Rao VK, Wilson WH. Burkitt's lymphoma: molecular pathogenesis and treatment. *Cancer Invest* 2000;18:574–83.
15. Xicoy B, Ribera JM, Miralles P, et al. Comparison of CHOP treatment with specific short-intensive chemotherapy in AIDS-related Burkitt's lymphoma or leukemia. *Med Clin (Barc)* 2011;136:323–8.
16. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;105:1417–23.
17. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–42.
18. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006;24:3121–7.
19. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
20. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860–1.
21. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;329:987–94.
22. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;17:1244.
23. Mead GM, Barrans SL, Qian W, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). *Blood* 2008;112:2248–60.
24. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer* 2002;94:1492–9.
25. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood* 2010;115:3008–16.
26. Shiels MS, Pfeiffer RM, Hall HI, et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980–2007. *JAMA* 2011;305:1450–9.
27. Bedimo R, Chen RY, Accortt NA, et al. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002. *Clin Infect Dis* 2004;39:1380–4.
28. Shiels MS, Cole SR, Wegner S, et al. Effect of HAART on incident cancer and noncancer AIDS events among male HIV seroconverters. *J Acquir Immune Defic Syndr* 2008;48:485–90.
29. Zoufaly A, Stellbrink HJ, Heiden MA, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. *J Infect Dis* 2009;200:79–87.
30. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. *Blood* 2005;105:1891–7.
31. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. *Cancer* 2003;98:1196–205.
32. Oriol A, Ribera JM, Bergua J, et al. High-dose chemotherapy and immunotherapy in adult Burkitt lymphoma: comparison of results in human immunodeficiency virus-infected and noninfected patients. *Cancer* 2008;113:117–25.
33. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* 2003;101:4653–9.
34. Daniels I, Abulayha AM, Thomson BJ, Haynes AP. Caspase-independent killing of Burkitt lymphoma cell lines by rituximab. *Apoptosis* 2006;11:1013–23.
35. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. *Blood* 2005;106:1538–43.
36. Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. *Br J Haematol* 2008;140:411–9.

●原 著

HIV 感染症患者に合併した結核に関する検討

笠井 大介　廣田 和之　伊熊 素子　小川 吉彦　矢嶋敬史郎
渡邊 大　西田 恭治　上平 朝子　白阪 琢磨

要旨：Human immunodeficiency virus（HIV）感染症患者に合併した結核に関して，検討を行った．対象は41例で平均年齢は44.6歳，34例はHIV未治療の状態での発症であった．肺結核のみで発症した症例は18例であり，23例で肺外結核を発症していた．Interferon-gamma release assay（IGRA）は19例に施行されており，18例が陽性，1例が判定保留であった．治療成績としては2例に重篤な後遺症が認められた．

キーワード：HIV，結核，肺外結核，IGRA，免疫再構築症候群
HIV, Tuberculosis, Extrapulmonary tuberculosis, IGRA, IRIS

緒　言

Human immunodeficiency virus（HIV）感染症患者の予後はhighly active antiretroviral therapy（HAART）の進歩により年々改善している．特に早期にHIV感染を発見され，CD4陽性リンパ球数（CD4数）が保たれている時期に治療を導入した症例では，多くにおいて長期の良好な予後が期待できるようになった．一方で免疫の低下が進み日和見感染を発症した症例では，今日においても治療に難渋することが多い．結核は免疫疾患のない患者にも発症するが，HIV感染症患者では非感染患者と比較して発症率が高く，HIV感染症患者の日和見疾患のなかでも比較的免疫が保たれた患者にも発症する重要な疾患である．さらにCD4数が低下した症例では，典型的な病像を呈さずに診断に苦慮する症例も多い．また結核合併例はHAART導入に伴う免疫の改善により症状が悪化する免疫再構築症候群（immune reconstitution syndrome：IRIS）を発症する頻度も高く，治療に難渋することもしばしば経験される．今回の我々の研究では国立病院機構大阪医療センターで経験した結核合併症例を後ろ向きに解析することにより，HIV感染症患者に合併した結核の臨床的特徴に関して検討を行うこととした．

連絡先：笠井　大介
〒540-0006　大阪府大阪市中央区法円坂2-1-14
独立行政法人国立病院機構大阪医療センター感染症内科
(E-mail: kasaidk@onh.go.jp)
(Received 21 May 2014/Accepted 6 Oct 2014)

対象と方法

1997年1月1日～2012年12月31日の間に国立病院機構大阪医療センターを受診したHIV感染症患者のうち，2013年12月31日までに結核を発症した症例を診療録より抽出して後ろ向きに解析を行った．解析内容は結核の診断方法，患者の性別，結核発症時の年齢，HIVウイルス量，CD4数，薬剤感受性，初発症状，発症部位，interferon-gamma release assay（IGRA），治療経過，免疫再構築症候群の有無とした．なおIGRAは2010年12月5日まではクオンティフェロン® TB-2G（QFT-2G）を，2010年12月6日からはクオンティフェロン® TBゴールド（QFT-3G）を用いて測定されている．

免疫再構築症候群に関しては現時点では明確な定義や診断基準は確立されていないが，多くの場合は免疫不全のあるHIV感染症患者に対して新規にHAARTを開始し，数ヶ月以内に日和見感染症などの疾患が発症，再発，再増悪した場合に免疫再構築症候群を発症したと考えられている．また免疫再構築症候群はHAART導入後に日和見感染症を発症するunmasking IRISと，日和見感染症の治療を行った後にHAARTを導入することにより再度日和見感染の増悪をきたすparadoxical IRISの2つの病態に分けて考えられることが多く[1]本研究においてもこの分類に準じて解析を行っている．

成　績

1．結核の診断

対象期間中に2437名のHIV感染症患者が国立病院機構大阪医療センターを受診し，62例が結核と診断され，全例に対して抗結核薬の投与がなされていた．このうち

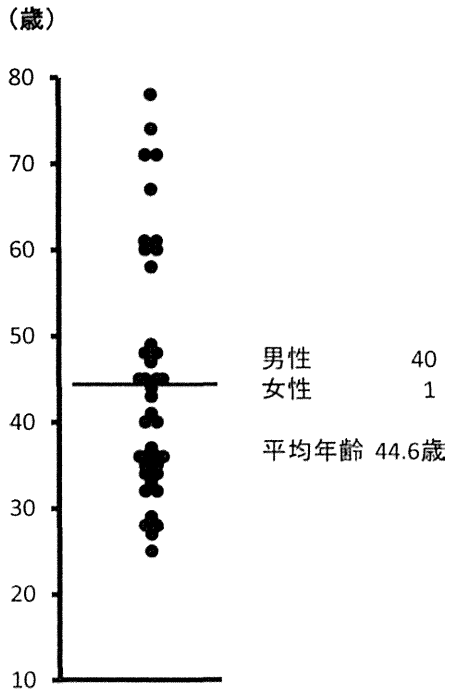


図1　結核発症時の年齢.

表1　結核発症時の臨床症状

発熱	32/41
咳嗽	8/41
リンパ節腫脹	4/41
意識障害	2/41
体重減少	2/41
胸部単純X線写真異常のみ	2/41
腹痛	1/41

重複あり.

表2　結核の発症部位

肺結核	18/41
肺外結核　または　肺結核＋肺外結核	23/41
肺外結核の発症部位	
粟粒結核	9
結核性リンパ節炎	6
結核性胸膜炎	4
結核性髄膜炎	4
腸結核	3
結核性腹膜炎	1
脳結核	1
結核性脊椎炎	1

重複あり.

