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Secondary Solid Cancers in Patients of Hodgkin's Lymphoma

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ÖZET

Hodgkin lenfoma tanılı hastalarda sekonder solid kanserler

Amaç: Bu yazımızda Dünya Sağlık Örgütü Uluslararası Kanser Araştırma Ajansı kanser kayıtçılığı standartlarına göre veri toplayan nüfus tabanlı Antalya Kanser Kayıt Merkezinin 1996-2008 verileri eşliğinde Hodgkin lenfoma (HL) tanılı hastalarda tespit edilen sekonder solid kanserler tartışılacaktır.

Gereç ve Yöntem: Çalışmaya 1996-2008 yılları arasında histopatolojik olarak HL tanısı konulan hastalar alınmıştır. Histopatolojik tanısı olmayan hastalar değerlendirilmeye alınmamıştır.

Bulgular: Çalışmaya 188'i (%58.8) erkek, 132'si (%41.3) kadın olmak üzere toplam 320 hasta alındı. Çalışmaya alınan hastaların 9'unda (%2.8) sekonder solid tümör saptandı. En sık saptadığımız solid tümörler nazofarenks (2 hasta), larenks (1 hasta) kanserleri ile ikişer hasta ile akciğer ve meme kanseri idi.

Sonuç: HL kür edebilen bir hastalık olmasına rağmen tedaviye bağlı komplikasyonlar önemli orandadır. Bu hastalardaki komplikasyonlardan biri olan sekonder solid tümör gelişimi açısından dikkatli takip edilmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Hodgkin lenfoma, sekonder solid kanserler, yan etki

ABSTRACT

Secondary solid cancers in patients of Hodgkin's lymphoma

Objective: In this article, we will discuss secondary solid cancers identified in patients diagnosed with Hodgkin's lymphoma (HL), with the 1996-2008 data of Antalya Cancer Recording Center which gathers population-based data in accordance with the cancer recording standards of World Health Organization's International Cancer Research Agency.

Material and Methods: The study included patients that were histopathologically diagnosed with HL from 1996 to 2008. The patients without histopathological diagnosis were not included in the assessment.

Results: The study covered 320 patients, including 188 (58.8%) males and 132 (41.3%) females. Nine out of 320 patients (2.8%) had developed secondary solid tumors. The most commonly identified tumors were seen in nasopharynx (2 cases) and larynx (1 case), followed by lung and breast with 2 cases for each.

Conclusion: Although HL can be cured, treatment-related complications prevail. Secondary tumor development, which is one of the complications in such patients, should be carefully monitored.

Key words: Hodgkin Lymphoma, secondary solid cancers, side effect

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INTRODUCTION

Hodgkin's lymphoma (HL) was first defined by Thomas Hodgkin in 1832, and comprises 10% of all lymphomas. Its incidence among all cancers is 0.6% (1). It has two peaks, one being around the age of 20, and the other being around the age of 65 (2).

HL is sensitive to both chemotherapy and radiotherapy with favourable results. Cure or long-term disease-free survival can be achieved in most patients. Long-term follow-up of these patients may reveal complications associated with the treatment. Treatment-related complications include radiation pneumonia secondary to radiotherapy, cardiac complications associated with cardiotoxic chemotherapy

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or radiotherapy and gonad dysfunction and infertility (3-7). Another important complication is development of solid cancers after chemotherapy and radiotherapy used in treatment (8). Combination of Mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) is responsible of the development of lung and breast cancer (9-14). In this article, we will discuss secondary solid cancers identified in patients diagnosed with Hodgkin lymphoma, within the period of 1996-2008 whose data were collected in Antalya Cancer Recording Center which gathers population-based data in accordance with the cancer recording standards of The International Agency for Research on Cancer (IARC) of WHO.

MATERIAL AND METHODS

Cancer has been accepted as a notifiable disease since 1982 in Turkey and data were collected on a voluntary basis nationwide. Due to its passive role of collecting data, Turkish Government enacted regulations for cancer reporting in 1992 and defined National Cancer Registry Project and established population-based cancer registry centers in 10 provinces covering 15 millions populations each. Turkey became a member of the International Agency for Research on Cancer (IARC) in May 2011. Each center collects data in accordance with the international standards of cancer recording. Simply, all data from the hospitals, oncology centers, private pathology and radiology centers are screened for any "cancer" diagnosis as well as data from death certificates. Repeated record is clarified using citizenship number and social security number.

Our study was screened Antalya Province, Cancer Registration Center during 1996 to 2008 and included patients that were histopathologically diagnosed as HL. Patients' data were extracted from the files of Antalya Provincial Health Directorate, Cancer Registration Center. The patients without histopathological diagnosis were not included in the assessment. The patient whose diagnosis was recorded as "Lymphoma" but not clarified as "Hodgkin or non-Hodgkin" was not included in the assessment as well. Patients' age, time of diagnosis, site of diagnosis, treatment protocols were recorded. For secondary solid tumors, histological type of solid tumor, date of diagnosis, age at diagnosis, interval between two tumors were recorded also.

RESULTS

During the period of 1996-2008, HL has been seen in 320 patients, including 188 (58.8%) males and 132 (41.3%) females. The average age of the patients was 37±18.7 (range 2-85). It was 29±18.9 years in females and 37±18.3 in males. Three hundred and eight patients had nodal involvement (96.3%). Extra nodal disease was seen in twelve patients (3.7%). The stomach was the most common extra nodal involvement site. Subtype information was not available in 90 patients. The most common subtype was nodular sclerosing type in evaluated subtype of 230 patients. It was seen in 123 patients (53.3%). Seventy eight patients (34.1%) had the mixed type, 19 patients (8.3%) had lymphocyte-rich type and 10 patients (4.3%) had lymphocyte-deprived type. The first-line treatment protocol for HL between 1996-2008 was given doxorubicin (25 mg/m2), bleomycin 10 units/m2), vinblastine 6 mg/m2, dacarbazine 375 mg/m2. Involved field radiotherapy was administered only when partial response was seen after chemotherapy.

Nine out of 320 patients (2.8%) had developed secondary solid tumors. The most commonly identified tumors were seen in nasopharynx (2 cases) and larynx (1 case), followed by lung and breast with 2 cases for each (Table 1).

Table 1: Patients of HL diagnosed with secondary cancer

Patient no	Age	HL diagnosis date	Secondary malignity	Date of diagnosing secondary malignity
1	54	07.1996	Breast	07.1998
2	53	12.1996	Nasopharynx	01.1999
3	50	07.2005	Larenx	02.2008
4	28	03.2006	Breast	03.2008
5	49	08.2006	Lung	01.2007
6	59	01.1998	Nasopharynx	01.2001
7	44	06.2001	Skin	04.2007
8	51	03.2001	Stomach	07.2007
9	68	07.1998	Lung	01.2008

DISCUSSION

HL is a curable disease. Since it is seen at young ages, long follow-up is allowed them to reveal treatment-related complications. Behringer et al. identified secondary solid tumors in 127 (2.4%) of 5367 patients monitored from 1983 to 1998. They identified the risk of developing cumulative solid tumors in HL as 2%. In their study, they found lung cancer, colorectal cancer and breast cancer are the most commonly identified secondary malignity with 23.6%, 20.5% and 10.2%, respectively (9). In another study which covered 2441 HL patients who were followed-up for 10.9 years, gastrointestinal cancer was diagnosed in 25 patients. The most common site was stomach and then pancreas and small intestine (10). Head and neck carcinoma was the most common site for the development of secondary solid cancers in our study. We did not find any colorectal tumors but gastric cancer in one patient. This patient had nodal involvement.

Leeuwen et al. found that 14 (1.8%) out of 744 patients of HL developed lung cancer during their follow-up from 1966 to 1983, and identified the risk of developing lung cancer in 14 patients as 4.9% (11). Other studies also demonstrated an increased risk of lung cancer after HL treatment (12-14). We identified lung cancer only in 2 patients (0.62%). It is lower than Leeuwen's study.

Sont et al. found 16 solid tumors in follow-up of 482 patients from 1969 to 1988. They calculated the relative risk ratio for developing haematological and solid tumors after HL treatment as 7% (15). Although the ratio seems higher, they counted haematological malignancies as well as solid cancers.

