Ann Hematol (2005) 84:223–226
DOI 10.1007/s00277-004-0860-0

ORIGINAL ARTICLE

Mohammad Mohammadianpanah · Shapour Omidvai · Ahmad Mosalei · Niloofar Ahmadloo

Treatment results of tonsillar lymphoma: a 10-year experience

Received: 9 November 2003 / Accepted: 9 February 2004 / Published online: 23 March 2004

Abstract Primary extranodal non-Hodgkin's lymphomas of the head and neck account for 10–20% of all non-Hodgkin's lymphomas. Primary tonsillar lymphoma accounts for less than 1% of head and neck malignancies, although the tonsil is the most common primary extranodal site of head and neck non-Hodgkin's lymphomas. In this study we analyzed our cases of tonsillar lymphoma treated in our institution during the last 10 years to compare the finding of this study with those of previous studies. We reviewed the cases of tonsillar lymphoma treated in the Radiation Oncology Department of Shiraz University from 1992 to 2002. Clinical data were obtained from patients' files. The patients were treated by combined chemotherapy [a median of six cycles of a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone)] and radiation therapy (40–50 Gy to the primary site and neck). Chemotherapy mainly preceded radiotherapy, although the sequence of radiotherapy and chemotherapy was determined by individual physicians and patients' choice. Surgery was used mainly to establish the diagnosis, and tonsillectomy was performed for localized small lesions. Between 1992 and 2002, 19 patients with stage IE (10), IIE (7), and IIIE (2) disease were treated. Median and mean age was 48 and 44 years (range: 22–76 years), respectively, at the time of diagnosis, with a male to female ratio of 1.2:1. The vast majority of patients presented in early stages with aggressive histology. High-grade tumors seemed to affect mainly young people (p=0.226). Diffuse large B-cell lymphomas were the most prevalent. Male patients were significantly younger than females (p=0.021). The patients were treated by combined chemotherapy and radiation therapy. All patients achieved and maintained complete remission with a median of 60 months relapse-free survival and a 5-year cause-specific survival rate of 100%. All patients developed some degree of oropharyngeal mucositis. Three patients (16%) experienced grade 3 or 4 neutropenia. Mild (grade I) xerostomia remained persistently in four patients (21%). A late fatal side effect was observed in one patient who developed radiation-induced sarcoma 7 years after initial diagnosis and died 8 months later without evidence of recurrent lymphoma. Complete follow-up was obtained in all patients. The follow-up period ranged from 18 to 141 months with a median of 60 and a mean of 60.4 months. At the time of last follow-up, all patients but one were alive. Age, sex, stage, bulk of disease, performance status, number of chemotherapy cycles, number of involved sites, histologic subtypes, and radiation dose were analyzed as prognostically significant for disease-specific survival in our cases. Significant prognostic factors were not identified by multivariate analysis. Combined chemotherapy and radiation therapy is safe, highly effective, and probably curative for most patients with primary tonsillar lymphoma.

Keywords Tonsillar lymphoma · Non-Hodgkin's lymphoma · Combined chemotherapy and radiation therapy

M. Mohammadianpanah (✉) · S. Omidvai · A. Mosalei · N. Ahmadloo
Department of Radiation Oncology,
Shiraz University of Medical Sciences,
Shiraz, Fars, Iran (Islamic Republic)
e-mail: mohpanah@sums.ac.ir

Introduction

Lymphoma is a general term for a complex group of malignancies of the lymphoreticular system. Lymphoma is the second most common neoplasm of the head and neck after squamous cell carcinoma. In the head and neck region, non-Hodgkin's lymphoma can involve any area, but Waldeyer's ring (including tonsil, nasopharynx, and base of tongue) is the most common extranodal site [1]. Among the non-Hodgkin's lymphomas of Waldeyer's ring, tonsillar lymphoma accounts for about 80% [2, 3]. Localized non-Hodgkin's lymphomas (NHLs) of the head and neck are treated with radiotherapy or/and combination chemotherapy [4, 5].

There are many reports that favor adjuvant chemotherapy with involved-field radiation therapy even for with localized lymphoma [3, 6, 7, 8]. This article describes the usefulness of radiation therapy combined with chemotherapy in the management of localized tonsillar lymphoma.

Patients and methods

A search was made of the files of all cases of malignant lymphoma presenting in the palatine tonsil between the 1 January 1992 and the end of September 2002. A total of 19 patients with primary tonsillar lymphoma had been treated during 10 years at the Radiation Oncology Department of Shiraz Medical School. There were ten men and nine women whose ages ranged from 22 to 76 years. Based on Ann Arbor staging criteria, there were ten patients with stage I disease, seven patients with stage II, and two patients with stage III (Table 1). Four patients had bulky disease in the primary site, two patients with stage III, one patient with stage I, and one patient with stage II. None of the patients had systemic B symptoms.