培養で結核菌が陽性となり確定診断がついた症例は41例で，24例が喀痰塗抹検査陽性，17例が喀痰塗抹検査陰性であった．培養陰性で補助診断や臨床経過より結核と診断した症例は21例で，診断根拠の内訳はPCR陽性での診断が10例，ADA上昇での診断が6例，臨床経過からの診断が3例，生検結果からの診断が1例，tuberculin skin test（TST）による診断が1例であったが，これら培養陰性の症例に関しては今回の解析から除外した．

2. 患者背景

培養にて結核菌が同定された確定診断例41例のうち，男性は40例，女性は1例で，発症時の平均年齢は44.6歳であった（図1）．発症時のHIVウイルス量とCD4数を図2に示した．発症患者の多くはCD4数が低値の症例であったが，CD4数＞200/μlとCD4数の保たれている症例にも結核の発症を認めた．結核発症患者のうち34例はHIV未治療例であったが，7例はHAART開始後に結核を発症していた．HAART開始後に結核を発症した症例のうち6例は開始後8週間以内に発症しており，unmasking IRISとして結核発症に至ったものと考えられたが，1例は開始後6年を経過して病態が安定した状態で結核を発症しておりunmasking IRISではないと考えられた．

3. 薬剤耐性

41例中4例で薬剤耐性を認めた．薬剤耐性のパターンは，①イソニアジド（isoniazid：INH），リファンピシン（rifampicin：RFP），エタンブトール（ethambutol：EB），カナマイシン（kanamycin：KM），エンビオマイシン（enviomycin：EVM）耐性，②EVM耐性，③INH耐性，④レボフロキサシン（levofloxacin：LVFX）耐性であった．

4. 初発症状

結核の初発症状では約80％の症例に発熱を認めた．一方，胸部単純X線写真の異常のみで自覚症状を有さない症例も認められた（表1）．

5. 病変の局在

結核の病変の部位に関しては肺結核のみで発症した症例が18例であったのに対して，肺外結核を伴う症例が23例と肺外結核の頻度が高かった．肺外結核では粟粒結核と結核性リンパ節炎，結核性胸膜炎，結核性髄膜炎の頻度が高かった（表2）．

結核発症時のCD4数を肺結核のみの症例と，肺外結核を合併した症例で比較検討したところ，CD4数の平均値は肺結核群で180/μl，肺外結核群で90/μlと肺外結核群で有意に低値であった（図3）．なお，この解析ではHAARTを開始したのちに結核を発症した症例は除外した．

6. IGRA

2007年以降に結核と診断された19例で補助診断としてIGRAが施行されていた．12例がQFT-2Gで，7例が

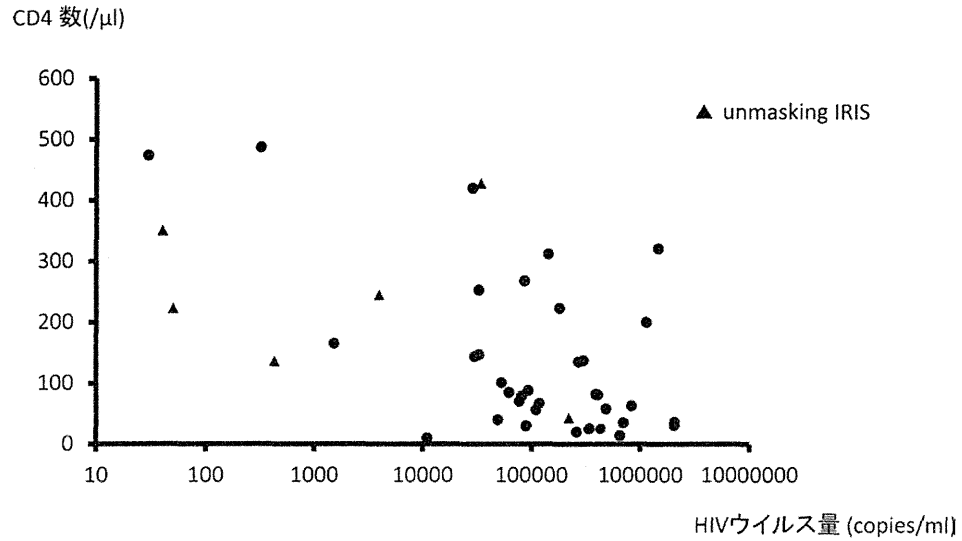


図2 結核発症時の HIV ウイルス量と CD4 数.

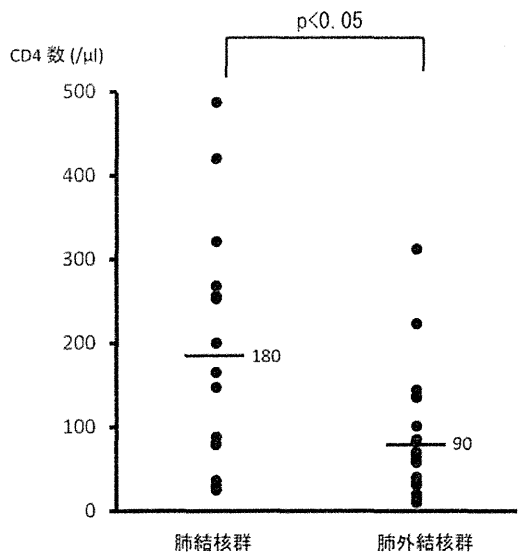


図3 結核発症時の CD4 数.

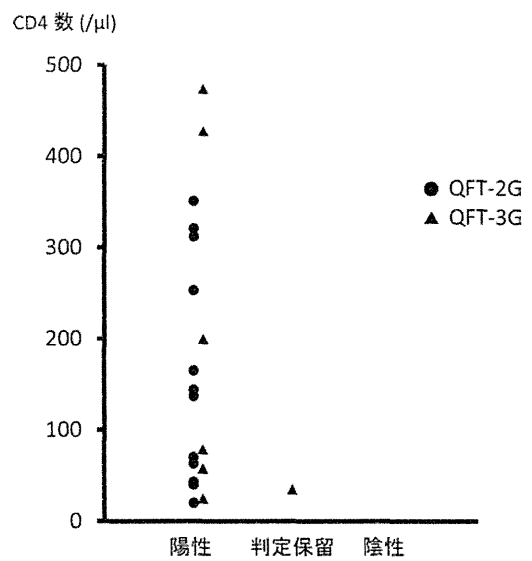


図4 IGRA 結果.

QFT-3G で測定されており，18 例が陽性，1 例が判定保留であった．陽性群には CD4 数 50/μl 以下が 3 例含まれており，判定保留例の CD4 数は 35/μl であった（図 4）．

7. 治療経過

41 例中 7 例は HAART 導入前に結核の既往はなく，HAART 開始後に結核を発症しており，開始後 6 年を経過して結核を発症した 1 例を除いては unmasking IRIS として発症したと考えられた．HIV 未治療の状態で結核を発症し，結核治療後に HAART を開始した 34 例のうち 8 例に paradoxical IRIS と考えられる病態を認め，そのうち 6 例では副腎皮質ホルモン併用による治療を要した（図 5）．治療後の転帰は 35 例で治癒となり再発を認めず経過しているが，2 例で重篤な後遺症を認めており，1 例は結核性髄膜炎で，1 例は結核性脊椎炎による対麻痺で長期臥床状態となった．このうち結核性髄膜炎の症例は INH，REF，EB，KM，EVM 耐性株によるものであり，初回治療後も再発を繰り返している．耐性菌は 4 例認められたが，前述の症例以外は初回治療後再発なく経過している．結核の治療後に死亡した症例は 3 例であったが，いずれも結核以外の疾患による死亡と考えられた（表 3）．

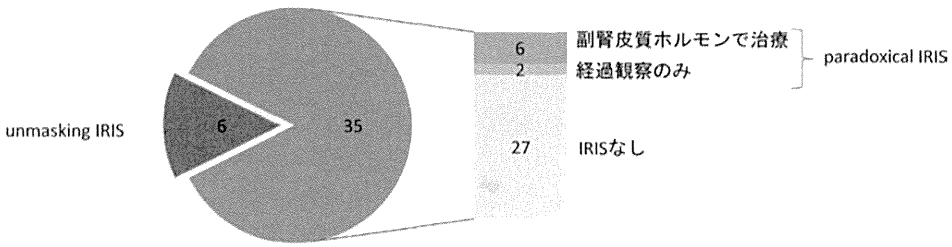


図5　HAART 導入後の臨床経過.