The incidence of secondary malignancy is higher in childhood period. The risk of the development of secondary solid tumor in childhood period was 3.9% in Bhatia's study. The most commonly identified solid tumor was of the breast cancer (16). In another study, the risk of developing breast cancer in female patients who underwent radiotherapy due to HL was investigated. This study has demonstrated that the risk was higher among patients under the age of 20, while the risk decreases in advanced ages. In this study, the secondary solid tumors before age 20 were identified as 2.6%, which is similar to our study (17). The risk of developing secondary solid tumors increases during the first 20 years in patients who were diagnosed with HL in the childhood period, while it draws a plateau during the next 25 years (18-20). Two out of 9 patients developed breast cancer in our study. They were 54 and 28 years old at the time of diagnosis of HL. There has been 58 patients younger than 20 years old (18.1%) in our study. Among them, we did not identify secondary solid tumors which, we believe, is due to the short follow-up period.

The incidence of secondary solid cancer after HL treatment increases with long follow-up. In a study which monitored 794 patients from 1969 to 1988 who were staged with laparoscopy, 53 (6.6%) solid tumors were identified (21). It is considered that the long follow-up led the highest incidence in their study. In a British cohort study with a long follow-up period, an increase incidence in the gastrointestinal, lung and breast cancer has been demonstrated (22). Beside these tumors, rare cancers such as mesothelioma could also be diagnosed (23). The meta-analysis of the studies investigating the development of secondary solid cancer after HL treatment has demonstrated that radiotherapy combined with chemotherapy increases the risk of malignancy. The risk of breast cancer increases particularly in women who received chest wall radiotherapy for the treatment of HL (24). There was no information whether our patients had radiotherapy or not.

In conclusion, although HL is a curable disease, patients can suffer development of secondary solid tumors. Head and neck region, respiratory tract and breast are the most common site for secondary tumor development and patients should be carefully monitored.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225-249.
2. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010; 116: 3724-3734.
3. Tarbell NJ, Thompson L, Mauch P. Thoracic irradiation in Hodgkin's disease: disease control and long-term complications. Int J Radiat Oncol Biol Phys 1990; 18: 275-281.
4. Moser EC, Noordijk EM, van Leeuwen FE, et al. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. Blood 2006; 107: 2912-2919.
5. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH. Gonadal function following ABVD therapy for Hodgkin's disease. Am J Clin Oncol 1997; 20: 354-357.
6. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group [GHSG]. Blood 2008; 111: 71-76.

7. Ng AK, Mauch PM. Late effects of Hodgkin's disease and its treatment. Cancer J 2009; 15: 164-168.

8. Valagussa P. Second neoplasms following treatment of Hodgkin's disease. Curr Opin Oncol 1993; 5: 805-811.

9. Behringer K, Josting A, Schiller P, et al. Solid tumors in patients treated for Hodgkin's disease: a report from the German Hodgkin Lymphoma Study Group. Ann Oncol 2004; 15: 1079-1085.

10. Birdwell SH, Hancock SL, Varghese A, Cox RS, Hoppe RT. Gastrointestinal cancer after treatment of Hodgkin's disease. Int J Radiat Oncol Biol Phys 1997; 37: 67-73.

11. van Leeuwen FE, Somers R, Taal BG, van Heerde P, et al. Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. J Clin Oncol 1989; 7: 1046-1058.

12. Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. New Engl J Med 1990; 322: 7-13.

13. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst 1995; 87: 1530-1537.

14. Swerdlow AJ, Schoemaker MJ, Allerton R, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. J Clin Oncol 2001; 19: 1610-1618.

15. Sont JK, van Stiphout WA, Noordijk EM, Molenaar J, Zwetsloot-Schonk JH, Willemze R. Increased risk of second cancers in managing Hodgkin's disease: the 20-year Leiden experience Ann Hematol 1992; 65: 213-218.

16. Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. New Engl J Med 1996; 334: 745-751.

17. Aisenberg AC, Finkelstein DM, Doppke KP, et al. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. Cancer 1997; 79: 1203-1210.

18. Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 2000; 18: 2435-2443.

19. van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000; 18: 487-497.

20. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol 2002; 20: 3484-3494.

21. Mauch PM, Kalish LA, Marcus KC, et al. Second malignancies after treatment for laparotomy staged IA-IIIB Hodgkin's disease: long-term analysis of risk factors and outcome. Blood 1996; 87: 3625-3632.

22. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort. The relation to age at treatment. J Clin Oncol 2000; 18: 498-509.

23. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. Blood. 2009; 16: 3679-3681.

24. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol 2006; 17: 1749-60.