Low-dose Total Body Irradiation in the Treatment of Advanced Non-Hodgkin's Lymphoma : A Case Report of an Elderly Patient

Ryoji TOKIYA, Yoshinari IMAJO, Junichi HIRATSUKA, Eisaku YODEN*, Shinya YAMAMOTO, Makito KOBATAKE**, Shigeki IMAI**, Yasumasa KAJIHARA**, Hideho WADA*** and Takashi SUGIHARA*****

Department of Radiation Oncology, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan
**Department of Radiology, The Hyogo Medical Center for Adults, 13-70 Kitaouji-cho, Akashi 698-8558, Japan*
***Department of Diagnostic Radiology, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan*
****Division of Hematology, Department of Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan*

Accepted for publication on March 10, 2005

ABSTRACT. A 73-year-old man underwent six courses of chemotherapy with THP-COP and external beam radiotherapy for primary non-Hodgkin's lymphoma (NHL) in the neck. The treatment turned out well and the patient experienced a complete response. Two months later, magnetic resonance imaging revealed involvement in the mediastinal, axillary, para-aortic, and inguinal lymph nodes. The patient remained clinically free of the disease for another two months with oral etoposides and prednisolone, but then relapse occurred, which was treated by low-dose total body irradiation (LTBI). LTBI improved the health of the patient and resulted in the second complete remission. The patient subsequently underwent four courses of chemotherapy with CEOP and maintained his health without major toxicity for further three months. Finally, however, relapse occurred throughout the entire body, and the patient died of NHL 28 months after the initial presentation. This report supports the notion that the LTBI is effective in salvage treatment for NHL patients in high risk groups.

Key words : low-dose total body irradiation — advanced non-Hodgkin's lymphoma — salvage treatments — in the elderly

Low-dose total body irradiation (LTBI) has been used in the treatment of lymphomatous malignancies since the beginning of the twentieth century. More recently, several studies have shown that LTBI may be classified among first-line treatments for advanced stage non-Hodgkin's lymphoma (NHL). Several reports have also indicated its effectiveness in salvage treatment for patients in high risk groups (the elderly, with intercurrent disease, or recurrence, or resistance to treatment). This report describes the

釋舎竜司, 今城吉成, 平塚純一, 余田栄作, 山本真也, 小畠牧人, 今井茂樹, 梶原康正, 和田秀穂, 杉原 尚
e-mail : radoncol@med.kawasaki-m.ac.jp

results of successful LTBI treatment through the case report of an elderly man with an advanced stage intermediate-grade NHL relapsed after systemic chemotherapy and local radiotherapy.

CASE REPORT

A 73-year-old man presented with swelling of the neck lymph nodes (LNs) in March 1999, and swelling of the bilateral inguinal LNs in June 1999. The patient had a history of Hashimoto's disease, and was taking levothyroxine sodium. Systemic workups including whole body magnetic resonance imaging (MRI) and ^{67}Ga scintigraphy revealed malignant lymphoma (Fig 1), with an initial pathological diagnosis of diffuse large B-cell lymphoma (CS III A, PS III N+M−) and elevated levels of serum lactate dehydrogenase (LDH : 624 IU/L ; normal range : 295 to 481 IU/L) and soluble interleukin-2 receptor (sIL-2R : 5,840 U/L ; normal range : 220 to 530 U/L) (Fig 2). The subject's International Prognostic Index[1] placed him in the high-intermediate risk group in the initial diagnosis. About once a month, he received a total of six courses of systemic chemotherapy (THP-COP) consisting of pirarubicin HCL (60 mg/body), cyclophosphamide (900 mg/body), vincristine sulfate (1.5 mg/body) intravenously for one day, and prednisolone (60 mg/body) orally for five days. The THP-COP regimen continued from June through November 1999. This treatment was combined with external beam radiotherapy (EBRT) of 30.6 Gy in 17 fractions over 23 days to the neck and bilateral fossa supraclavicularis. The EBRT initially included the neck and bilateral fossa supraclavicularis LNs with a superior border between the second and third cervical vertebrae. These treatments turned out well and complete disappearance of swelling in the locoregional LNs was observed in December 1999 (Fig 3). However, two months later,

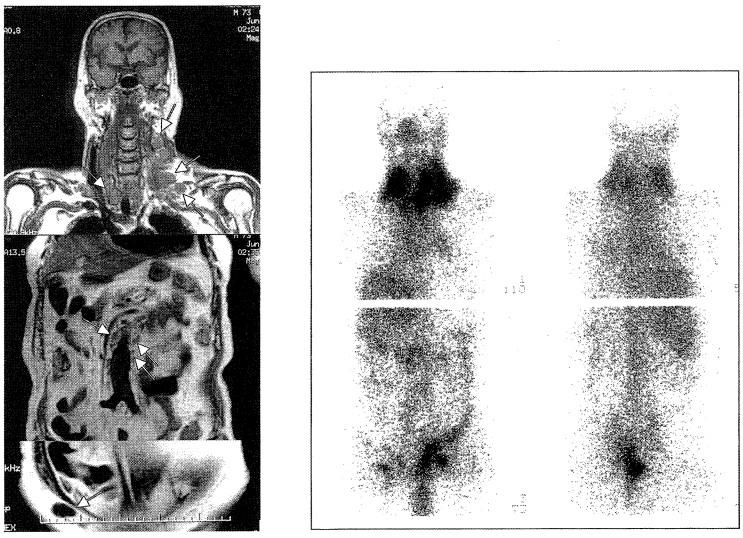

Fig 1. Whole body magnetic resonance imaging (left) and ^{67}Ga scintigraphy (right) on June 1999. Swelling of the locoregional lymph nodes (arrows) and increased tracer accumulation are shown.

follow-up whole body MRI and computed tomography revealed multiple involvements in the mediastinal LN, abdominal para-aortic LNs, bilateral axillary LNs and bilateral inguinal LNs with elevated levels of serum LDH (948 IU/L) and sIL-2R (8,560 U/L) (Fig 2), although no recurrent lesion was found in the neck. We considered administering an even more intensive course of chemotherapy, but did not undergo such an intensive course of

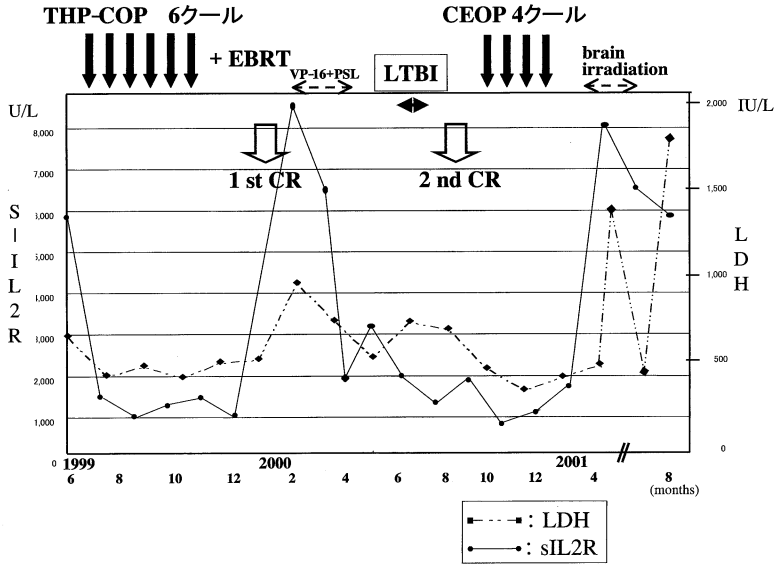

Fig 2. Trends in the serum levels of tumor markers (LDH, sIL2R) with changes in the clinical course.

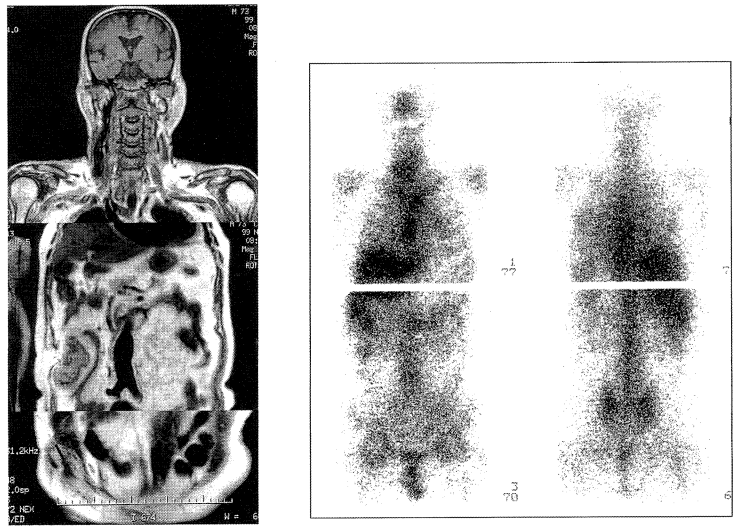

Fig 3. Follow-up whole body magnetic resonance imaging (left) and ^{67}Ga scintigraphy (right) on November 1999. The lymph node swelling and increased tracer accumulation have completely disappeared after THP-COP chemotherapy and external beam radiotherapy.

chemotherapy because we felt that he had insufficient physical strength to withstand it. We judged that the hematopoietic functions in his bone marrow had not yet returned to normal. Therefore, the patient was treated with oral etoposides (50 mg/day for two weeks, repeated once five weeks later) and prednisolone (5 mg/day for two weeks, repeated once five weeks later) from February through April 2000. Thereafter, the patient was clinically free of the disease for approximately two months, with improvement of his serum LDH level (from 948 to 480 IU/L) and the sIL-2R level (from 8,560 to 1,990 U/L) in April 2000 (Fig 2). However, in May 2000, the patient had relapsed (slight fever, weight loss, renewed increase in LDH, more swelling of mediastinal LNs, abdominal para-aortic LNs, bilateral axillary LNs and bilateral inguinal LNs) (Fig 4).

Given this worsening situation, we consulted with a hematologist on the next approach to treatment. Choices of treatment to improve his condition were proposed, and deliberated on. There had been several side effects relating to the chemotherapy previously, so we chose LTBI which is minimally invasive. The patient was given therapeutic LTBI of 0.1 Gy in 15 fractions over 22 days from June through July 2000. This treatment resulted in a second complete response (CR) observed on the following whole body MRI and ^{67}Ga scintigraphy (Fig 5), with normalization of his serum LDH level from 697 to 322 IU/L (Fig 2). LTBI thus successfully maintained the subject's health and provided complete remission for three months without major toxicity. Based on the above results, we considered performing salvage chemotherapy with a hematologist. The patient received four courses of a second round of systemic chemotherapy (CEOP) consisting of epirubicin HCL (60 mg/body), cyclophosphamide (500 mg/body), and vindesine sulfate (3 mg/body) intravenously for one day, and prednisolone

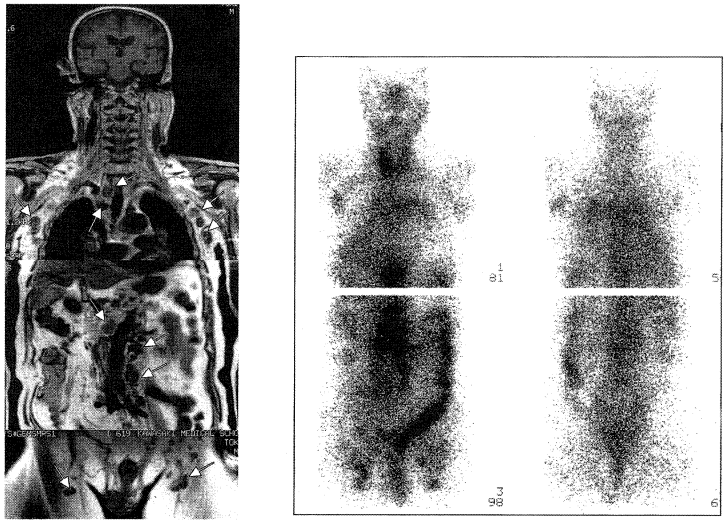

Fig 4. Follow-up whole body magnetic resonance imaging (left) and ^{67}Ga scintigraph (right) on February 2000. Multiple lymph node involvements (arrows) were found in the mediastinum, bilateral axillae, abdominal para-aortic region, and bilateral inguinal region.

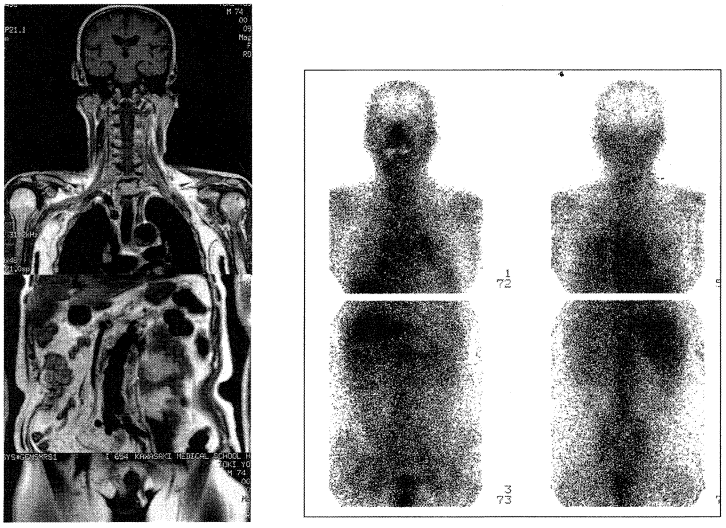

Fig 5. Follow-up whole body magnetic resonance imaging (left) and ^{67}Ga scintigraphy (right) on September 2000. Complete remission was achieved again through the therapeutic low-dose total body irradiation (LTBI).

(60 mg/body) orally for five days. CEOP was administered from October 2000 through January 2001. As a result of treatment, the patient remained clinically free of the disease for another two months, with normalization of his serum LDH level (Fig 2). However, he then experienced a relapse in the brain in March 2001. Next, he received whole brain irradiation of 1.0 Gy in 24 fractions over 18 days. Then, with the field reduced and confined to the involved lesion, the patient received a total dose of 50 Gy from March through July 2001. This treatment resulted in partial remission seen on the following brain MRI. However, he was not in a state to receive further chemotherapy. His condition became critical (LDH : 1,794 IU/L, sIL-2R : 58,400 U/L) (Fig 2), and was complicated by DIC and acute renal failure (CRN : 1.85 mg/dl, BUN : 74 mg/dl). He died from NHL 28 months after the initial diagnosis. Autopsy indicated that this case was attributable to diffuse large B-cell lymphoma generated from the thyroid gland.

DISCUSSION

LTBI has been used since the beginning of the twentieth century. In the 1970s, Johnson[2] and Del Regato[3] published the first encouraging results on the treatment of chronic lymphocytic leukemia and other hematological malignancies. More recently, several studies have shown that LTBI may be classified among the first-line treatments for advanced stage low-grade and intermediate-grade NHL.[4-7] Typically, LTBI has been used in the treatment of advanced stage NHL, and the standard schedule has consisted of administration of 0.1-0.25 Gy per fraction, one to five times a week at a total dose of 1.5-2 Gy. LTBI has yielded a high overall response rate ranging from 70 to 90% for nodular lymphomas and from 50 to 80% for

diffuse types.[6,8] Although the total dose of TBI has varied among reports from 1 to 3 Gy, there seems to be no difference in outcome at the various dose levels.[9]

LTBI has often been used as a salvage therapy for previously treated patients. Typical results have reflected an overall response rate of approximately 60% and a CR rate of 25%. The reported two- and five-year actuarial survival rates were approximately 45 and 25%, respectively, with the best results achieved in those with low-grade NHL.[10-13]

This paper considers one case of intermediate-grade NHL in an elderly patient to whom LTBI was administered prior to salvage chemotherapy. In this case there were no critical side effects, and good results were obtained.

In general, LTBI has no troubling acute effects such as lassitude, nausea, or vomiting. The major acute effects of a cumulative dose of 1.5-2 Gy are thrombocytopenia and neutropenia. The major concern is that LTBI may increase the risk of secondary leukemia after long periods of administration.[14-16] Late myelo-proliferative disorders seem to occur after cumulative TBI doses in excess of 2 Gy[2] in patients given extensive nodal irradiation as a supplement to TBI,[2] or in patients receiving a combination of LTBI and alkylating agents.[16]

It is not completely clear why LTBI produces such good results and the detailed action of this treatment has not been fully elucidated. Experimental data in previous publications, however, suggest that the efficacy of LTBI may be explained by three mechanisms; namely, immune enhancement,[17-19] induction of apoptosis,[20,21] and intrinsic hypersensitivity to low-radiation doses.[22] These mechanisms are not mutually exclusive and it is quite plausible that more than one mechanism may function simultaneously.[9] Studies supporting the immunity function have included experimental animal data showing that LTBI may augment the proliferative reactive response of T-cells to antigenic and allogenic stimulation, as well as increase the cytotoxic activity in tumor cells.[17,23]

The medical treatment of NHL has shown significant progress with the introduction of combination chemotherapy, and patients now benefit from higher recovery rates and greater probability of long-term survival. The elderly, however, are more susceptible to significant side effects due to the effects of the treatment on a generally weaker metabolism. Moreover, no effective chemotherapy regimen has been established specifically for NHL in the elderly. This report supports the notion that the LTBI is effective in salvage treatment for NHL patients in high risk groups (the elderly, with intercurrent disease or recurrence, or resistance, or resistance to treatment) and suggests its potential application to palliate the recurrent lesions before salvage chemotherapy.

REFERENCES

1) The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgikin's lymphoma. N Engl J Med **329**: 987-994, 1993
2) Johnson RE: Management of generalized malignant lymphoma with "systemic" radiotherapy. Br J Cancer **31**(suppl.2): 450-455, 1975
3) Del Regato JA: Total body irradiation in the treatment of chronic lymphogenous leukemia. Am J Roentgenol Rad Therapy & Nuclear Med **120**: 504-520, 1974

4) Brereton HD, Yung RC, Longo DL, Kirkland LR, Berard CW, Jaffe ES, De Vita VT, Johnson RE : A comparison between combination chemotherapy and total body irradiation plus combination chemotherapy in non-Hodgkin's lymphoma. Cancer **43** : 2227-2231, 1979
5) Lybeert ML, Meerwaldt JH, Deneve W : Long-term results of low dose total body irradiation for advanced non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys **13** : 1167-1172, 1987
6) Meerwaldt JH, Carde P, Burgers JMV, Monconduit M, Thomas J, Somers R, Sizoo W, Glabbeke MV, Duez N, De Wolf-Peeters CH : Low-dose total body irradiation versus combination chemotherapy for lymphomas with follicular growth patterns. Int J Radiat Oncol Biol Phys **21** : 1167-1172, 1991
7) Sakamoto S, Takai Y, Nemoto K, Ogawa Y, Yamada S. Radiotheraphy on malignant lymphoma by total body irradiation of low dose. Hematology & Oncology Dec **21** : 447-453, 1990
8) Hoppe RT : The role of radiation therapy in the management of non-Hodgkin's lymphomas. Cancer **55** : 2176-2183, 1985
9) Safwat A : The role of low-dose total body irradiation in treatment of non-Hodgkin's lymphoma : a new look at an old method. Radiother Oncol **56** : 1-8, 2000
10) Dobbs HJ, Barrett A, Rostom AY, Peckham MJ : Total- body irradiation in advanced non-Hodgkin's lymphoma. Br J Radiol **54** : 878-881, 1981
11) Mendenhall NP, Noyes WD, Million RR : Total body irradiation for stage II-IV non Hodgkin's lymphoma : ten-year follow up. J Clin Oncol **7** : 67-74, 1989
12) Rees GJ, Bullimore JA, Lever JV, Pizey NCD : Total body irradiation as a secondary therapy in non-Hodgkin's lymphoma. Clin Radiol **31** : 437-439, 1980
13) Van Dijk-Milatz A : Total-body irradiation in advanced lymphosarcoma. Br J Radiol **52** : 568-570, 1979
14) Travis LB, Curtis RE, Glimelius B, Holowaty E, Van Leeuwen FE, Lynch CF, Adami J, Gospodarowicz M, Wacholder S, Inskip P, Tucker MA, Fraumeni JF, Boice, Jr JD : Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst **85** : 1932-1937, 1993
15) Travis LB, Curtis RE, Stovall M, Holowaty EJ, van Leeuwen FE, Glimelius B, Lynch CF, Hagenbeek AH, Li CY, Banks PM, Gospodarowicz MK, Adami J, Wacholder S, Inskip PD, Tucker MA, Boice, Jr JD : Risk of leukemia following treatment for non-Hodgkin's lymphoma. J Natl Cancer Inst **86** : 1450-1457, 1994
16) Travis LB, Weeks J, Curtis RE, Chaffey JT, Stovall M, Bank PM, Boice, Jr JD : Leukemia following low-dose total body irradiation and chemotherapy for non-Hodgkin's lymphoma. J Clin Oncol **14** : 565-571, 1996
17) Liu SZ, Hann ZB, Liu WH : Changes in lymphocyte reactivity to modulatory factors following low dose ionizing radiation. Biomed Environ Sci **7** : 130-135, 1994
18) Nogami M, Huang JT, James SJ, Lubinski JM, Nakamura LT, Makinodan T : Mice chronically exposed to low dose ionizing radiation possess splenocytes with elevated levels of HSP70 mRNA, HSC70 and HSP72 and with an increased capacity to proliferate. Int J Radiate Biol **63** : 775-783, 1993
19) Shen RN, Lu L, Feng GS, Miller J, Taylor MW, Broxmeyer HE : Cure with low-dose total-body irradiation of the hematological disorder induced in mice with Friend virus : possible mechanism involving interferon-γ and interleukin-2. Lymphokine Cytokine Res **10** : 105-109, 1991
20) Nomura T, Kinuta M, Hongyo T, Nakajima H, Toshihiro H : Programmed cell death in whole body and organ systems by low dose radiation. J Radiat Res **33**(suppl.) : 109-123, 1992
21) Wang X, Matsumoto H, Takahashi A, Nakano T, Okaichi K, Ihara M, Ohnishi T : p53 accumulation in the organs of low-dose X-ray- irradiated mice. Cancer Lett **104** : 79-84, 1996
22) Marples B, Lambin P, Skov KA, Joiner MC : Low dose hyper-radiosensitivity and increased radioresistance in mammalian cells. Int J Radiat Biol **71** : 721-735, 1997
23) Ishii K, Yamaoka K, Hosoi Y, Ono T, Sakamoto K : Enhanced mitogen-induced proliferation of rat splenocytes by low-dose whole-body X-irradiation. Physiol Chem Phys Med NMR **27** : 17-23, 1995