考　察

HIVによる免疫不全が示唆される患者に発症した，活動性肺結核と活動性肺外結核はエイズ指標疾患の一つであり，HIV感染症患者においてきわめて重要な疾患である．結核感染者における結核の生涯発症率は一般的に約5～10%であるが，未治療のHIV感染症患者では年間発症率が5～10%とされており，HIV非感染者と比較して50～100倍程度の発症リスクがある[2]．世界的にみると結核による死亡患者は年々減少しているが，単一の感染症としてはHIV/AIDSに続き世界で2番目に死亡患者が多い疾患であり，2011年には870万人が罹患し，140万人が死亡している[3]．また結核はHIV感染症患者の主要な死因の一つであり，HIV感染症患者の約1/4が結核で亡くなるとされている[3]．一方でHAARTが導入されてからはHIV感染症の予後は著明に改善しており，エイズ関連疾患とHIV感染症患者の死亡率は大きく減少してきている．またHAARTはHIV感染症患者における活動性結核の合併リスクを減少させることも報告されている[4)5)]．

臨床所見としては，HIV感染症患者では結核に典型的ではない経過や画像所見をとることが多い．日本の結核の罹患率は人口10万人に対して17.7人で，米国の約4倍となっており[6)7)]，新規発症患者の半数以上は70歳以上の高齢者が占めている．しかし我々の結果では結核発症時の平均年齢は44.6歳であり，非HIV感染患者と比較してHIV感染症患者では明らかに若年で結核を発症する傾向が認められた．また病変の広がりに関しては，本研究では41例中23例に粟粒結核や結核性胸膜炎をはじめとする肺外結核の合併が認められた．非HIV感染者の結核患者における肺外結核の頻度は報告によりさまざまであるが，10～20%程度を占めるとの報告が多いことより[8)～10)]，HIV感染症患者においては肺外結核の頻度が高いことが示唆された．HIV感染患者における肺外結核はCD4数が100/μl以下の症例で有意に増加するとの報告があるが[11)]，本研究においても肺外結核群の平均CD4数は90/μlであり，肺結核のみの群と比較して有意に低値であった．これらの結果よりHIV感染症患者では肺外結核を有する症例が多く，なかでもCD4数が低い症例に発症しやすいことが明らかとなった．

表3　治療成績

経過良好	35
結核以外の疾患で死亡	3
後遺症を残して改善	2
治療中	1

結核の補助診断にはIGRAが近年広く用いられており，TSTと比較して有用性が高いとの報告が数多くなされている[12)13)]．一方でHIV感染症患者をはじめとした免疫抑制状態にある症例では，細胞性免疫の低下によりT細胞からのinterferon-γ(IFN-γ)の産生が減少するため，IFN-γの産生能を指標とするIGRAの感度が低下するとされており，CD4数が低値の症例においては結果を注意深く検討する必要がある[14)15)]．またHIV感染症患者のIGRAに関しては，CD4＜100/μlの症例ではT-SpotがQFT-3Gと比較して有意に感度が良いとの報告があり，T-Spotの有用性が示唆されている[16)]．本研究においてはIGRAを施行した症例のうちCD4≧100/μlの症例では100%(10/10)，CD4＜100/μlの症例においても89%(8/9)が陽性となっており，CD4数の低いHIV感染症患者においてもIGRAは補助診断として有用であると考えられた．本研究では全例QFT-2GもしくはQFT-3Gで検査を施行しているが，T-Spotに関しても今後症例の蓄積を行う予定である．

HAART導入後には免疫機能の改善により，結核の症状が悪化する免疫再構築症候群を発症する頻度も高い．結核をはじめとした抗酸菌感染における免疫再構築症候群は難治性となることも多く，コントロールに難渋する症例では抗HIV治療の中断や，副腎皮質ホルモンの長期間にわたる併用を余儀なくされることも多い．免疫再構築症候群の重症例では不可逆的な障害を残すこともあり，本研究においても結核性髄膜炎と結核性脊椎炎の症例で長期の神経障害を認めている．

このようにHIV感染症患者では結核の発病率が高いものの，肺外結核症例など典型的な経過をとらないことも多く，時に診断に難渋する．また抗結核薬と抗HIV薬の薬剤相互作用により薬剤の選択が制限されることや，免疫再構築症候群を発症する頻度が高いことなど，治療においても難渋する症例をしばしば経験する．そのためHIV感染症患者に日和見感染を疑う所見を認めたときには鑑別疾患として結核を常に念頭に置き，肺外結核の可能性に関しても留意すべきである．また治療経過中に病状が悪化した際には結核以外の日和見感染症の存在や結核の初期悪化，治療の失敗，免疫再構築症候群などの治療方針の異なる病態を適切に鑑別して治療を選択する必要がある．また日本における結核患者のうちHIV感染症患者が占める割合は0.2～3.2%程度との報告があるが[17][18]，HIV感染症患者では結核を契機にHIV感染症が診断されることも多く[19]，結核患者を診察した際には，HIV感染症の存在を念頭に置くことも重要である．

著者のCOI (conflicts of interest) 開示：白阪　琢磨：研究費・助成金など（シミック株式会社，株式会社日本アルトマーク）．他は本論文発表内容に関して特に申告なし．

引用文献

1) Haddow LJ, et al. Defining immune reconstitution syndrome: Evaluation of expert opinion versus 2 case definitions in South African cohort. Clin Infect Dis 2009; 49: 1424-32.
2) Daley CL, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. N Engl J Med 1992; 326: 231-5.
3) World Health Organization. Fact sheet October 2012. http://www.who.int/mediacentre/factsheets/fs104/en/
4) Ledergerber E, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy. JAMA 1999; 282: 2220-6.
5) Girardi E, et al. Changing clinical presentation and survival in HIV-associated tuberculosis after highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 26: 326-31.
6) Ministry of Health, Labour and Welfare. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou03/11.html
7) World Health Organization. Global tuberculosis report 2012. http://www.who.int/tb/publications/global_report/en/
8) 井上武夫，他．肺外結核患者の疫学的意義．結核 2011; 86: 493-8.
9) Ducomble T, et al. The burden of extrapulmonary and meningitis tuberculosis: an investigation of national surveillance data Germany, 2002 to 2009. Euro Surveill 2013; 18: 20436.
10) Forssbohm M, et al. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. Eur Respir J 2007; 31: 99-105.
11) Naing C et al. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung 2013; 191: 27-34.
12) Diel R, et al. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. Chest 2010; 137: 952-68.
13) Mazurek GH, et al. Update guidelines for using Interferon Gamma Release Assay to detect Mycobacterium tuberculosis infection—United States 2010. MMWR Recomm Rep 2010; 59: 1-25.
14) Fujita A, et al. Performance of a Whole-Blood Interferon-Gamma Release Assay with Mycobacterium RD-1 Specific Antigens among HIV-Infected Persons. Clin Dev Immunol 2011; 325295.
15) Aabye MG, et al. The impact of HIV infection and CD4 cell count on the performance of an interferon gamma release assay in patients with pulmonary tuberculosis. PLoS One 2009; 4: e4220.
16) Leidl L, et al. Relationship of immunodiagnostic assays for tuberculosis and numbers of circulating CD4+ T-cells in HIV infection. Eur Resipr J 2010; 35: 619-26.
17) Uchimura K, et al. Characteristics and treatment outcomes of tuberculosis cases by risk groups, Japan, 2007-2010. Western Pac Surveill Response J 2013; 4: 11-8.
18) 永井英明，他．結核患者における抗HIV抗体陽性率の検討．結核 2001; 76: 679-84.
19) 森　亨，他．日本におけるHIV感染結核の実態．結核 1997; 72: 649-57.

Abstract

Clinical status analysis of tuberculosis in patients infected with human immunodeficiency virus

Daisuke Kasai, Kazuyuki Hirota, Motoko Ikuma, Yoshihiko Ogawa, Keishiro Yajima, Dai Watanabe, Yasuharu Nishida, Tomoko Uehira and Takuma Shirasaka

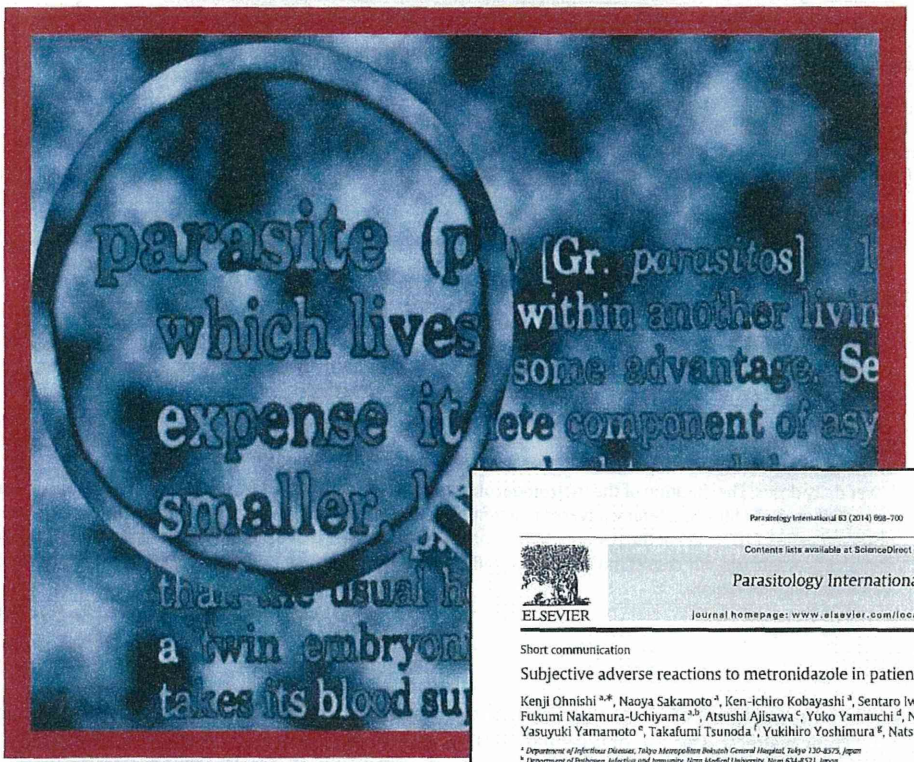
Department of Infectious Disease, National Hospital Organization Osaka National Hospital

