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Original research article

Low dose palliative radiotherapy for refractory aggressive lymphoma

Osamu Tanaka[a,*], Masahiko Oguchi[b], Takayoshi Iida[a], Senji Kasahara[c], Hideko Goto[c], Takeshi Takahashi[c]

[a] Department of Radiation Oncology, Gifu Municipal Hospital, 7-1 Kashima-cho, Gifu 500-8513, Japan
[b] Department of Radiation Oncology, Cancer Institute Hospital, 3-8-31 Koto Ariake, Tokyo 135-8550, Japan
[c] Department of Hematology, Gifu Municipal Hospital, 7-1 Kashima-cho, Gifu 500-8513, Japan

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ABSTRACT

Aim: To determine the efficacy of low-dose palliative radiotherapy in patients with refractory aggressive lymphoma.
Background: There are few reports on the administration of palliative radiotherapy to patients with aggressive lymphoma.
Materials and methods: The present study included 11 patients with 30 sites of aggressive lymphoma (diffuse large cell lymphoma, $n=7$; mantle cell lymphoma, $n=2$; follicular large cell lymphoma, $n=1$; and peripheral T cell lymphoma, $n=1$). The patients received local palliative radiotherapy after receiving a median of 4 chemotherapy regimens. The radiotherapy doses administered to the 30 sites were as follows: 8 Gy, single fraction ($n=27$); 6 Gy, single fraction ($n=1$); 4 Gy, single fraction ($n=1$); and 4 Gy, 2 fractions ($n=1$).
Results: The complete response rate was 45% (5/11); the partial response rate was 36% (4/11). Toxicity occurred at one irradiated site (the mandibular), which showed temporal acute gingivitis; however, medication was not required. Retreatment was required for 3 sites on the head (parotid, face and mandible) due to persistent discomfort. None of the other sites (27/30) required retreatment. A patient with refractory DLBCL underwent radiotherapy (4 Gy, single fraction) for hepatic hilar lymph node involvement but did not recover from jaundice and died of DLBCL.
Conclusions: Eight Gray single fraction radiotherapy was one of meaningful options for the treatment of refractory aggressive lymphoma in terms of its efficacy and the incidence of adverse events. The use of 8 Gy single fraction radiotherapy is therefore recommended for achieving local control in patients with refractory aggressive lymphoma.

* *Corresponding author.*
E-mail address: c.bluered@gmail.com (O. Tanaka).

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1. Background

Non-Hodgkin's lymphomas are heterogeneous group of lymphoproliferative malignancies that are divided into two prognostic groups: indolent lymphomas and aggressive lymphomas.

Many relapses in the initial 2 years after therapy can be salvaged by second- and third-line chemotherapy. However, some patients develop refractory lymphomas that are resistant to all types of chemotherapy and require palliative treatment.[1–12]

Several studies have demonstrated the value of low-dose involved-field radiotherapy (LD-IF-RT) at doses of up to 4 Gy in recurrent follicular lymphoma.[1–3,5–7,9–11] In contrast, there are few reports on the administration of palliative radiotherapy to patients with aggressive lymphoma [4,8,12]. Due to the histological nature of both indolent and aggressive lymphomas, their sensitivity to radiation therapy varies.[11] Lowry et al. reported that 24 Gy is an effective dose for indolent NHL, while a randomized controlled trial found that the effective dose for aggressive NHL is 30 Gy[10] Patients with refractory aggressive lymphoma are treated with more intensive chemotherapy than those with refractory indolent lymphoma.

2. Aim

Recently, 8 Gy single fraction radiotherapy has been applied in the treatment of bone metastasis. Toxicity related to 8 Gy single fraction radiotherapy do not appear to impact the patient's quality of life after treatment. We therefore evaluated the use of 8 Gy single fraction radiotherapy.

3. Materials and methods

We retrospectively analyzed the results of palliative radiotherapy in 11 patients, with a total of 30 sites of refractory aggressive lymphoma, who were treated at our institution between 2002 and 2015. Institutional Review Board approved this study (H19-1). The pathological subtypes were classified according to the World Health Organization (WHO) classification system. The classifications were as follows: follicular lymphoma (FL) grade III ($n = 1$), mantle cell lymphoma (MCL) ($n = 2$), peripheral T cell lymphoma ($n = 1$) and diffuse large B-cell lymphoma (DLBCL) ($n = 7$).

All of the patients had previously received systemic combination chemotherapy, including salvage regimens. The median number of previous chemotherapy regimens was 4 (range: 2–8).

The patients consulted the Department of Radiation Oncology because they had symptomatic lesions and were diagnosed with incurable disease. The majority of the patients received 8 Gy single fraction radiotherapy. A few of the patients from the early part of the study period were treated with dose escalation.

The planning target volume was defined as the gross target volume with a margin of at least 1 cm in all directions. Fifteen sites were treated with a photon beam and 15 sites were treated with an electron beam. Prophylactic anti-emetics were given to patients who were treated with a wide abdominal radiotherapy field. The response was evaluated at 2–4 weeks after radiotherapy.

The primary endpoint of this study was in-field lymphoma control. Thus, the response definitions of the Revised Response Rate Criteria for Malignant Lymphoma [13] (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) were applied based on the size of the irradiated lesion. CR required the complete clinical disappearance and/or a normal radiologically detectable size. PR was defined as a ≥50% decrease in diameter. SD was defined as a failure to attain a CR/PR or PD. PD was defined as a ≥50% increase in diameter. The patients were assigned to the most appropriate category during the follow-up period.

Due to the shortness of the remaining life, the time to progression was measured rather than the time to local control (TLC). Toxicity was assessed using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

4. Results

A patient with refractory DLBCL received 4 Gy single fraction radiotherapy for hepatic hilar lymph node involvement; however, he did not recover from jaundice and died of DLBCL. Another patient received 6 Gy single fraction radiotherapy for the same condition. He recovered from jaundice and obtained relief from itchiness. Although too small and too heterogeneous in this analysis, we introduced 8 Gy single fraction radiotherapy for patients with refractory aggressive lymphoma.

The patients' characteristics and clinical courses are shown in Table 1. Among the 11 patients, the overall response rate was 82% (9/11), the CR rate was 45% (5/11), and the PR rate was 36% (4/11). A representative patient in whom a CR was achieved (patient 2 and 11) is shown in Figs. 1 and 2. There was only one case (patient 4) in whom radiotherapy (4 Gy single fraction) failed to achieve a response (SD). The dose was delivered to hepatic hilar lymph node involvement for jaundice; however, the patient did not recover from jaundice and eventually died. Patient 9, who had DLBCL, received 6 Gy (single fraction), which was delivered to the hepatic hilar lymph node to treat jaundice. Patient 9 recovered from jaundice without any adverse side effects. Radiotherapy resulted in good responses in patients with FL (grade III) and MCL.

A toxic event was documented at one irradiated site, the mandibular bone in patient 9, which showed temporal acute gingivitis; however, medication was not required and the patient subsequently recovered. Re-irradiation was required for 3 sites on the head (parotid, face and mandible) due to persistent discomfort. No other sites (27/30) required retreatment.

The time to local recurrence (TLR) was short, because the patients were referred to the radiation oncology department in a relapsed, uncontrollable state. The majority of the patients with refractory aggressive lymphoma died due to systemic failure.