Lymphomas were classified according to the Working Formulation classification. All patients had been treated with combined chemotherapy and radiation therapy. Patients received a median of six treatment courses (range: four to eight) of chemotherapy with a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone). However, the sequence of radiotherapy and chemotherapy was determined by individual physicians and patients' choice; chemotherapy preceded radiotherapy in most patients. Staging evaluation consisted of thorough history taking, physical examination with indirect laryngoscopy, chest radiographs, complete blood count, sedimentation rate, and abdominopelvic sonography in all cases. Bone marrow examination was performed in the majority of cases including young patients and high-grade histologies. Staging laparotomy was not performed.

In the current study, the patients were classified as having a tonsillar location when the initial presentation was mainly due to involvement at this site and it was confirmed by pathological examination. A secondary tonsillar involvement of a systemic disease was excluded from the study. Acute and late radiation-induced adverse effects were graded according to the Radiation Therapy Oncology Group (RTOG) scoring criteria. The degree of xerostomia was graded based on subjective evaluations of patient symptoms and clinical examination. Chemotherapy-induced hematotoxicity was graded according to the WHO scoring system. The survival rate was measured from the date of the first visit to the date of the last follow-up visit or death.

Table 1 Stage and sex distribution

	Stage				
	I	II	III	IV	Total
Male	6	2	2	0	10
Female	4	5	0	0	9
Total	10	7	2	0	19

Results

Patients and clinical characteristics

During the 10-year time period between 1992 and 2002, 19 patients were diagnosed with primary tonsillar lymphoma at the study institution. There were ten men and nine women, with a male to female ratio of 1.2:1. The age range was 22–76 years [mean: 44 years (37 for men and 53 for women), median: 48 years (40 for men and 50 for women)]. Male patients were statistically younger than females (p=0.021). The peak incidence was during the 4th and 5th decades.

Pathology

The vast majority of the patients (14 cases) had aggressive histology. Diffuse large B-cell lymphomas were the most common subtype, followed by small cell lymphoma, immunoblastic lymphoma, and anaplastic large cell lymphoma (Table 2). Comparing the Working Formulation classification with the Revised European-American Lymphoma (REAL) classification, extranodal marginal zone B-cell lymphoma (MALT type) may be the second most common histological subtype in these patients.

Treatment

All patients were treated with curative intent and combined chemoradiation. They received a median six cycles of chemotherapy with a combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen). Reducing the dose of either doxorubicin or vincristine was considered in elderly patients to avoid the risk of fatal myelosuppression or vincristine-induced neuropathy. Radiation therapy was administered by megavoltage unit (cobalt 60) to the primary site and neck lymph nodes through parallel opposed fields, which included the nasopharynx in the majority of patients. In general, tumor dose to the primary site and neck ranged from 40 to 50 Gy, given over 4–5 weeks at 10 Gy/week. The mean tumor

Table 2 Histological characteristics of 19 patients with tonsillar lymphoma. *SLL* small lymphocytic lymphoma, *LP*= lymphoplasmacytoid, *DSCC* diffuse small cleaved cell, *DMSLC* diffuse mixed small and large cell, *FMSLC* follicular mixed small and large cell, *DLC* diffuse large cell, *IL* immunoblastic lymphoma, *LL* lymphoblastic lymphoma, *UC (ALC)* unclassified (anaplastic large cell lymphoma)

	Low-grade		Intermediate-grade				High-grade		
	SLL	LP	DSCC	DMSLC	FMS LC	DLC	IL	LL	UC (ALC)
Male	0	0	1	1	1	7	0	0	0
Female	1	1	1	0	0	3	1	1	1
Total	1	1	2	1	1	10	1	1	1

dose approximated 46 Gy. Complete response was achieved in all patients in the course of chemoradiation.

Survival

Complete follow-up was obtained in all patients and the last follow-up was performed in January 2004. Up to the time of writing this paper, none of the patients had developed locoregional or distant relapse. All except one patient were alive at the time of final follow-up, with the latter patient dying of radiation-induced chondrosarcoma after 90 months from initial treatment. The follow-up period ranged from 18 to 141 months with a median of 60 and a mean of 60.4 months. The overall cause-specific survival for all patients at 5 years was 100% and the median overall survival for the 19 patients was 60 months (95% confidence interval 18–141 months).

Prognostic factors

Multivariate analysis was performed, including age, sex, stage, performance status, number of chemotherapy cycles, number of involved sites, histologic subtypes, radiation dose, and bulky disease. No significant prognostic factor was noted in this study and the 5-year disease-free and cause-specific survival rates were not influenced by these prognostic factors.