Tuberculosis is a serious complication in patients infected with human immunodeficiency virus (HIV). To clarify the clinical features, a retrospective observational study was conducted from 1997 to 2013 at the Osaka National Hospital, using a cohort of HIV-infected patients diagnosed with tuberculosis. Forty-one patients were evaluated in this study; 40 patients were men, and one was a woman. The mean age was 44.6 years, and 34 patients were not taking antiretroviral therapy at the time of tuberculosis onset. Pulmonary tuberculosis was diagnosed in 18 patients, and 23 were diagnosed with extrapulmonary tuberculosis or extrapulmonary tuberculosis complicated with pulmonary tuberculosis. An interferon-gamma release assay was performed by using samples from 19 patients that revealed the following: 18 patients had positive test results, and 1 had an indeterminate result. Two patients experienced permanent damage. Our analysis revealed that the clinical features of tuberculosis in HIV-infected patients are sometimes different from those of tuberculosis in non-HIV-infected patients. Proper diagnosis and treatment are important for HIV-infected patients diagnosed with tuberculosis.

Volume 63, issue 5 October 2014 ISSN 1383-5769

ELSEVIER

PARASITOLOGY INTERNATIONAL



Parasitology International 63 (2014) 698–700

Contents lists available at ScienceDirect

Parasitology International

journal homepage: www.elsevier.com/locate/parint

Short communication

Subjective adverse reactions to metronidazole in patients with amebiasis

Kenji Ohnishi [a,*], Naoya Sakamoto [a], Ken-ichiro Kobayashi [a], Sentaro Iwabuchi [a], Fukumi Nakamura-Uchiyama [a,b], Atsushi Ajisawa [c], Yuko Yamauchi [d], Nozomi Takeshita [d], Yasuyuki Yamamoto [e], Takafumi Tsunoda [f], Yukihiro Yoshimura [g], Natsuo Tachikawa [g], Tomoko Uehira [h]

[a] Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, Tokyo 130-8575, Japan
[b] Department of Pathogen, Infection and Immunity, Nara Medical University, Nara 634-8521, Japan
[c] Department of Infectious Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo 113-8677, Japan
[d] Department of Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo 162-8655, Japan
[e] Department of Laboratory Medicine and Molecular Genetics of Coagulation Disorders, Tokyo Medical University Hospital, Tokyo 162-0023, Tokyo, Japan
[f] Department of Infectious Diseases, Tokyo Health Medical Treatments Corporation Ebara Hospital, Tokyo 145-0065, Japan
[g] Department of Infectious Diseases, Yokohama Municipal Citizen's Hospital, Yokohama 240-8555, Japan
[h] Department of Infectious Diseases, National Hospital Organization Osaka National Hospital, Osaka 540-0006, Japan

ARTICLE INFO

Article history:
Received 2 August 2013
Received in revised form 22 May 2014
Accepted 26 May 2014
Available online 12 June 2014

Keywords:
Amebiasis
Metronidazole
Adverse reaction
Nausea

ABSTRACT

Subjective adverse reactions to metronidazole were analyzed in 111 patients with amebiasis. Metronidazole was administered to 36 patients at a daily dose of 2250 mg and 75 patients at daily doses lower than 2250 mg. The reactions reported included nausea without vomiting in 11 (9.9%) patients, nausea with vomiting in 2 (1.8%), dysgeusia in 2 (1.8%), diarrhea in 1 (0.9%), headache in 1 (0.9%), numbness in 1 (0.9%), dizziness in 1 (0.9%), urticaria in 1 (0.9%), exanthema in 1 (0.9%), and discomfort in 1 (0.9%). Nausea was reported by 28% (10/36) of the patients receiving metronidazole at a daily dose of 2250 mg and 4% (3/75) of the patients receiving lower daily doses. The duration of the metronidazole administration in days was not associated with the appearance of nausea. No life-threatening adverse reactions were identified, and good clinical therapeutic effects were observed in 96% (107/111) of the patients. While metronidazole appears to be a safe anti-protozoal agent for patients with amebiasis, our results indicate that a daily metronidazole dose of 2250 mg is excessive for amebiasis, as it often induces nausea.

Metronidazole is used widely around the world for the treatment of amebiasis due to *Entamoeba histolytica*, with good clinical effects. This antiprotozoal agent is now covered for some conditions under Japan's national health insurance system, but there have been no earlier investigations of adverse reactions to metronidazole in patients with amebiasis in Japan. We investigated subjective adverse reactions and the clinical therapeutic effect of metronidazole against amebiasis due to *E. histolytica* in patients treated with metronidazole at several institutions throughout Japan between April 1, 2007 and June 30, 2011. To collect the data, we sent questionnaires to physicians in charge at the following institutions: Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital (Tokyo); Department of Infectious Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo); Department of Disease Control and Prevention Center, National Center for Global Health and Medicine (Tokyo); Department of Laboratory Medicine and Molecular Genetics of Coagulation Disorders, Tokyo Medical University Hospital (Tokyo); Department of Infectious Diseases, Tokyo Health Medical Treatments Corporation Ebara Hospital (Tokyo); Department of Infectious Diseases, Yokohama Municipal Citizen's Hospital (Yokohama); and Department of Infectious Diseases, National Hospital Organization Osaka National Hospital (Osaka). We were unable to collect adequate laboratory data in this study, as no uniform method or interval was applied to the blood tests performed at the different institutions.

Amebic colitis was diagnosed when the trophozoites of *E. histolytica* were identified in stool or biopsied specimens of colon mucosa, or when elevated serum antibodies against *E. histolytica* were detected in patients with diarrhea. Amebic liver abscess was diagnosed when elevated serum antibodies against *E. histolytica* were detected or *E. histolytica* was found in the aspirated liver abscess fluid of patients with CT- or ultrasound-confirmed liver abscesses. All undesirable symptoms found from the start of the metronidazole administration to 1 week after the end of the metronidazole administration were regarded as adverse reactions to the metronidazole unless the physicians in charge expressly deemed them to be unrelated to the agent. The treatment was regarded to be of good clinical efficacy when symptoms and physical signs

* Corresponding author at: Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, 4-23-15 Kotobashashi, Sumida City, Tokyo 130-8575, Japan. Tel.: +81 3 3633 6151; fax: +81 3 3633 6173.
E-mail address: infection@bokutoh-hp.metro.tokyo.jp (K. Ohnishi).

http://dx.doi.org/10.1016/j.parint.2014.05.006
1383-5769/

ELSEVIER

Parasitology International 63 (2014) 698–700

Contents lists available at ScienceDirect

Parasitology International

journal homepage: www.elsevier.com/locate/parint

Short communication

Subjective adverse reactions to metronidazole in patients with amebiasis

Kenji Ohnishi [a,*], Naoya Sakamoto [a], Ken-ichiro Kobayashi [a], Sentaro Iwabuchi [a], Fukumi Nakamura-Uchiyama [a,b], Atsushi Ajisawa [c], Yuko Yamauchi [d], Nozomi Takeshita [d], Yasuyuki Yamamoto [e], Takafumi Tsunoda [f], Yukihiro Yoshimura [g], Natsuo Tachikawa [g], Tomoko Uehira [h]

