Second Malignant Neoplasms in Pediatric Oncology Patients: A Single Center Experience

Pediatrik Onkoloji Hastalarında İkincil Kanserler: Tek Merkez Deneyimi

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ABSTRACT

Objective: The pediatric malignancy survival rate has increased with new and intensive treatment modality advancements. This has led to an approximately 70% chance of surviving more than 5 years in children diagnosed with cancer. However, the secondary tumor incidence has also increased with these advances. The patient's quality of life, late side effects, and prevention of secondary malignancies in the future are as important as treating the primary tumor in pediatric cancer patients.
Methods: We retrospectively evaluated the charts of 2100 pediatric cancer patients who were diagnosed in our clinic between 1985 and 2012.
Results: There were 11 secondary tumors. Male-to-female ratio was 6:5 and median age at diagnosis was 7 years (range, 1 year 3 months–11 years 6 months). Secondary tumor diagnosis was AML in five patients, paraganglioma in one patient, liposarcoma in one patient, rhabdomyosarcoma in one patient, papillary thyroid carcinoma in one patient, malignant fibrous histiocytoma in one patient, and squamous cell carcinoma of the tongue in one patient. AML was the most commonly detected secondary malignancy.
Conclusion: We suggest that using less toxic systemic chemotherapy and reduced-dose radiotherapy is increasingly important with targeted treatment modalities to decrease the risk of secondary malignancy.

Key Words: Cancer, childhood, secondary tumor

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ÖZET

Amaç.Son yıllarda kanser tedavisinde kullanılmaya başlanılan yeni ve yoğun tedavi modalitelerinin katkısı ile çocukluk çağı malinitelerinde sağkalım oranlarının arttığı görülmektedir. Bununla ilişkili olarak kanser tanısı alan çocuklarda yaklaşık %70 oranında 5 yılın üzerinde yaşam şansı beklenmektedir. Ancak tedavideki yüz güldürücü sonuçların yanısıra sekonder tümör oranlarında da artış olduğu bir gerçektir. Çocukluk çağı kanserlerinde primer tümörün tedavisi kadar hastanın hayat kalitesi, geç dönem yan etkiler ve ilerleyen süreçte karşılaşılabilecek sekonder malignensilerinin önlenebilmesinin de önemli olduğunu düşünmekteyiz.
Yöntemler. Bu amaçla 1985-2012 yılları arasında kliniğimizde tanı alan toplam 2100 çocukluk çağı kanser olgusunun dosyası retrospektif olarak incelendi.
Bulgular. Toplam 11 sekonder tümör olgusunun olduğu görüldü. Erkek kız oranı 6/5, median tanı yaşı 7 olarak saptandı (1 yaş 3 ay-11 yaş 6 ay). Sekonder tümör olarak 5 olguda AML, 1 olguda paraganglioma, 1 olguda liposarkom, 1 olguda rabdomiyosarkom, 1 olguda papiller tiroid karsinomu,1 olguda malign fibröz histiositoma ve 1 olguda dilde skuamöz hücreli karsinom görüldü. AML en sık görülen sekonder malignite olarak gözlendi.
Sonuç. Daha az toksik etkili sistemik kemoterapi ve azaltılmış doz radyoterapi uygulamasının hedefe yönelik tedavi modalitelerinin gündeme gelmesi ile önem kazanacağını ve sekonder malinite riskini azaltacağını düşünmekteyiz

Anahtar Sözcükler: Kanser, çocukluk çağı, sekonder tümörler

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INTRODUCTION

One of the most common problems following cancer treatment in oncology is the late side effects and secondary malignancies. Childhood cancer survivors have an increased risk of a secondary cancer later in life. A different primary cancer that occurs at least two months after the completion of cancer treatment is called a secondary cancer. Although the success rate of cancer treatment is increasing, the secondary cancers appearing in the long term cause a decrease in survival. The secondary cancer rate is reported to be 6–10% in the United States and these cancers usually appear at around 40 to 50 years of age. The most commonly reported secondary tumors are leukemia, sarcoma, central nervous system tumors, and thyroid gland carcinomas (1-4). Certain genetic patterns or syndromes may increase the risk of a second cancer. Patients who have been treated for cancer need regular screening tests to check for a second cancer. Our present study aimed to determine: 1) the types of second malignant neoplasms (SMNs) occurring after diagnosis of the first cancer; and 2) the latency of the second cancer. Here, we report our single-center experience with secondary tumors in pediatric cancer patients diagnosed in the last 27 years.

