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Clinical Outcomes of 67 Patients Treated with Chemoradiotherapy for Primary Thyroid Non-Hodgkin's Lymphoma in Osaka Medical College

Tsuyoshi Komori*#, Isamu Narabayashi#, Yoshifumi Narumi, Taisuke Inomata

Department of Radiology, Osaka Medical College, Takatsuki, Japan
Email: *komoyan1@gmail.com

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Abstract

Background: The reports of clinical outcomes of patients treated with chemoradiotherapy for primary thyroid non-Hodgkin's lymphoma are rare. We report our results of chemoradiotherapy for primary thyroid non-Hodgkin's lymphoma. Materials and Methods: The subjects were 67 patients with thyroid non-Hodgkin's lymphoma among 269 patients with malignant lymphoma who received radiotherapy in our hospital during a period between May 1990 and June 2005. The patients included 16 men and 51 women, with a mean age of 66.2 ± 10.7 years (30 - 84 years). The disease stage was stage I in 42 patients, stage II in 24, and unclear in 1. The histologic type was B-cell lymphoma in 66 patients, MALT in 9, diffuse type in 52, follicular type in 5, and diffuse and follicular type in 1. CHOP chemotherapy regimen for malignant lymphoma patients was as follows. Intravenous drip infusion of cyclophosphamide 750 mg/m², (drip) infusion of doxorubicin 50 mg/m², and intravenous injection of vincristine 1.4 mg/m² were administered on day 1, followed by 5 consecutive days of oral prednisolone 100 mg/m². This regimen was repeated every 3 weeks (21 days) in 6 to 8 courses. Modified CHOP chemotherapy regimen was as follows. Intravenous drip infusion of cyclophosphamide 600 mg/m², intravenous (drip) infusion of doxorubicin 40 mg/m², intravenous infusion of vindesine 3 mg/m², and intravenous drip infusion of prednisolone 60 mg/body were administered on day 1, and intravenous prednisolone was changed to oral prednisolone with the dose tapered gradually. After completing one course of this regimen, two courses of radiotherapy (a total of 36 Gy) were performed, followed by 6 courses of the chemotherapy regimen at lower doses (80% of the initial doses) repeated once a month. Results: Results of chemoradiotherapy in all patients were excellent. The 15-year survival rate was over 80%. Although there were no significant differences in the results of chemoradiotherapy among different histo-

*Corresponding author.
#Tsuyoshi Komori and Isamu Narabayashi were equally contributed in this study.

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logic types of thyroid malignant lymphoma, the survival rate was 100% for MALT type, as compared with poor results for diffuse large type or diffuse mixed type. The analysis of the results of chemoradiotherapy according to the stage of malignant thyroid lymphomas revealed that therapeutic results were significantly better in stage I than in stage II. Conclusion: The CHOP chemoradiotherapy regimen and modified CHOP chemoradiotherapy regimen were excellent for primary thyroid non-Hodgkin's lymphoma.

Keywords

Thyroid Non-Hodgkin's Lymphoma, Chemoradiotherapy

1. Introduction

Malignant lymphoma is a collective term for malignant neoplasms of lymphoid tissue caused by proliferation of lymphocytes. The incidence of malignant lymphoma in Japan has been increasing with aging of the population. Three mechanisms underlying the development of this malignancy are considered as follows: gene abnormalities that cause an increase in cell proliferation, prolongation of cellular life span due to inhibition of apoptosis by overexpression of BCL-2 gene, and involvement of exogenous factors such as viruses and bacteria.

A diagnosis of malignant lymphoma basically depends on pathological evaluation of tissue biopsies, and the new WHO classification of malignant lymphoma has been used since 2008 (**Table 1**). This classification is based on the Revised European American Lymphoma (REAL) classification published in 1994. Modified classification of lymphomas is attributable to an increased knowledge of kinds of monoclonal antibodies identifying the immune surface phenotype of lymphocytes and molecular genetics of lymphomas. Malignant lymphomas are roughly classified into Hodgkin's lymphomas and non-Hodgkin's lymphomas, and the WHO classification includes more than 20 subtypes of non-Hodgkin's lymphomas. More specifically, non-Hodgkin's lymphomas are firstly classified as precursor cell-type, B cell-type, or T cell-type, and are further subclassified in terms of cell morphology and immune surface materials based on chromosomal analysis and molecular genetic analysis. Diffuse Large B-Cell Lymphoma (DLBCL) and follicular lymphomas account for 50% of all malignant lymphomas. DLBCL with expression of CD10 is known to have a poor prognosis.

2. Etiology of Malignant Lymphomas

Overexpression of c-myc oncogene on chromosome 8 and Cyclin D1 gene facilitates cell proliferation, and overexpression of Bcl-2 gene that causes Burkitt's lymphoma and mantle cell lymphoma leads to prolongation of cellular life span due to inhibition of apoptosis and causes follicular lymphoma.

Exogenous factors include viruses and bacteria. In Hodgkin's lymphoma, Epstein-Barr virus is found in RS cells, and this is reported to be the cause of the disease.

3. Classification of Malignant Lymphomas

Malignant lymphomas are divided into two groups: Hodgkin's lymphoma and non-Hodgkin's lymphoma. The incidence of Hodgkin's lymphomas in Japan is 4% - 5%, which is lower than the corresponding rates of 40% - 50% in Europe and the United States. The incidence of non-Hodgkin's lymphomas is about 95%, combining B-cell lymphomas and T-cell lymphomas. Hodgkin's lymphoma was first reported by Hodgkin in UK in 1832, and called Hodgkin's disease. Non-Hodgkin's disease was distinguished from Hodgkin's disease around 1900. Virchow used the term lymphosarcoma in 1863.

The incidence of Hodgkin's lymphoma is decreasing annually. This might be explained by a definitive diagnosis of non-Hodgkin's lymphomas due to advances in the techniques of pathological diagnosis, which had been misdiagnosed as Hodgkin's lymphoma.

Non-Hodgkin's lymphomas were classified by the National Cancer Institute Working Formulation (WF) classification in the US in the 1980s, and the REAL classification began to be used in 1994. Since 2008, the WHO classification (**Table 1**) has been used worldwide as the standard classification of lymphoid neoplasms [1] [2]. Modified classification of lymphomas from the WF classification and the REAL classification to the WHO

Table 1. WHO 2008: the mature B-cell neoplasms.

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma[*]
Hairy cell leukemia-variant[*]
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
Alpha heavy chain disease
Gamma heavy chain disease
Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated
lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma (MZL)
Pediatric type nodal MZL
Follicular lymphoma
Pediatric type follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
T cell/histiocyte rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Epstein-Barr virus (EBV) + DLBCL of the elderly
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK + large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric
Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate
between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between
diffuse large B-cell lymphoma and classical Hodgkin lymphoma
Hodgkin Lymphoma
Nodular lymphocyte-predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

[*]These represent provisional entities or provisional subtypes of other neoplasms. Diseases shown in italics are newly included in the 2008 WHO.

classification was attributable to an increased knowledge of the types of monoclonal antibodies that identify the immune surface phenotype of lymphocytes and the progress in molecular genetics of lymphomas, but there always seems to be a difference in the viewpoint between pathologists who are in charge of classification and clinicians who places much value on prognostication.

The WHO classification is advantageous in that it reflects clinical characteristics of lymphomas and subclassifies morphology, antigenicity, and genetics in a consistent manner. It is speculated that DLBCL, the most frequent type of lymphoma, is comprised of multiple subtypes with different prognoses, and its subclassification is now under consideration. It has become apparent that CD10 expression in DLBCL is associated with a poor prognosis.

4. Treatments of Malignant Lymphomas

1) Radiotherapy (external irradiation: Mantle/inverted Y, etc.)
2) Chemotherapy (anticancer agents: CHOP, modified CHOP, fludarabine phosphate)
3) Biological products: anti-CD20 antibody (Rituxan)
4) Follow-up observation (watchful waiting, careful observation)
5) Hematopoietic stem cell transplantation: autologous transplantation, allogeneic transplantation
6) Radioimmunotherapy (Zevalin, Bxxar)

5. Patients with Thyroid Non-Hodgkin's Lymphoma Treated in Osaka Medical College

The subjects were 67 patients with thyroid non-Hodgkin's lymphoma among 269 patients with malignant lymphoma who received radiotherapy in our hospital during a period between May 1990 and June 2005. The patients included 16 men and 51 women, with a mean age of 66.2 ± 10.7 years (30 - 84 years). The disease stage was stage I in 42 patients, stage II in 24, and unclear in 1. The histologic type was B-cell lymphoma in 66 patients, MALT in 9, diffuse type in 52, follicular type in 5, and diffuse and follicular type in 1.

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Figure 1 shows the results of chemoradiotherapy for cases of thyroid non-Hodgkin's lymphoma treated in Osaka Medical College. These results were excellent.

Although there were no significant differences in the results of chemoradiotherapy among different histologic types of thyroid malignant lymphoma, the survival rate was 100% for MALT type, as compared with poor results for diffuse large type or diffuse mixed type (**Figure 2**).

As shown in **Figure 3**, the analysis of the results of chemoradiotherapy according to the stage of malignant thyroid lymphomas revealed that therapeutic results were significantly better in stage I than in stage II.

As for the results of radiography for malignant thyroid lymphomas treated in Osaka Medical College according to the pre-therapeutic IL-2R value, the survival rate was 100% when the IL-2R value was 530 U/ml or less, showing a tendency to better outcome with IL-2R values of 531 U/ml or more. As for the LDH value, the results of chemoradiotherapy were significantly better in those with LDH values of 2501 U/L or less than those with higher LDH values.

6. Discussion and Conclusion

In Osaka Medical College, ^{67}Ga scintigraphy or FDG-PET has been performed to evaluate the staging, and modified CHOP chemotherapy has always been administered even when radiotherapy was requested. Treatment of malignant lymphomas performed in Osaka Medical College has also been reported frequently in the literature [3]-[5].

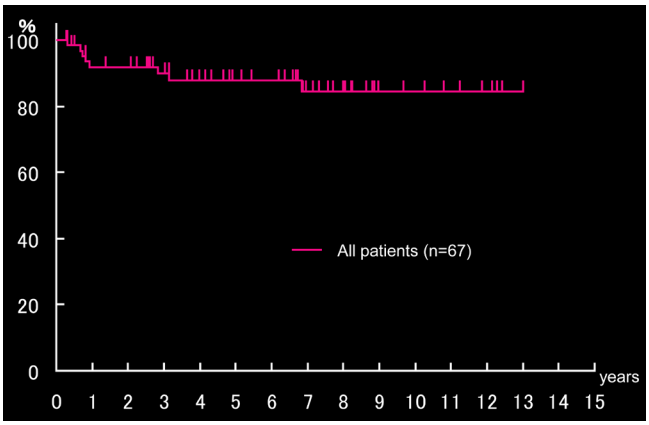

Figure 1. Patients with malignant thyroid lymphoma treated in Osaka Medical College: Results of chemoradiotherapy in all patients.

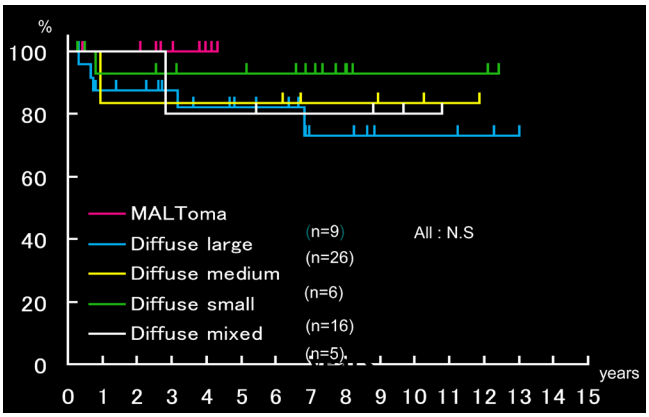

Figure 2. Patients with malignant thyroid lymphoma treated in Osaka Medical College: Results of chemoradiotherapy by disease stage.

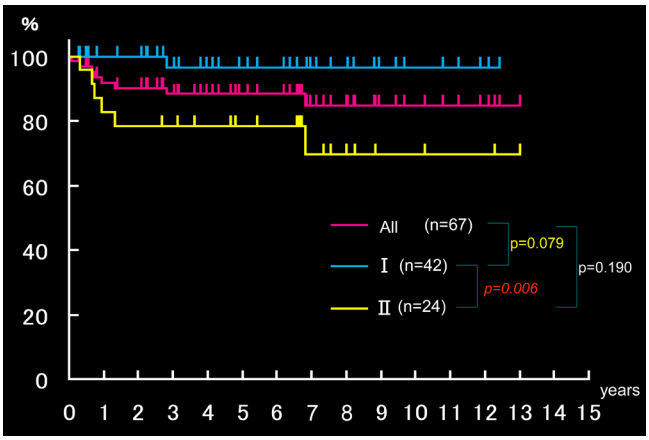

Figure 3. Patients with malignant thyroid lymphoma treated in Osaka Medical College: Results of chemoradiotherapy by histologic type.

Patients with malignant lymphoma have been increasing with aging of the society, and therefore, preparation of guidelines for staging by diagnostic imaging using PET with FDG, CT, or MRI, evaluation of therapeutic results, and diagnosis of recurrence is required. In the beginning, PET/CT apparatus, which is indispensable for disease staging, evaluation of therapeutic results, and diagnosis of recurrence, was not available at Osaka Medi-

cal College, but it was introduced in 2014. If a schedule for combined use of R-CHOP and radiotherapy is available at the time when the diagnosis is established, it would improve therapeutic outcomes. It is essential to cooperate between radiologists (diagnostic radiologists, radiation oncologists) and medical oncologists.

The clinical utility of radioimmunotherapy, employing nuclear medicine technology, is encouraging. In particular, it can help to improve prognosis in patients with stage III or IV malignant lymphomas or with recurrent disease. The use of Zevalin is considered overseas as a first-line therapy or high-dose therapy. This drug appears to be promising for non-Hodgkin's lymphomas; in particular, dramatic improvement is awaited not only for progressive malignant lymphomas of moderate to high malignancy but also for indolent non-Hodgkin's lymphomas of low malignancy.

Dosimetry of ^{90}Y-labeled anti-CD20 monoclonal antibody (Zevalin) in malignant lymphoma tissue is a future topic of discussion.

When external irradiation using appropriate irradiation field by scintigraphy (Ga-67 citrate and F-18 FDG) is used, a dose of 36 Gy should be delivered as a preferred dose to prevent the recurrence of malignant lymphoma. A dose of 30 Gy is sufficient for regional lymph nodes when there is no evidence of mass on imaging. For solid epithelial cancer, a dose of 70 - 80 Gy is necessary, which suggests that there are few clinical expectations of radioimmunotherapy for the treatment of solid cancer.

Acknowledgements

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Conflict of Interest Statement

None.

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