[a] Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, Tokyo 130-8575, Japan
[b] Department of Pathogen, Infection and Immunity, Nara Medical University, Nara 634-8521, Japan
[c] Department of Infectious Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo 113-8677, Japan
[d] Department of Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo 162-8655, Japan
[e] Department of Laboratory Medicine and Molecular Genetics of Coagulation Disorders, Tokyo Medical University Hospital, Tokyo 162-0023, Tokyo, Japan
[f] Department of Infectious Diseases, Tokyo Health Medical Treatments Corporation Ebara Hospital, Tokyo 145-0065, Japan
[g] Department of Infectious Diseases, Yokohama Municipal Citizen's Hospital, Yokohama 240-8555, Japan
[h] Department of Infectious Diseases, National Hospital Organization Osaka National Hospital, Osaka 540-0006, Japan

ARTICLE INFO

Article history:
Received 2 August 2013
Received in revised form 22 May 2014
Accepted 26 May 2014
Available online 12 June 2014

Keywords:
Amebiasis
Metronidazole
Adverse reaction
Nausea

ABSTRACT

Subjective adverse reactions to metronidazole were analyzed in 111 patients with amebiasis. Metronidazole was administered to 36 patients at a daily dose of 2250 mg and 75 patients at daily doses lower than 2250 mg. The reactions reported included nausea without vomiting in 11 (9.9%) patients, nausea with vomiting in 2 (1.8%), dysgeusia in 2 (1.8%), diarrhea in 1 (0.9%), headache in 1 (0.9%), numbness in 1 (0.9%), dizziness in 1 (0.9%), urticaria in 1 (0.9%), exanthema in 1 (0.9%), and discomfort in 1 (0.9%). Nausea was reported by 28% (10/36) of the patients receiving metronidazole at a daily dose of 2250 mg and 4% (3/75) of the patients receiving lower daily doses. The duration of the metronidazole administration in days was not associated with the appearance of nausea. No life-threatening adverse reactions were identified, and good clinical therapeutic effects were observed in 96% (107/111) of the patients. While metronidazole appears to be a safe anti-protozoal agent for patients with amebiasis, our results indicate that a daily metronidazole dose of 2250 mg is excessive for amebiasis, as it often induces nausea.

Metronidazole is used widely around the world for the treatment of amebiasis due to *Entamoeba histolytica*, with good clinical effects. This antiprotozoal agent is now covered for some conditions under Japan's national health insurance system, but there have been no earlier investigations of adverse reactions to metronidazole in patients with amebiasis in Japan. We investigated subjective adverse reactions and the clinical therapeutic effect of metronidazole against amebiasis due to *E. histolytica* in patients treated with metronidazole at several institutions throughout Japan between April 1, 2007 and June 30, 2011. To collect the data, we sent questionnaires to physicians in charge at the following institutions: Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital (Tokyo); Department of Infectious Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo); Department of Disease Control and Prevention Center, National Center for Global Health and Medicine (Tokyo); Department of Laboratory Medicine and Molecular Genetics of Coagulation Disorders, Tokyo Medical University Hospital (Tokyo); Department of Infectious Diseases, Tokyo Health Medical Treatments Corporation Ebara Hospital (Tokyo); Department of Infectious Diseases, Yokohama Municipal Citizen's Hospital (Yokohama); and Department of Infectious Diseases, National Hospital Organization Osaka National Hospital (Osaka). We were unable to collect adequate laboratory data in this study, as no uniform method or interval was applied to the blood tests performed at the different institutions.

Amebic colitis was diagnosed when the trophozoites of *E. histolytica* were identified in stool or biopsied specimens of colon mucosa, or when elevated serum antibodies against *E. histolytica* were detected in patients with diarrhea. Amebic liver abscess was diagnosed when elevated serum antibodies against *E. histolytica* were detected or *E. histolytica* was found in the aspirated liver abscess fluid of patients with CT- or ultrasound-confirmed liver abscesses. All undesirable symptoms found from the start of the metronidazole administration to 1 week after the end of the metronidazole administration were regarded as adverse reactions to the metronidazole unless the physicians in charge expressly deemed them to be unrelated to the agent. The treatment was regarded to be of good clinical efficacy when symptoms and physical signs

* Corresponding author at: Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, 4-23-15 Kohtohbashi, Sumida City, Tokyo 130-8575, Japan. Tel.: +81 3 3633 6151; fax: +81 3 3633 6173.
E-mail address: infection@bokutoh-hp.metro.tokyo.jp (K. Ohnishi).

http://dx.doi.org/10.1016/j.parint.2014.05.006
1383-5769/

deemed by the physicians to be causally linked to amebiasis disappeared in the course of metronidazole administration.

In total, 113 Japanese patients with amebiasis were treated with metronidazole, and adverse reactions were analyzed in 111 patients. One patient was excluded for failing to visit the hospital for treatment and another was excluded for choosing to halt the metronidazole treatment. The 111 patients analyzed were 104 males and 7 females, ranging in age and body weight from 24 to 78 years old ($n = 111$, mean ± S.D. = 45.0 ± 12.8 years old) and 43 to 88 kg ($n = 73$, mean ± S.D. = 62.1 ± 9.7 kg), respectively. The types of amebiasis were as follows: colitis 67 (male = 62, female = 5), liver abscess 28 (male = 26, female = 2), and colitis with liver abscess 16 (male = 16, female = 0). HIV co-infection was present in 66 patients, absent in 41, and of unknown status in 4. The 111 patients accounted for 137 cases of metronidazole administration. Seventeen patients received from 2 to 5 courses of the metronidazole. The case receiving the highest daily dose of metronidazole was enrolled among the 17 patients receiving several courses, and the case receiving metronidazole for the longest duration (in days) was enrolled among the cases with the same daily administration doses. The daily doses of metronidazole were left unchanged throughout the treatment course in 99 patients and changed in the other 12 patients. Table 1 shows the daily doses and duration of metronidazole treatment. Twenty-eight percent (19/67) of the colitis patients received daily metronidazole at a dose of 2250 mg and 72% (48/67) received doses lower than 2250 mg. Twenty-nine percent (8/28) of the liver abscess patients received daily metronidazole at a dose of 2250 mg and 71% (20/28) received lower doses. Fifty-six percent (9/16) of the patients with colitis with liver abscess received daily metronidazole at a dose of 2250 mg and 44% (7/16) received lower doses.

Nausea without vomiting was reported in 11 (9.9%) patients, nausea with vomiting in 2 (1.8%), dysgeusia in 2 (1.8%), diarrhea in 1 (0.9%), headache in 1 (0.9%), numbness in 1 (0.9%), dizziness in 1 (0.9%), urticaria in 1 (0.9%), exanthema in 1 (0.9%), and discomfort in 1 (0.9%). Nausea was reported by 28% (10/36) of the patients receiving metronidazole at the daily dose of 2250 mg versus only 4% (3/75) of the patients receiving lower daily doses. Significant difference was found in the incidence of nausea between patients treated with the daily dose of 2250 mg and those treated with lower daily doses (Chi-square test, $p < 0.001$). Among the patients treated with the daily dose of 2250 mg, body weight of those who complained of nausea was 45–75 kg ($n = 8$, m ± S.D. = 61.8 ± 11.0), and those with no complaints of nausea was 43–78 kg ($n = 25$, m ± S.D. = 62.8 ± 9.3), and no significant difference was found in the body weight between the 2 groups (Student's t-test, $p = 0.792$). Four patients treated with 2250 mg of metronidazole daily complained of nausea at the 2nd day of the treatment, 2 patients complained of nausea at the 3rd day of the treatment, 1 patient complained of nausea at the 5th day, 2 patients complained of nausea at the 6th day, and 1 patient complained of nausea without clear memory of onset. No significant correlation was observed in between the duration of treatment and the incidence of nausea (linear regression analysis, $R^2 = 0.284$, $p = 0.355$). Nausea was reported in 9.0% of the patients with colitis (6/67), 14.3% of the patients with liver abscess (4/28), and 18.7% of the patients with colitis with liver abscess (3/16), but the differences in the incidence of nausea among these 3 groups were not significant (Chi-square test, $p = 0.487$). Few patients complained of other subjective adverse reactions, and all of those who did were treated with daily doses of 1500 mg or more. No serious subjective adverse reactions were observed in our study. Table 2 shows the daily doses of

Table 1
Dose and duration of metronidazole.

(A) Daily doses and duration of metronidazole administration in 99 patients with amebiasis (daily doses unchanged during the treatment course).