PATIENTS and METHOD

This study was planned as a retrospective study in our pediatric oncology clinic. A total of 2100 childhood cancer patients diagnosed before the age of 18 years presented to our center between 1985 and 2012. We excluded 520 (25%) patients who died without a secondary tumor diagnosis and 173 patients who continued their treatment at a different center or had incomplete chart data. Patients with a follow-up period less than 36 months after treatment discontinuation were also excluded. Overall, the patients' diagnoses were ALL (n=473), AML (n=235), non-Hodgkin lymphoma (n=265), Hodgkin lymphoma (n=224), neuroblastoma (n=137), Wilms tumor (n=42), and rhabdomyosarcoma (n=30). The patients underwent laboratory investigations such as blood count, sedimentation, CRP, AST, ALT, LDH, urea, creatinine, serum ferritin, and radiologic imaging for staging (ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography). The type of surgery at the time of diagnosis (such as only biopsy or subtotal/gross total extraction) and whether lymph node or distant organ metastasis was present were taken into account in the staging of the patients. Tumor groups were also classified according to whether they were metastatic (advanced stage) or non-metastatic (early stage) at the time of diagnosis. For example, we used the STS-COG (Soft-Tissue Sarcoma Children's Oncology Group) staging system for rhabdomyosarcoma, the INSS (International Neuroblastoma Staging System) staging system for neuroblastoma, and the Ann Arbor staging system for Hodgkin lymphoma patients. Patient's demographic characteristics, steroid response to treatment, failure at the end of induction treatment, some cytogenetic positivities such as t (9;22) and central nervous system involvement were considered in ALL patients for high risk stratification. MLL rearrangement, monosomy 5 or 7, and FLT-3 positivity were evaluated for risk stratification of AML patients. Solid tumor patients had mostly advanced stage disease and received intensive chemotherapy protocols. All leukemia patients except one were considered high risk and received radiation treatment in addition to chemotherapy. The median follow-up duration of these remaining 1407 patients whose charts we could retrospectively access was 8 years. The median follow-up duration of patients diagnosed with a secondary tumor was 11 years. We evaluated the demographic characteristics, treatment regimens radiotherapy doses, and fields.

RESULTS

The male-to-female ratio of the 11 secondary tumor patients was 6:5 and the median age at the time of primary diagnosis was 7 years (range, 1 year 3 months–11 years 6 months). The median follow-up duration between the primary and secondary tumor was 5 years (range, 2 years 8 months–11 years), the median duration between the diagnosis of the primary tumor and treatment discontinuation was 2.5 years (range, 1 year 2 months–3 years 6 months), and the median follow-up duration between treatment discontinuation and diagnosis of the second tumor was 4 years (range, 7 months–12 years). Radiotherapy was administered to 7 of the 11 patients with a secondary tumor. The radiotherapy field was the cranium because there was central nervous system (CNS) involvement of leukemia in five patients, and the tumor region because of ganglioneuroblastoma or Wilms tumor in the other two patients.

Malignant fibrous histiocytoma developed in the temporal region in one patient with central involvement because of a diagnosis of T-ALL 9 years 5 months after St. Jude XIII treatment protocol (1800 c Gy cranial RT). Surgery, chemotherapy, and radiotherapy were administered to treat the secondary cancer. The patient has been followed and was disease free for 5 years following the termination of secondary cancer treatment.

Papillary thyroid carcinoma developed in the other B-ALL patients receiving the St. Jude XIII treatment protocol. The patient had received 1800 c Gy radiotherapy to the cranium as per St. Jude XIII leukemia protocol, and the duration between the two diagnoses was 7 years. This patient underwent thyroidectomy and received radioactive iodine treatment, and has been disease free for 4 years. Another patient developed alveolar rhabdomyosarcoma in the head and neck region 11 years after B-ALL (treatment was with chemotherapy and 1800 c Gy cranial radiotherapy). The patient developed two recurrences while being monitored for a diagnosis of refractory sarcoma, and died as a result of disease progression.

AML developed following the St. Jude XIII protocol in four B-ALL patients. Two of these were lost to follow-up and the other one is being followed-up in remission. The first patient who developed AML had received St. Jude XIII protocol and 1800 c Gy radiotherapy at the time of the first diagnosis. When AML-M3 developed 3 years 6 months later during follow-up, remission was achieved with a treatment protocol including ATRA and idarubicin. The second patient who developed AML had been treated for ALL with St. Jude XIII protocol. When secondary AML developed 3 years 5 months later, the AML-BFM-2004 protocol was used but remission was not achieved and the patient died as a result of disease progression. The third ALL patient had also received the St. Jude XIII protocol and 1800 c Gy cranial radiotherapy. Secondary AML was diagnosed 2 years 8 months later and the patient died as a result of disease progression during follow-up. The fourth AML patient had been treated for ALL with the St. Jude XIII protocol. AML-M4 developed during follow-up and was treated with the AML-BFM-2004 protocol. The patient is still in remission following allogeneic bone marrow transplantation. Table 1 presents the administered radiotherapy doses and treatment regions, and the secondary tumor fields.

DISCUSSION

Cancer treatment success has been increasing in recent years. However, the 10-fold increase in secondary cancer risk must also be taken into account. Oncology patients need to be followed up for long periods with regular visits because secondary tumors appear, on average, 1 to 2 decades after the primary tumor (1-11). Data loss that occurs when patients abandon the center where they were first diagnosed or the patient refusing treatment can create problems in determining the incidence of secondary tumors. The Turkish Pediatric Oncology Group (TPOG) established in our country collects all childhood cancer record data and one of its aims is to eliminate this problem. The median follow-up between the diagnosis of the primary tumor and secondary tumor was 5 years in our study, while the median follow-up duration of all our patients (n=1407) was 8 years. Median latency between first and second cancers in our study was shorter than that in the Childhood Cancer Survivor Study (CCSS) cohort (5 years versus 11.7 years), but the CCSS does not take into account early leukemias arising less than 5 years after the first cancer. This was partially attributable to the shorter latency of our secondary leukemias (3 year and 5 months versus 7.1 years) (12). However, Rihani et al. also noted a shorter latency at 3 years for secondary acute myeloblastic leukemias (13).

Table 1. Clinical Characteristics of Patients

N	Sex	Age at diagnosis	Primary diagnosis	Stage or risk classification	Cancer history of family	Radiotherapy dosages and application area	Chemotherapeutics	SMNs	Origin of second malignancy	Latency between primary and second cancer	Outcome
1	M	3 years 7 months	Wilms tumor	III	None	1800 c Gy to abdomen and renal area	ACT-D, ADR, VCR	Paraganglioma	Paraaortic region	6 years 3 months	Alive
2	F	1 year 3 months	Ganglio-neuroblastoma	IV	None	3000 c Gy boost to the lesion	VCR, CDDP, DTIC, ADR, VP16	AML-M1	Bone marrow	3 years	Deceased
3	F	10 years 5 months	NHL	IV	None	None	VCR, CYC, ADR, ARA-C, MTX, 6-MP	Squamous carcinoma	Tongue	5 years	Alive
4	M	3 years 3 months	HL	III	None	None	VCR, ADR, DTIC, Bleo	Liposarcoma	Abdomen	5 years	Alive
5	M	9 years 6 months	T-ALL	High risk	None	1800 c Gy cranium	VCR, CYC,VP-16, ADR, ARA-C MTX, L-ASP, 6-MP	Malignant fibrous histiocytoma	Temporal and parietal bone	5 years 5 months	Alive
6	M	11 years 4 months	B-ALL	Standard risk	None	None	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6-MP	AML-M3	Bone marrow	3 years 6 months	Alive
7	F	11 years 6 months	B-ALL	High risk	None	1800 c Gy cranium	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6-MP	Papillary carcinoma	Thyroid	7 years	Alive
8	F	4 years 6 months	B-ALL	High risk	None	1800 c Gy cranium	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6-MP	AML	Bone marrow	3 years 5 months	Deceased
9	M	4 years 6 months	B-ALL	High risk	None	1800 cGy cranium	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6-MP	AML	Bone marrow	2 years 8 months	Deceased
10	F	7 year 5 months	B-ALL	Standard risk	None	None	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6-MP	AML	Bone marrow	4 years	Alive
11	M	7 years	B-ALL	High risk	Lung carcinoma, skin carcinoma	1800 cGy cranium	VCR, CYC, VP-16, ADR, ARA-C, MTX, L-ASP, 6MP	Alveolar rhabdo-myosarcoma	Neck	11 years	Deceased

ACT-D indicatesactinomycin-D, ADR, adriamycin; ALL, acutelymphoblasticleukemia; AML, acutemyeloidleukemia; ARA-C, cytarabine; BLEO, bleomycin; CDDP, cisplatin; CYC, cyclophosphamide; DTIC, dacarbazine; L-ASP, L-asparaginase, MFH, Malignantfibroushistiocytoma; MTX, methotrexate

Carcinogenesis is a complex process and can develop as a result of many factors. Environmental agents, inflammation, radiation and genetic predisposition can act as triggers for the process. Childhood malignancies have a different biological spectrum than adult cancers regarding histological distribution, tumor regions, and prognosis. A familial cancer tendency can be an important risk factor in the development of both primary and secondary malignancies in children (14-19). The family history of our patients with a secondary tumor revealed increased cancer incidence in the family of only one child (with T-ALL/malignant fibrous histiocytoma). We learned that this patient's father had been diagnosed with NHL and that two nephews had been diagnosed with NHL and ALL when they were over 40 years old; they later died of disease progression during follow-up. The effect of chemotherapy agents on carcinogenesis is well known. Anthracyclines, topoisomerase inhibitors, and drugs that add an alkyl group to the DNA chain, such as cyclophosphamide, cisplatin, busulfan, and procarbazine, have an especially high secondary cancer risk (20-26). The risk of secondary cancer development following cancer therapy in childhood is nine-times higher than that of the normal population. The secondary cancer incidence peaks in the first four years and gradually decreases thereafter. Leukemia can be seen in the first 10 years as a secondary cancer that results from chemotherapy and the frequency is higher in the first 3 years. However, secondary solid tumors can appear even years after the end of treatment (26-28).

The cumulative risk of secondary neoplasm is ranging from 3.2 to 9% in St. Jude protocols but it is much lower (0.5%) in our results (29). It may be associated with our median follow up period which was shorter than 10 years.

The incidence of AML as a secondary tumor is increased because of the alkylating agents used in chemotherapy and because of the radiotherapy. The treatment success and survival rates were low in our patients who developed leukemia secondary to chemotherapy. Four of our patients with secondary cancer died and three of these patients had a secondary cancer diagnosis of AML. An important point was that the primary diagnosis in most patients who developed a secondary tumor (n=7, 64%) was leukemia (ratio of T-ALL-to-B-ALL = 1:6). These patients were classified as having high-risk leukemia at diagnosis and they received high-dose etoposide and cranial radiotherapy, according to the St. Jude XIII protocol. We believe that the high-dose etoposide administration (13 g/m^2) in the St. Jude XIII treatment protocol increases the incidence of secondary tumors.

The St. Jude treatment protocol has currently been modified to administer etoposide in patients with refractory or relapsed disease and those who are candidates for hematopoietic stem cell transplantation, and to use cranial radiotherapy in those with a CNS relapse, because of the high secondary AML incidence caused by etoposide (29).

Another major cancer of childhood and adolescence with an increased risk of secondary cancers is Hodgkin lymphoma. We monitored a total of 224 Hodgkin lymphoma patients (109 early stage and 115 advanced stage) in our clinic between 1985 and 2012. The patients received alternate COPP and ABVD protocols. Relapse was seen in 21 patients and 19 patients died because of disease progression. The survival rate was 91.3%. We had one patient where secondary malignancy appeared during follow-up for Hodgkin lymphoma, and this patient developed abdominal liposarcoma 5 years after lymphoma treatment was discontinued. The diagnosis was well-differentiated liposarcoma following treatment and the patient has been disease free for 10 years. The most common hematological malignancies in patients recovering from Hodgkin lymphoma are secondary AML and MDS (30). The main factors increasing the secondary malignancy risk in Hodgkin lymphoma patients are alkylating agents and radiotherapy. The secondary AML development risk is high in the first 5–10 years after treatment completion (31). The risk of leukemia is low in patients who have received radiotherapy only. Various solid tumors have been reported in patients treated for HL. The risk of secondary mass development increases in the years after the diagnosis and the latent period is over 20 years. The incidence especially of breast, thyroid, and skin cancers in childhood, and of gastrointestinal tumors and lung cancers in the adult period, are higher in children who are diagnosed with HL during childhood and survive (32-36). Reduced-dose involved field radiotherapy has been used in recent years because of the late side effects of radiotherapy. Many studies have reported successful results with combined chemotherapy protocols without RT in childhood HL patients. It has been suggested that the development of secondary malignancies is prevented with this treatment method (35,37-38). We believe that the low rate of secondary cancer in our Hodgkin lymphoma patients is because we do not use involved field radiotherapy and we induce remission with appropriate chemotherapy combinations only. Travis et al. have reported a 6–7-times higher breast cancer risk following radiotherapy to the chest and lung cancer development after mediastinum radiation in Hodgkin lymphoma patients.

There is also an increased secondary cancer risk that does not decrease even 20 years after treatment discontinuation (11, 39). Although the cytotoxic agents used for treatment are known to increase the secondary cancer risk, such an increase has not been seen in our patients. In conclusion, treatment for AML that develops secondarily is difficult and the survival rate is low. Exposure to alkylating agents in the protocols is an important factor in the incidence of secondary AML. Radiotherapy administered in addition the chemotherapy regime in Hodgkin lymphoma is also an important factor that increases the secondary cancer rate. We have seen an increased cancer incidence that results from alkylating agents and a decreased cancer incidence in HL patients treated without radiotherapy. We believe that our 27 years of experience has provided important information regarding the diagnosis and monitoring of childhood cancers.

Conflict of interest

No conflict of interest was declared by the authors.

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