Treatment-related toxicity

Major toxicity was not seen in the study. Within the course of radiation, all patients developed some degree of oropharyngeal mucositis: 15 patients (79%) grade I and 4 patients (21%) grade II. All cases of mucositis resolved completely up to 2 weeks after completion of radiation therapy. Three patients (16%) experienced grade 3 or 4 neutropenia, but grade 3–4 anemia or thrombocytopenia did not occur. Hematopoietic growth factors were not used routinely.

Grade I xerostomia remained persistently in four patients (21%). An 80-year-old woman developed radiation-induced well-differentiated chondrosarcoma in the left maxillary sinus after 7 years from initial treatment and died 8 months later due to extensive locoregional disease.

Discussion

Non-Hodgkin's lymphomas are a broad heterogeneous category of neoplasms arising in the reticuloendothelial and lymphatic system. These neoplasms originate in B-cell lines and, less commonly, in T-cell lines [9, 10, 11]. Extranodal NHLs constitute 25–40% of all NHLs [12]. Depending on the primary site involvement, extranodal NHLs show a variable clinical course and outcome. A tonsillar location in early stages has a better survival in comparison with other extranodal sites [13]. The majority of tonsillar lymphomas have an aggressive histology [13, 14, 15]. In the reviewed patients, high-grade tumors affected mainly younger patients (p=0.226), and diffuse large B-cell lymphoma was the most common histological subtype. Primary tonsillar lymphoma has a peak incidence in the 6th and 7th decades of life in published series. The median and mean age of our patients was significantly lower compared with other studies. The peak incidence was during the 4th and 5th decades in our patients versus 6th and 7th decades in other series [3, 15]. We identified a statistically significant difference in mean age of the male and female patients. Men were significantly younger than women.

Localized non-Hodgkin's lymphomas of the palatine tonsil are treated with radiotherapy or/and combination chemotherapy in most centers [5]. However, combination chemotherapy alone has proven an effective treatment for stages I or II, and despite excellent initial complete response rates, the incidence of local relapse has been significant, particularly in patients who had bulky disease or aggressive histology [5, 16, 17]. For this reason, combined chemoradiation has been more frequently used as the primary treatment for localized aggressive non-Hodgkin's lymphomas. In most studies, complete remission and survival rates were better when combined therapy was used [6, 14, 18, 19, 20, 21, 22, 23].

The possible benefits of a short course of chemotherapy followed by involved-field radiation therapy are the potential for eliminating microscopic sites of disease; however, radiation therapy alone is still a very important treatment modality for localized low-grade lymphomas [24].

The results of locoregional control and response and survival rates in our patients seem to be better compared with other studies [3, 6, 7, 8, 15, 25]. In most series and our experience too, local and systemic-related toxicities were minimal, and patients generally tolerated treatment well [26]. Long-term side effects were mild and late toxicities and second malignancies were infrequent, although in this study one patient developed fatal radiation-induced sarcoma after 7 years. The exclusion of some of the important risk factors [systemic B symptoms, high lactic dehydrogenase (LDH) level, achievement of complete remission] from the study or overtreatment of low-risk patients may be the reasons of the lack of prognostic factors in this study.

Our results in the treatment of tonsillar lymphoma are excellent; however, some of the patients may have been overtreated, particularly those with low-grade, non-bulky stage I disease. With respect to excellent prognosis of localized tonsillar lymphoma, the modification of combined modality therapy may be a more rational approach in low-risk patients to avoid the significant acute or late side effects such as profound neutropenia and radiation-induced sarcoma.

A definitive recommendation for treatment of primary tonsillar lymphoma is difficult to make based on this

study with such a small number of patients, albeit the excellent results.

Conclusion

Tonsillar lymphomas tend to be localized and to have good outcome, albeit a high frequency of aggressive histology in these patients. Our limited data suggest that combined chemotherapy and radiation therapy is safe, highly effective, and probably curative, with mild and infrequent long-term side effects for the majority of patients with primary tonsillar lymphoma.

References

1. Depena CA, Van-Tassel P, Lee YY (1990) Lymphoma of the head and neck. Radiol Clin North Am 28:723–743
2. Jacobs C, Hoppe RT (1985) Non-Hodgkin's lymphomas of the head and neck extranodal sites. Int Radiat Oncol Biol Phys 11:357–364
3. Endo S, Kida A, et al. (1996) Clinical analysis of malignant lymphomas of tonsils. Acta Otolaryngol Suppl (Stockh) 523:263–266
4. Richard W, Tsang MD, Mary YK, Gospodarowikz MK, et al. (2002) Staging and management of localized non-Hodgkin's lymphomas: Variation among experts in radiation oncology. Int J Radiat Oncol Biol Phys 52:643–651
5. Ruijs CD, Dekker AW, van Kempen-Harteveld ML, van Barrelen J, Hordijk GJ (1994) Treatment of localized non-Hodgkin's lymphomas of the head and neck. Cancer 74:703–707
6. Aviles A, Delgado S, Ruiz H, de la Torre A, Guzman R, Talavera A (1996) Treatment of non-Hodgkin's lymphoma of Waldeyer's ring: radiotherapy versus chemotherapy versus combined therapy. Eur J Cancer Oral Oncol J 32B:19–23
7. Fujitani T, Takahara T, Hattori H, Imajo Y, Ogasawara H (1984) Radiochemotherapy for non-Hodgkin's lymphoma in palatine tonsil. Cancer 54:1288–1984
8. Artese L, Di Alberti L, Lombardo M, et al. (1995) Head and neck non-Hodgkin's lymphomas. Eur J Cancer Oral Oncol 31B:299–300
9. Epstein JB, Epstein JD, Le ND, et al. (2001) Characteristics of oral and paraoral malignant lymphoma: a population-based review of 361 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endol 92:519–525
10. American Cancer Society (1999) Cancer facts and figures 1999. American Cancer Society, Atlanta, GA
11. SEER (surveillance, epidemiology and results), National cancer institute (1999) Cancer statistics review 1973–1996 initial content, update 5 November 1999, https://cissecure.nci.nih.gov/ncipubs/
12. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM (2003) Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 14:131–139
13. Economopoulos T, Fountzilas G, Kostourou A, Daniilidis J, Pavlidis N, Andreopoulou H, Nicolaou A, Papageorgiou E, Mellou S, Dervenoulas J, Stathakis N (1998) Primary extranodal non Hodgkin's lymphoma of the head and neck in adults: a clinicopathological comparison between tonsillar and non tonsillar lymphomas. (Hellenic Co-operative Oncology Group). Anticancer Res 18:4655–4660
14. Sasai K, Yamabe H, Kokubo M, Shibata T, Oya N, Nagata Y, Hiraoka M (2000) Head-and-neck stages I and II extranodal non-Hodgkin's lymphomas: real classification and selection for treatment modality. Int J Radiat Oncol Biol Phys 48:153–160
15. Barton JH, Osborne BM, Butler JJ, Meoz RT, Kong J, Fuller LM, Sullivan JA (1984) Non-Hodgkin's lymphoma of tonsil: a clinicopathologic study of 65 cases. Cancer 53:86–95
16. Velasquez WS, Fuller LM, Jagannath S, et al. (1991) Stage I and II diffuse large cell lymphoma. Prognostic factors and long-term results with CHOP-Bleo and radiotherapy. Blood 77:942–947
17. Miller TP, Jones SE (1982) Initial chemotherapy for clinically localized lymphomas of unfavourable histology. Blood 62:413–418
18. Sullivan KM, NeimanPE, Kadin ME, et al. (1983) Combined modality therapy of advanced non-Hodgkin's lymphoma. An analysis of remission duration and survival in 95 patients. Blood 62:51–61
19. O'Connell MJ, Harrington DP, Earle JD, et al. (1988) Chemotherapy followed by consolidation radiation therapy for the treatment of clinical stage II aggressive histologic type non-Hodgkin's lymphoma. Cancer 61:1754–1758
20. Mirza MR, Brinker H, Spetch L (1992) The integration of radiotherapy into the primary treatment of non-Hodgkin's lymphoma. Crit Rev Oncol Hematol 12:217–229
21. Tondini C, Zanini M, Lombardi F, et al. (1993) Combined modality treatment with primary CHOP chemotherapy followed by locoregional irradiation stage I or II histologically aggressive non-Hodgkin's lymphoma. Clin Oncol 11:721–725
22. Wilder RB, Rodriguez MA, Tucker SL, Ha CS, Hess MA, Cabanillas FF, Cox JD (2001) Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. Int J Radiat Oncol Biol Phys 50:743–749
23. Gao YH, Li YX, Zhao LJ, Yuan ZY, Liu XF, Yu ZH (2003) Treatment of early stage primary tonsil non-Hodgkin's lymphoma. Zhonghua Xue Ye Xue Za Zhi 24:190–192
24. Miller TP, Dahlberg S, Cassady JR, et al. (1998) Chemotherapy alone with chemotherapy plus radiotherapy for localized intermediate and high-grade non-Hodgkin's lymphoma. N Engl J Med 339:21–26
25. Makepeace AR, Fermont DC, Bennett MH (1987) Non-Hodgkin's lymphoma of the tonsil. Experience of treatment over a 27-year period. J Laryngol Otol 101:1151–1158
26. Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, Crump M (2001) Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys 50:1258–1264