Duration (in days)	Daily doses (mg/day)						
	<750	750	1000	1500	2000	2250	2250<
~<5	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
6	0	0	0	0	0	1	0
7	0	8	1	3	0	3	0
8	0	0	0	1	0	0	0
9	0	0	0	1	0	1	0
10	0	1	14	25	2	18	0
11	0	0	0	1	0	1	0
12	0	0	0	1	0	1	0
13	0	0	1	1	0	0	0
14	0	0	0	4	2	3	0
15	0	0	0	0	0	2	0
15<~	0	0	0	2	0	1	0
Total	0	9	16	39	4	31	0

(B) Initial and altered doses of metronidazole in 12 patients with amebiasis (daily doses changed during the treatment course)

Initial doses (days) → following doses (days)	No. of patients
500 mg (2 days) → 1500 mg (10 days)	1
750 mg (1 day) → 1500 mg (5 days)	1
750 mg (5 days) → 1500 mg (18 days)	1
1000 mg (1 day) → 1500 mg (9 days)	1
1000 mg (3 days) → 1500 mg (9 days)	1
1000 mg (13 days) → 1500 mg (12 days)	1
1500 mg (3 days) → 1000 mg(5 days)	1[a]
1500 mg(6 days) → 2250 mg(5 days) → 1500 mg(2 days)	1
2250 mg (2 days) → 1500 mg (5 days)	1[a,b]
2250 mg (2 days) → 1500 mg (13 days)	1[a]
2250 mg (4 days) → 1000 mg (11 days)	1[a]
2250 mg (5 days) → 1500 mg (5 days)	1

[a] Daily doses were decreased in the course of administration because of nausea.
[b] Metronidazole administration was interrupted because of nausea.

Table 2
Number of amebiasis patients with symptomatic adverse reactions to metronidazole and the daily doses they received.

	Dose of metronidazole (mg/day)				
	<1000	1000	1500	2000	2250
Nausea without vomiting		1	1		9
Nausea and vomiting			1		1
Dysgeusia			1	1	
Diarrhea			1		
Headache					1
Numbness					1
Dizziness			1		
Urticaria			1		
Exanthem			1		
Discomfort			1		
Total	0	1	8	1	12

metronidazole and the number of patients with adverse subjective reactions. The metronidazole administration was stopped because of nausea in 1 patient and reduced in dosage because of nausea in 4 patients (from an initial daily dose of 2250 mg in 3 patients and an initial daily dose of 1500 mg in 1 patient). The metronidazole administration was continued without dosage reductions in the other patients suffering from symptomatic adverse reactions.

Of the patients who complained of nausea, 10 were co-infected with HIV and 3 were not. Differences in proportions were analyzed using the Chi-square test, and no significant difference in the incidence of nausea was found between the patients with and without HIV co-infection ($p = 0.228$). Many amebiasis patients in Japan are co-infected with HIV [1]. About 60% of the amebiasis patients analyzed in this investigation had the HIV co-infection, but no significant difference in the incidence of nausea was found between them and the patients negative for HIV. Our results show that co-infection with HIV does not increase the incidence of nausea as an adverse reaction to metronidazole.

The clinical effect was good in 96% (107/111) of the patients, poor in 2% (2/111), and unknown in 2% (2/111). The daily doses of metronidazole in the 2 patients with poor clinical results were 1000 mg and 1500 mg, respectively.

Nausea, vomiting, anorexia, diarrhea, abdominal discomfort, unpleasant metallic taste or aftertaste, disulfiram-like intolerance reactions to alcohol, paresthesia, incoordination, dizziness, vertigo, ataxia, confusion, irritability, and convulsion have all been reported as symptomatic adverse reactions to metronidazole [2–4]. The most common subjective adverse reaction in our study was nausea. Only a small number of the patients in our investigation reported adverse reactions other than nausea, and all of those who did receive metronidazole at daily doses of 1500 mg or more. Yet as far as we can ascertain, there have been few earlier reports on the incidence of nausea in relation to the daily doses of metronidazole in amebiasis patients. According to one report from India, nausea developed in 64% patients with amebic liver abscess receiving a daily metronidazole dose of 2400 mg for 10 days [5]. According to other reports from England, 30% and 41% of patients with non dysenteric intestinal amebiasis due to *E. histolytica* or *E. hartomanni* infection experienced nausea when receiving 10-day and 5-day courses of metronidazole at a dose of 2400 mg/day, respectively, and another 5.6% of experienced nausea when receiving a 10-day course of metronidazole at a dose of 1200 mg/day [6]. In another report from Colombia, nausea or vomiting developed in 10.2% of symptomatic intestinal amebiasis patients receiving a daily metronidazole dose of 1000 mg for 10 days [7]. Nausea predominantly appeared in patients treated with daily metronidazole doses of 2250 mg in our study, but the duration of the metronidazole treatment (in days) was not related to the incidence of nausea. We investigated adverse reactions to metronidazole in Japanese patients in our study, and our results and the results from the abovementioned studies clearly demonstrated that daily metronidazole doses as high as 2250 mg and 2400 mg are likely to induce nausea in patients with amebiasis, regardless of their nationality. Our results also indicate that good clinical results and a low incidence of nausea can be attained when patients are given daily doses lower than 2250 mg (e.g., 1000 mg or 1500 mg). An oral or intravenous dose of 750 mg metronidazole 3 times daily for 10 days has been widely used against amebiasis and is recommended in famous textbooks [8,9]. However, our results indicate that a daily metronidazole dose of 2250 mg is too much from the point of adverse reaction like nausea. We propose here that a daily metronidazole dose of 2250 mg is excessive for amebiasis treatment and a daily dose of 1000–1500 mg is recommended to avoid adverse reaction.

Some physicians may think that a daily metronidazole dose of 2250 mg should be continued in combination with stomach medicines or antiemetics when an amebiasis patient receiving the agent complains of nausea. We do not concur with this strategy, as good clinical therapeutic results are obtained by metronidazole administered at daily doses lower than 2250 mg. We think that patients should receive metronidazole at the minimal effective doses and that the co-administration of other drugs should be reduced to avoid adverse reactions.

References

[1] Ohnishi K, Kato Y, Imamura A, Fukayama M, Tsunoda T, Sakaue Y, et al. Present characteristics of symptomatic *Entamoeba histolytica* infection in the big cities of Japan. Epidemiol Infect 2003;132:57–60.
[2] Stanley Jr SL. Amoebiasis. Lancet 2003;361:1025–34.
[3] Molavi A, LeFrock JL, Prince RA. Metronidazole. Med Clin N Am 1982;66:121–33.
[4] Haque R, Huston CD, Hughes M, Houpt E, Petri Jr WA. Current concepts. Amebiasis. N Engl J Med 2003;348:1565–73.
[5] Muzaffar J, Madan K, Sharma MP, Kar P. Randomized, single-blind, placebo-controlled multicenter trial to compare the efficacy and safety of metronidazole and satranidazole in patients with amebic liver abscess. Dig Dis Sci 2006;511:2270–3.
[6] Kanani SR, Knight R. Experiences with the use of metronidazole in the treatment of non dysenteric intestinal amoebiasis. Trans R Soc Trop Med Hyg 1972;66:244–9.
[7] Botero DR. Double blind study with a new nitroimidazole derivative, RO 7-0307, versus metronidazole in symptomatic intestinal amebiasis. Am J Trop Med Hyg 1974;23:1000–1.
[8] Petri Jr WA, Haque R. *Entamoeba* species, including amebiasis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 3411–25.
[9] Stanley Jr SL. Amebiasis and infection with free-living amebas. In: Longo DL, Fauci A, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill Companies; 2012. p. 1683–8.

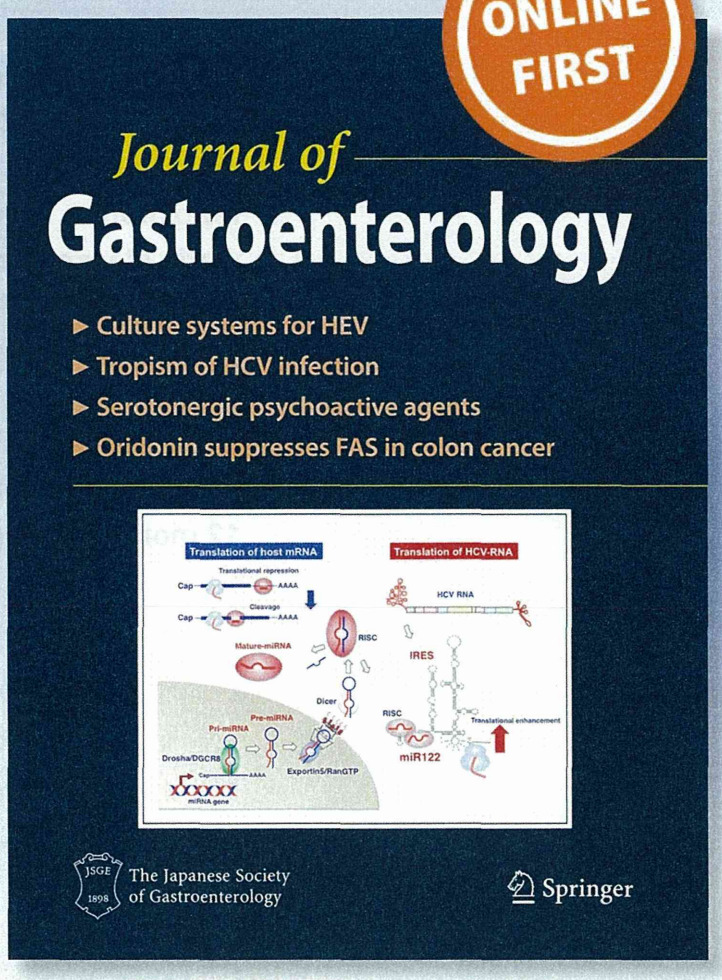
Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

Takuya Genda, Takafumi Ichida, Shotaro Sakisaka, Michio Sata, Eiji Tanaka, Ayano Inui, Hiroto Egawa, Kouji Umeshita, Hiroyuki Furuk et

Journal of Gastroenterology

ISSN 0944-1174

J Gastroenterol
DOI 10.1007/s00535-013-0782-5



Springer

J Gastroenterol
DOI 10.1007/s00535-013-0782-5

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

Takuya Genda · Takafumi Ichida · Shotaro Sakisaka · Michio Sata · Eiji Tanaka · Ayano Inui · Hiroto Egawa · Kouji Umeshita · Hiroyuki Furukawa · Seiji Kawasaki · Yukihiro Inomata

Received: 10 December 2012 / Accepted: 18 February 2013

Abstract
Background The present study aimed to evaluate etiology-based differences in the risk of waiting list mortality, and to compare the current Japanese transplant allocation system with the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems with regard to the risk of waiting list mortality in patients with primary biliary cirrhosis (PBC).
Methods Using data derived from all adult candidates for deceased donor liver transplantation in Japan from 1997 to 2011, we assessed factors associated with waiting list mortality by the Cox proportional hazards model. The waiting list mortality risk of PBC patients was further estimated with adjustment for each scoring system.
Results Of the 1056 patients meeting the inclusion criteria, 743 were not on the list at the end of study period; waiting list mortality was 58.1 % in this group. In multivariate analysis, increasing age and PBC were significantly associated with an increased risk of waiting list mortality. In comparison with patients with hepatitis C virus (HCV) infection, PBC patients were at 79 % increased risk and had a shorter median survival time by approximately 8 months. The relative hazard of PBC patients was statistically significant with adjustment for CTP score and medical point score, which was the priority for ranking candidates in the Japanese allocation system. However, it lost significance with adjustment for MELD score. Stratification by MELD score indicated a comparable waiting list survival time between patients with PBC and HCV.

The Assessment Committee of Indication for Transplantation: T. Ichida, S. Sakisaka, M. Sata, E. Tanaka, A. Inui, H. Egawa, K. Umeshita, H. Furukawa, S. Kawasaki, Y. Inomata.

T. Genda (✉) · T. Ichida
Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, 1129 Nagaoka Izunokuni-shi, Shizuoka 410-2295, Japan
e-mail: genda@rice.ocn.ne.jp

S. Sakisaka
Department of Gastroenterology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

M. Sata
Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

E. Tanaka
Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan

A. Inui
Division of Hepatology and Gastroenterology, Department of Pediatrics, Eastern Yokohama Hospital, Yokohama, Japan

H. Egawa
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

K. Umeshita
Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan

H. Furukawa
Department of Gastroentrologic and General Surgery, Asahikawa Medical University, Asahikawa, Japan

S. Kawasaki
Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, Tokyo, Japan

Y. Inomata
Department of Transplantation and Pediatric Surgery, Postgraduate School of Medical Science, Kumamoto University, Kumamoto, Japan

Published online: 12 March 2013

Conclusions PBC patients are at high risk of waiting list mortality in the current allocation system. MELD-based allocation could reduce this risk.

Keywords: Child–Turcotte–Pugh · Liver transplantation · Model for End-Stage Liver Disease

Introduction

Liver transplantation is the only curative treatment option with excellent long-term results in patients with end-stage liver diseases. At present, the number of patients waiting to undergo liver transplantation is increasing in Japan, as well as in both Europe and the United States. However, many patients are dying on the waiting list because of the donor organ shortage. For example, recent waiting list mortality was reported as being 22.8 % in the United States [1]. Management of liver transplant waiting lists is aimed at minimizing waiting list deaths by prioritization of those with a higher mortality risk, and by ensuring allocation of available organs to these patients. Therefore, prioritization and allocation decisions require the accurate prediction of the survival probability of patients.

The indications for liver transplantation include a wide variety of liver diseases, including viral hepatitis, autoimmune hepatitis, cholestatic disease, metabolic disorders, and hepatic neoplasms. Because each type of liver disease has disease-specific therapeutic options and associated risk of complications, liver disease etiology can influence the patient's natural disease course and risk of death. Moreover, disease-specific clinical tools are widely used to determine prognosis in patients with primary biliary cirrhosis (PBC) [2, 3] and primary sclerosing cholangitis [4]. However, it is uncertain whether patients waiting for liver transplantation have a disease-specific risk for waiting list mortality, and whether the ability of the currently used allocation system to assess the urgency of transplantation could be generalized to every patient with heterogeneous etiology.

By consensus, a disease severity index used to allocate liver donor organs should be able to predict the probability of death in patients with end-stage liver diseases of heterogeneous etiology. In the United States, where a large number of patients are registered for liver transplantation, the Child–Turcotte–Pugh (CTP) score [5] was initially applied to assess the severity of liver disease in the United Network for Organ Sharing (UNOS) allocation algorithms, because of its simplicity and recognized ability to assess prognosis in patients with heterogeneous chronic liver disease. Subsequently, a number of studies have demonstrated the accuracy of the Model of End-Stage Liver Disease (MELD) score [6] in predicting short-term mortality risk in patients with end-stage liver disease [7–9]. Since February 2002, the MELD score has therefore been used as a UNOS criterion for allocating organs to patients waiting for liver transplantation [10].

On the other hand, in the countries with a small number of registrations for liver transplantation, a system of prioritization based on a detailed clinical review, which includes CTP score, MELD score, and other disease-specific prognostic scores, as well as patients' demographics, laboratory data, and disease histories, by a small number of expert clinicians is likely to be used to judge disease severity and potential mortality accurately. This clinical judgment-based prioritization of patients awaiting liver transplantation was initiated in October 1997 in Japan and, at present, little information is available concerning the prognostic ability of this allocation system.

The aims of the present retrospective study were: (1) to clarify the disease-specific risk for waiting list mortality in patients waiting for liver transplantation; and (2) to compare the current system of waiting list prioritization and organ allocation in Japan with the MELD and CTP scoring systems with regard to the risk in PBC patients, who have the highest risk of waiting list mortality.

Patients and methods

Patients and liver allocation policy in Japan

This was a nationwide retrospective cohort study. We used the Japan Organ Transplant Network (JOT)/the Assessment Committee of Indication for Transplantation database to identify all patients listed for deceased donor liver transplantation in Japan between October 15, 1997 and August 31, 2011. We excluded patients who were less than 18 years of age because they had a spectrum of primary diagnoses substantially different from those of patients older than 18 years. We also excluded patients listed for retransplantation to ensure that all observations represented unique individuals. Finally, we excluded patients who were diagnosed with acute liver failure because these patients rarely have chronic liver disease and are assigned the highest priority.

For JOT registration, the demographic, clinical, and laboratory data including CTP score, MELD score, or disease-specific prognostic score of all candidates are reviewed, and each candidate is assigned a clinical priority by the Assessment Committee of Indication for Transplantation (four physicians, five surgeons, and one pediatrician). The priority of candidates is represented by a medical point system, in which points are awarded according to estimated survival: 9 points for estimated survival <30 days, 6 points for <180 days, 3 points for

<360 days, and 1 point for ≥360 days. In patients with hepatocellular carcinoma, the points were determined only by the degree of hepatic decompensation. Additional points are awarded according to ABO blood group compatibility: 1.5 points for an identical blood group and 1 point for a compatible blood group. Patients with higher total points have a higher priority for donor liver allocation. For patients with identical points, waiting time is a liver allocation measure.

Age of the patient, blood type, etiology of liver disease, and medical point at listing were available for all the patients. Detailed demographic, clinical, laboratory data, including CTP score and MELD score at the time of listing, were available only in patients registered since June 22, 2006. The CTP score uses two clinical variables (ascites and encephalopathy), and three laboratory parameters (serum bilirubin and albumin levels and prothrombin time). Each variable is assigned a score from 1 to 3, with the aggregate score representing the CTP score [5]. Although the original CTP score used different criteria for total bilirubin level between patients with cholestatic disease and those with other etiologies, the criteria for the CTP score in the current Japanese allocation system did not change according to the etiology of liver disease. The MELD score was calculated using the most recent version of the formula documented on the UNOS website [11]: $9.57 \times \log_e$(creatinine mg/dL) $+ 3.78 \times \log_e$(bilirubin mg/dL) $+ 11.2 \times \log_e$(international normalized ratio [INR]) + 6.43, rounded to the nearest integer. Liver disease etiology was not incorporated in this version of the formula. Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL. The serum creatinine was set to 4.0 mg/dL if the patients had received dialysis at least twice within the week prior to the serum creatinine test. The MELD score was not capped at a score of 40. In PBC patients, the spontaneous survival predicted by the updated Mayo model was calculated as described previously [3].

Outcome

The patients' follow-up ended on 30 September 2011. The primary endpoint "waiting list mortality" or "waiting list death" was a combination of death and removal from the waiting list because the patient became too sick for transplantation or was otherwise medically unsuitable. We considered patients who were removed from the transplant list on account of clinical deterioration to be equivalent to patients who died, because these chronic liver diseases are almost uniformly fatal in the short term without transplantation. All other outcomes were censored, with the most common censoring events being transplantation or list removal due to an improvement in the patient's condition resulting in the patient no longer requiring transplantation.

Statistical analysis

Cox proportional hazards ratios (HRs) with 95 % confidence intervals (CI) for waiting list mortality were estimated with univariate models using age, gender, blood type, etiology of liver disease, as well as multivariate models using age and etiology of liver disease. To compare patients' characteristics between chronic hepatitis C virus (HCV) infection and PBC, we used the Mann–Whitney *U* test for numerical variables or the chi-square test for categorical variables. The HRs with 95 % CI for waiting list mortality of PBC patients were adjusted for each disease severity index, such as medical point, CTP score, and MELD score by bivariate Cox proportional hazards models. The rates of survival were estimated by the Kaplan–Meier method, and compared by log-rank test. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA). A P value below 0.05 was considered to be statistically significant.

Results

Patient characteristics and outcome

A total of 1,407 patients were listed for deceased donor liver transplantation through the JOT registry during the study period. Of these patients, 1,295 (92.0 %) were aged ≥18 years. The etiology of liver disease in these subjects is shown in Table 1. The most prevalent diagnoses in patients ≥18 years were HCV infection (254 of 1,295, 19.6 %), hepatitis B virus infection (157 of 1,295, 12.1 %), and PBC (156 of 1,295, 12.0 %), and these accounted for 43.7 % of all patients ≥18 years. Of 1,295 patients, 239 were excluded from the study: 142 for acute liver failure and 97 for repeat liver transplant. Thus, a total of 1,056 patients formed the study cohort. In the study cohort, 64 % of patients were men and the median age of all patients was 51 years (range, 18–69 years). At listing, 78 patients were registered at medical point 1, 297 at point 3, 682 at point 6, and 29 at point 9. A flow diagram of the patient outcomes is shown in Fig. 1. At the end of study period, 313 patients were still listed and 743 had been removed from the list, with 267 removed for liver transplantation, 378 for death, and 98 for other reasons, including 54 who were too sick, 11 for improvement in their condition, and 33 for an unknown reason. Of the 267 patients who received liver transplantation, only 81 cases were able to receive deceased donation in Japan, and this accounted for 10.9 % of all patients removed from the list. Waiting list mortality, a combination of death and becoming too sick for transplantation, accounted for 58.1 % of all the patients removed from the list.

Factors associated with waiting list mortality

In univariate analysis, age, biliary atresia, PBC, hepatocellular carcinoma, metabolic diseases, polycystic diseases, and vascular diseases showed statistically significant association with waiting-list mortality. In multivariate analysis, age (HR 1.04; 95 % CI 1.03–1.05, $P < 0.001$), PBC (HR 1.79; 95 % CI 1.34–2.39, $P < 0.001$), and polycystic diseases (HR 0.27; 95 % CI 0.10–0.73, $P = 0.01$) were independently associated with waiting list mortality (Table 2). Hence, PBC patients had a 79 % higher risk of waiting list mortality compared with HCV patients with adjustment for age.

Table 1 Etiology of liver disease

	Total ($n = 1,407$)	≥18 years ($n = 1,295$)	<18 years ($n = 112$)
Cholestatic diseases	381	325	56
BA	93	48	46
PBC	156	156	0
PSC	105	99	6
Caroli disease	8	7	1
Others	18	15	3
Hepatocellular diseases	567	565	2
HCV	254	254	0
HBV	157	157	0
HCV and HBV	8	8	0
Alcoholic	48	48	0
AIH	22	22	0
NASH	25	25	0
Cryptogenic cirrhosis	53	51	2
HCC	76	76	0
Acute liver failure	163	142	21
Graft failure	121	97	24
Vascular disease	12	12	0
Metabolic disease	62	53	9
Polycystic disease	24	24	0
Others	1	1	0

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Waiting list mortality of PBC patients

The Kaplan–Meier waiting list survival curves for all PBC and HCV patients are shown in Fig. 2. The 1- and 2-year survival probabilities in HCV patients were 63 and 49 %, respectively (median 631 days, 95 % CI 355–907 days), whereas those in PBC patients were 51 and 33 %, respectively (median 392 days, 95 % CI 283–500 days); the differences between them represented a statistically significant difference (log-rank test, $P < 0.001$). Detailed demographic and clinical characteristics were available in 189 of 254 HCV patients and 81 of 156 PBC patients who were registered after June 2006. A comparison of the characteristics of patients with PBC and HCV is shown in Table 3. In comparison with HCV patients, PBC patients were younger and predominantly female. Patients with PBC had significantly higher platelet counts and serum bilirubin values, and lower INR and serum creatinine values. Neither the CTP score nor the medical point at listing was different between the groups. Conversely, the MELD score at listing was significantly higher in patients with PBC than in those with HCV. In addition, the median of the updated Mayo risk score was 9.4 in the PBC patients, and this predicted 1- and 2-year spontaneous survival rates of 74 and 54 %, respectively.

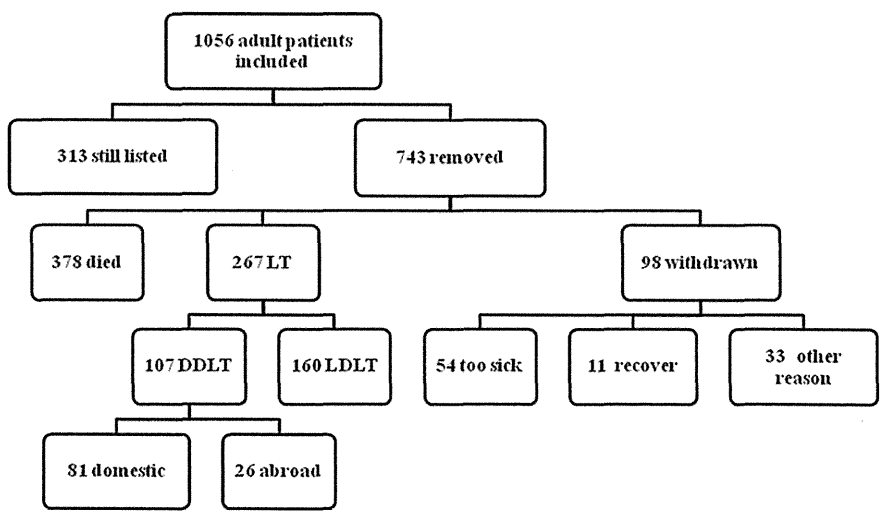


Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation