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Late Side Effects of Cancer Therapy

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ABSTRACT

In cancer treatment, control of advanced stage disease and cure chances are increased after the introduction of new agents and combined treatments. Late side effects can be described as the effects that have not been recovering after treatment or developing after completion of treatment. Nowadays, patients who achieve long term cure are increasing therefore, thus many late side effects are more evident. These patients should be evaluated by a multidisciplinary team. Detection and early diagnosis programs should be performed to cancer survivors lifelong. In this rapidly growing population, we need guidelines that follow and describe late side effects objectively about cancer and cancer treatment. In this way, complications of cancer treatment can be detected earlier. By preventing sequelae formation with early treatment, quality of life and long term survival can be improved.

Keywords: Cancer therapy, Chemotherapy, Late side effects

ÖZET

Kanser Tedavisinin Geç Yan Etkileri

Kanser tedavisinde yeni ajanlar ve eş zamanlı tedaviler ile ileri evrelerde dahi hastalık kontrol edilmekte ve kür şansı artmaktadır. Geç yan etkiler tedavi sonrası geçmeyen veya tedavi tamamlanmasından sonra ortaya çıkan etkiler olarak tanımlanır. Günümüzde tedavi sonrası uzun dönem kür elde edilen hasta sayısının artması ile çok sayıda geç yan etki daha fazla dikkat çekmektedir. Bu hastalar multidisipliner bir ekip tarafından takip edilmelidir. Hastalara ömür boyu sürecek tarama ve erken tanı programları uygulanmalıdır. Bu hızla büyüyen grupta, kanser ve kanser tedavisinin takibi ve geç yan etkilerini objektif olarak ortaya koyan kılavuzlara ihtiyacımız vardır. Böylelikle kanser tedavisi komplikasyonlarını erken tespit edebilir, erken tedavi ile sekel oluşumunu engelleyerek hastaların hayat kalitesini ve uzun dönem sağkalımlarını olumlu yönde etkileyebiliriz.

Anahtar Kelimeler: Kanser tedavisi, Kemoterapi, Geç yan etkiler

INTRODUCTION

New therapeutic agents and concomitant therapies introduced in cancer treatment during the last 30 years made cancer a controllable disease with higher cure chances even in advanced stages.[1] Nowadays, survival of more than 5 years in newly diagnosed cancer patients is awaited and the cure rate is 75% in childhood cancers.[2,3] With increasing number of patients obtaining long-term cure, many long-term or late side effects draw more attention. It is predicted that one of every 350 adolescents or young adults and one of every 570 adults with a cancer diagnosis will be a long-term survivor.[4] Because cancer is a difficult-to-treat disease, a desire to have effective therapies overweighs the side effect profile of those treatments. It is known that the desires of optimal survival and efficacy cause ignorance of late side effects of cancer treatment especially in younger patients.

Late side effects are defined as the effects that continue or appear after the completion of treatment. They impair the quality of life (QoL) and cause early mortality.[5,6] Late side effects change according to the age at diagnosis, genetic susceptibility of the patient and treatment regimen (Table 1). Many of them cannot be recognized after the completion of the treatment, however appear during puberty, growth and normal aging. There is at least one observed chronic side effect due to cancer treatment in these patients.[7,8] For this reason, awareness of late side effects is as important as the therapeutic efficacy. However the long-term complications due to cancer treatment are largely ignored by clinicians. In a study conducted in our country, only 53% of side effects due to treatment were recorded. Intensive work-load and not being able to recognize these side effects were reported as the main obstacles against recording them.[9] Most of the information about late side effects of cancer treatment come from the studies on childhood and adolescent cancers.[10,11] These side-effects are increasingly known from the long-term follow-up results of the studies conducted in adults with curable cancers such as breast cancer treated with adjuvant therapies and Hodgkin lymphoma (HL) or testicular cancers.[12,13] Albeit there is no standardised guide, there are commonly used guidelines. In a study of National Cancer Institute (NCI), it has been shown that half of the patients in this group were not followed properly.[6] These patients ought to be followed by a multidisciplinary team through life-long scanning and early diagnosis programs.

Table 1. Late side effects of cancer treatment by treatment modality

Systemic treatment	Radiotherapy
Cardiomyopathy, coronary artery disease, valvular diseases, arryhtmias, pericarditis	Pericardial diseases, cardiomyopathy, coronary artery disease, valvular diseases
Pneumonitis, pulmonary fibrosis, non-cardiogenic pulmonary edema	Pneumonitis, pulmonary fibrosis
GH* deficiency, hypothyroidism, obesity, gonadal insufficiency	Hypothyroidism
Cognitive disorders, peripheral neuropathy, seizures, loss of vision and hearing, neuropathic pain, depression	Cognitive disorders, social problems
decreased GFR**, tubular dysfunction	Infertility, early menopause
Chronic liver injury	Radiation proctitis, gut obstructions
Osteoporosis	Musculoskeletal diseases
Secondary cancer	Secondary cancer

* GH: Growth hormone ** GFR: Glomerular filtration rate

Table 2. Cardiovascular side effects of systemic therapeutic agents

Carditoxicity	Drug
Heart failure	Anthracyclines, mitomycin-C, cyclophosphomide, cisplatin, trastuzumab
Myocardial injury	Flouropyrimidines, cisplatin, vinca alkaloids, bevacizumab, interleukin-2, sunitinib, sorafenib
Thromboemboli	Bevacizumab, paclitaxel, tamoxifen, thalidomide
Myocarditis	Busulfan, cyclophosphamide
Hypotension	Etoposide, thalidomide, interferon, paclitaxel, cetuximab, alemtuzumab, rituximab, ATRA*, interleukin-2
Hypertension	Bevacizumab, cisplatin, interferon

*ATRA: All-trans retinoic acid

Cardiovascular Side Effects

Cardiovascular late side effects of cancer treatment consist of a wide spectrum including cardiomyopathy, coronary artery disease, arrythmias and pericardial disease.[14-17] Anthracycline associated cardiomyopathy is the most studied late side effect. Doxorubicin-associated cardiotoxicity is well known; its incidence is less than 5% and manifests itself with diastolic dysfunction.[18] The reported rate of congestive heart failure (CHF) due to anthracycline cardiomyopathy is 1-2% and it emerges with additional factors such as labor and heavy physical activity.[3,19,20] In a study of patients with acute lymphoblastic lymphoma (ALL), echocardiographic abnormalities were detected in 57% of patients. These effects are prominent especially in patients treated with concomitant chemoradiotherapy.[21,22] Younger age at diagnosis, female gender, cumulative dose of anthracycline (doxorubicin >550 mg/m^2, epirubicin >900 mg/m^2), concomitant use with other cardiotoxic agents, mediastinal or spinal radiotherapy (RT) (especially more than 40 Gy) are the other known risk factors for anthracycline cardiotoxicity in addition to the type of cancer being treated and its treatment protocol.[23] The mechanisms leading to anthracycline cardiotoxicity are not completely understood. Studies and hypotheses on the pathophysiology of anthracycline cardiotoxicity examining oxidative stress with free radical production, apoptosis in myocyte damage and the iron metabolism support that antioxidants may prevent this toxicity. Cardiovascular effects of platinum-based chemotherapy regimens are clear and they may lead to Raynaud-like symptoms and coronary artery disease directly. These regimens increase the negative effects of the known risk factors (e.g. obesity, lipid abnormalities and hypertension) indirectly and may cause atherosclerosis.[24] Other systemic agents may also lead to cardiac toxicity via oxidative stress, coronary artery fibrosis and vasospasm (Table 2).

CHF due to anthracycline treatment and other causes cannot be differentiated clinically. History and physical examination are at the forefront for diagnosis. Electrocardiography (ECG), echocardiography and multigated radionuclide angiography (MUGA) can be used in assessing the cardiac damage.[25] Increased QTc interval in ECG may point out cardiac failure. Decrease by more than 20% in left ventricular ejection fraction (LVEF) or a LVEF lower than 50% of predicted, are diagnostic. Natriuretic peptides have been studied in subclinical left ventricular dysfunction. Endomyocardial biopsy is the gold standard but mostly echocardiography is used as being neither invasive nor expensive. Physical activity is not limited in patients without symptoms or with a decrease equal or less than 20% in basal EF. It is recommended that the total

dose should never exceed the proposed levels. The use of liposomal anthracycline and cardioprotective agents (dextrazoxan, iron chelators) are important especially in higher risk patients, but have limited use. Classical drugs for the treatment of CHF such as ACE inhibitors, beta-blockers, spironolactone and other diuretics are used.

Side effects associated with targeted therapeutic agents are also reported. Trastuzumab cardiotoxicity is the best known and specific one and causes dose-independent type II myocardial dysfunction. It may be reversible upon discontinuation of the drug[26-28], but because of inadequate follow up, it does not have a place in the late side effects; the incidence of cardiotoxicity was found higher than controls only in a 3-years study.[29] In another study[30], there was no increase in cardiac events with trastuzumab used concomitantly with docetaxel or vinorelbine. Trastuzumab should not be combined with anthracyclines. The age of the patient and decrease in EF are known risk factors for cardiotoxicity.[31] Another targeted agent bevasizumab is known to increase the thrombotic tendency and causes hypertension.

Heart is amenable for RT damage and this damage may occur in every part of the heart, especially in pericardium. Coronary heart disease, cardiomyopathy, valve disorders (aortic and mitral insufficiency), pericardial disease can all occur as late cardiovascular side effects of RT. Pericarditis and pericardial effusions are frequent.[32,33] By using modern techniques, the toxicities of RT including cardiac toxicity were decreased after 1985. More than 40 Gy of total RT dose, anthracycline-based chemotherapeutic regimens, the proximity of the irradiated region to heart, less than 18 years of age, history of cardiac disease and longer duration of follow-up are risk factors for late cardiac toxicity due to RT.[34,35] Carotid stenosis and increase in stroke risk are well-known late side effects after head and neck irradiation.[35,36]

Pulmonary Side Effects

Incidence of late pulmonary side effects are less than 10%. They are mainly observed in young patients due to developmental defects in their thoracic wall and pulmonary capacity. Other risk factors include advanced age (>70 years), concomitant or sequential use with RT and concomitant use of drugs with pulmonary toxicities. Interstitial pneumonitis/fibrosis, hypersensitivity reactions and non-cardiogenic pulmonary edema are clinical manifestations of late pulmonary toxicity.[37,38] Morbidity and mortalitiy are especially associated with radiation pneumonitis. Dose-toxicity relationships are especially important in drugs such as bleomycin, busulphan and nitrosurea (BCNU). Pulmonary toxicity associated with taxanes, gemcitabine and etoposide were also reported. Pneumonitis and fibrosis associated with recently introduced targeted agens such as gefitinib, erlotinib and imatinib were reported and may be fatal. Late pulmonary toxicities, e.g. idiopathic pneumonia and bronchiolitis obliterans were seen after stem cell transplantation.[39-41]

Histopathological findings may include endothelial cell damage, hyaline membranes, nodular inflammation areas and fibrosis. Diffuse alveolar damage (bleomycin, busulphan, BCNU, cyclophosphamide, mitomycin-C), non-specific interstitial pneumonia (methotrexate, BCNU), pneumonia organised in the setting of bronchiolitis obliterans (bleomycin, methotrexate, cyclophosphamide) and pulmonary hemorrhage may occur.[37,40]

Diffuse pulmonary fibrosis is prominent with busulphan and may occur anytime after treatment. Diffuse interstitial damage and intraalveolar pattern may be seen radiologically. It is associated with progressive restrictive loss of pulmonary functions and known as 'busulphan lung' but may be associated also with cyclophospamide.

Bleomycin is mainly used in the treatment of pediatric germ-cell tumors and lymphomas. Bleomycin-associated pulmonary toxicity is reported with total doses of more than 200 mg/m^2 and 450 mg/m^2 in children and adults, respectively. Inspiratory rales are heard followed by decreased oxygen capacity. Pulmonary X-ray demonstrates pulmonary infiltrates and diffuse alveolar damage. Toxicity risk increases if bleomycin is used concomitantly with other chemotherapeutic agents or RT.

Pulmonary damage due to RT is often seen in HL treated with mantle or mediastinal RT, sarcomas with lung metastases and brain tumors treated with RT especially in higher (more than 20 Gy) doses. Radiation pneumonitis is a late acute reaction and develops in 1-3 months following RT. It is self-li-

mited generally, but in some cases progresses to pulmonary fibrosis in 6-24 months. Pulmonary fibrosis may result in cor pulmonale and respiratory failure in late stages.[42] High dose chemotherapy and whole-body irradiation increase the risk of pulmonary toxicity also.[43]

Clinical course may be insidious at the beginning with non-productive cough and dyspnea. History and physical examination findings are very important. Fever, tacyhpnea, rales and decrease in chest expansion may occur. Chronic pulmonary diseases, infections, lymphangitic metastases, pulmonary hemorrhage and radiation pneumonitis must be ruled out in differential diagnosis. Radiological findings may be normal but basal linear densities, nodular or interstitial pneumonitis pattern and pleural effusion may be seen. Other diagnostic tests include pulmonary function tests (PFT's), measurement of arterial blood gases and if needed, bronchoscopic or open lung biopsies. PFT's generally show restrictive pattern with decreased diffusion capacity of lung for carbon monoxide (DLCO) and forced vital capacity. The causal drug must be interrupted for treatment. Corticosteroids are the most important agents in the treatment of radiation-related pneumonitis. Bronchodilators may be used for symptomatic relief.

Endocrine Side Effects

Endocrine side effects are common following cancer treatment; an endocrine abnormality is observed in 40% of the patients. While growth hormone (GH) deficiency is frequent in younger ages like childhood, hypothyroidism is the most frequent endocrine side effect following cancer treatment in older ages.[44,45] Younger age groups are more affected. GH deficiency, primary hypothyroidism and primary ovarian failure are the most frequent endocrine side effects. Hypothalamic-pituitary axis, thyroid and gonads are affected following both chemotherapy and RT. Hypothalamus is more commonly affected than pituitary gland. First GH, then gonadotropins and ACTH are affected. While panhypopituitarism is rare, GH deficiency is a frequent complication.[47,48] Other hypothalamic-pituitary dysfunctions especially in childhood tumors contain puberta precox and diabetes insipidus.

GH deficiency following cranial RT is frequent especially before the 4th year of life and dose-dependent. It may develop with low doses such as 18 Gy. GH deficiency causes increase in lipid percentage, decrease in exercise tolerance and in QoL and a disordered lipid profile. GH deficiency, hypothyroidism and retarded skeletal development are responsible for growth retardation. Growth rate is decreased in children with GH deficiency than other children in the same age group whom cannot reach the expected body weight in adulthood. Prepubertal GH replacement may be useful but this response is short-term and the patient cannot reach the expected values in adulthood. GH replacement improves QoL, bodily composition, cardiac side effects and bone mass.[49] Conflicting results were reported about the relationship between GH replacement therapy and the increased relapse risks of brain tumors.[50,51]

Thyroid gland is radiosensitive. Hypothyroidism generally develops following RT to head and neck region. It is a frequent complication after RT in HL, head and neck tumors and spinal RT. It may develop as a secondary complication of hypothalamic-pituitary axis irradiation. Thyroid dysfunction develops mostly in the following 5 years.[52] Hypothyroidism developed in 14-25% of HL patients who received more than 40 Gy and in 9% of ALL patients received more than 24 Gy. The reported incidences of thyroid nodules, Grave's disease, thyroid cancer and Hashimoto thyroiditis were 3.3, 3.1, 1.7 and 0.7%, respectively, in the same patient population. In a study of HL patients treated with RT, the incidence of clinical hypothyroidism was 47% after 26 years following RT.[52] The risk of developing thyroid nodules was 27-fold higher in comparison with the healthy controls. In the same study the relative risk for thyroid cancer was 1.83 in comparison to the general population. Thyroid cancers due to RT are generally well-differentiated papillary cancers.[53] The risk of hyperparathyroidism is also clearly increased in patients received RT to head-and-neck region.[54]

Obesity is another frequent late endocrine side effect in children and is more frequent especially in girls who were treated with cranial RT. Higher frequency in girls was explained with late myelinisation when compared to boys. It is thought that dama-

ge in hunger center, disordered bodily composition and increase in leptin levels have some roles in obesity. Obesity may develop in patients treated with chemotherapeutics.[55] Disordered lipid profile characterised with decreased HDL-cholesterol and increased total cholesterol levels is a frequent metabolic disorder and may lead to early atherosclerosis even in the absence of GH insufficiency. Hyperinsulinemia was linked to increased risk of metabolic syndrome in another study.[56]

Chemotherapy, RT and surgical interventions may have negative effects on the sexual functions and fertility. Gonadal failure may be observed as a complication of cancer treatment. Testes are more predisposed than ovaries. Many chemotherapeutic (especially alkylating) agents have potential to cause gonadal failure. This risk is especially high in pubertal males and cause testosterone insufficiency and decrease in testicular volume due to Leydig cell damage. Females are more sensitive to RT; degree of female gonadal failure is dependent on RT dose and type. ABVD regimen leads to less gonadal failure than MOPP regimen in HL patients and azospermia improves many of the patients treated with ABVD regimen.[57] Hundred percent azoospermia follows even low-dose (2-3Gy) testicular irradiation after 40 months.[58] Retrograde ejection following retroperitoneal lymph node dissection for testicular cancer may influence fertility.[59] Both cranial and abdominal RT may lead to gonadal failure with their effects on hypothalamus-pituitary axis and germ cell function, respectively. Prepubertal males and postpubertal females are more affected than the opposite gender. Reversibility is higher in male gonadal failure.

Similarly, chemotherapy with alkylating agents and RT (ovarian, whole abdominal, craniospinal) may result in dose-dependent amenorrhoea in females. Prebupertal or adolescent females are less sensitive to such effects of chemotherapeutics and RT. Amenorrhea is a frequent late side effect in females especially treated for breast cancer. Pharmacologic ovarian suppression may be used to protect fertilization. In addition, embryo or oocyte/sperm cryopreservation, storage of ovarian tissue and oocyte donation are other fertility preserving techniques. Early menopause is one of the main concerns. In a large study conducted in women treated with abdominal RT and alkylating ages, the mean age for menopause was 31 years. The incidence of congenital malformations was 3-4% in children of patients and there are no major differences between them and general population. The possibility of fertility was reported low however there is no consensus about the rates of spontaneous abortion, low birth-weight and prematurity.[60]

Neuropsychiatric Side Effects

Cognitive and intellectual disorders may be seen especially in patients with ALL and brain tumors who received cranial RT and in patients treated with high-dose intrathecal methotrexate. Dose-dependent memory disorders, attention deficiency, disordered concentration, mental retardation, lower IQ and learning problems were reported in these patients especially with more than 36 Gy dose. In addition female gender, tumor type (e.g. brain tumors) and localization of the tumor, type of surgical intervention and cranial RT in young patients are some of the other risk factors (61). Leucoencephalopathy and microangiopathy were reported in ALL patients who received cranial RT in MRI examinations.[62] Their IQ levels were lower than healthy controls in the same age groups. Neurocognitive disorders are major problems in children who received total body irradiation especially before ages 2-3 and become clear in ages 3-6.

Peripheral neuropathy is a frequent complication following (e.g. vincristine and cisplatin) chemotherapy. Vincristine causes axonal damage, however myeline sheats are protected. Central nervous system is also affected. Neuropathy is one of the most important side effect of paclitaxel and oxaliplatin. Other agents leading to neuropathy include thalidomide, cytarabine (especially in higher doses), methotrexate, ifosfamide, procarbazine and fludarabine. Other complications include epileptic attacks, leucoencephalopathy, visual or auditory losses, motor neuropathy, ataxia and neuropathic pain.[63]

Patients are at long-term risk because of their disease, its treatment and late physical effects. Besides, education, relationship and insurance problems have negative influences on their QoL. Many patients have cognitive problems hindering their integration with social life. Psychiatric problems such as depression, somatization, anxiety, post-traumatic stress disorder are frequent following cancer treatment.

Compliance problems, social phobia, bodily pains with no reason, phobias without reason and tiredness were reported in some patients. They have difficulties in education, getting married or finding a job in comparison with healthy persons of the same age. Suicidal ideation and attempts were reported in a small, however, significant percentage of patients.[64]

Genitourinary Late Side Effects

Renal toxicity is one of the serious late side effects of chemotherapy and manisfests itself with tubular dysfunction and decrease in glomerular filtration rate (GFR). Hypertension, proteinuria, glucosuria, phosphaturia, hypomagnesemia and renal tubular acidosis may develop in these patients. There is magnesium-losing tubulopathy in every patient. Decrease in GFR occurs early but may manifests itself after 10-15 years because of the compensatory hyperperfusion.[65] Renal toxicity is a dose-limiting side effect of platinum-based chemotherapies. If GFR is less than 60 mL/min/1.73 m^2, platinum dose must be decreased or discontinued. Carboplatin is a platinum analogue with similar properties and because it has no metabolites, its nephrotoxic effect is less than cisplatin but is more myelotoxic. However its combination with ifosfamide was conflictingly found more nephrotoxic compared to its combination with cisplatin.[66] Renal, glomerular and tubular toxicity may develop due to cyclophosphamide and ifosfamide. Proximal tubular dysfunction is the most frequent side effect. Mesna can prevent hemorrhagic cystitis and probable late effects during treatment. These are especially frequent with carboplatin-cisplatin (more than 600 mg/m^2) and ifosfamid (more than 60-90 g/m^2). Tubular damage due to chemotherapy may continue months or years; and may lead to Fanconi syndrome. Prior nephrectomy, younger age at diagnosis, RT to renal region, concomitant use of the other nephrotoxic drugs (aminoglycosides, amphotericin B) and previous, but latent renal disease are among the predisposing factors. Probable toxicity must be followed with creatinine clearence.[65,67]

RT to kidney or a nearby localization may lead to renal toxicity, renal failure and hypertension. After a latent period of 3-12 months, these side effects may be apparent. RT more than 15-20 Gy may result in renal artery stenosis, tubular damage and hypertension. Nephrectomised patients diagnosed at younger age with Wilms tumor are at risk. In these patients, radiosensitizing agents (e.g. actinomycine, doxorubicine) may have a role in late renal effects.[68,69]

Bladder fibrosis, renal tubular necrosis and bladder carcinoma are among the other genitourinary complications. High dose ifosfamide-cyclophosphamide, history of hemorrhagic cystitis and longer follow-up periods are reported risk factors for bladder cancer.[70]

Gastrointestinal Side Effects

RT and many chemotherapeutic agents have acute gastrointestinal side effects but their late side effects are rare. Hepatic damage risk is associated with many agents, primarily methotrexate, busulfan and 6-mercaptopurin.[71] Chronic liver damage is incidious and asymptomatic. Continuous low-dose therapy is more risky than high doses given intermittently. Secondary chronic liver damage is infrequent with whole abdominal irradiation except in Wilms patients. Intestinal adhesions and fibrosis, motility disorders, malabsorption, perforation and lactose intolerance may be associated with abdominal RT. Bowel is affected during spinal RT. Transfusions increase viral hepatitis risk; hepatitis C was diagnosed in 4-8% of patients. Patients must be immunised against hepatitis B.

Visual and Auditory Side Effects

Some patients with retinoblastoma and orbital rhabdomyosarcoma are treated with RT. RT decreases bitemporal diameter; besides can cause orbital hypoplasia, decrease in lacrimation, keratoconjunctivitis and ptosis. RT-related retinopathy is more frequently seen with doses more than 40 Gy. In a study of 102 patients with orbital rhabdomyosarcoma, cataract and decreased vision were developed in 82% and 70% of patients, respectively.[72] Cataract may develop with smaller doses also. Cranial RT in some brain tumors and whole body irradiation following bone marrow transplantation may affect eye and orbita.[73]

Hearing loss as a late side effect of cancer treatment may lead to communication and learning difficulties. Platinum-based agents, aminoglycoside antibiotics, loop diuretics and cranial RT may cause loss of hearing through cochlear damage; children are more sensitive. This side effect is more frequent during concomitant treatment with cisplatin and RT

Musculoskeletal Side Effects

Osteoporosis is one of the most important late side effects. It may develop as a consequence of bone metastases, cancer treatment, immobility, gonadal failure and frequently associated with increased morbidity. Chemotherapy, especially with concomitant steroid use, causes trabecular bone loss. Patients with gonadal failure must be carefully evaluated for osteoporosis and must be treated concomitantly with hormone replacement if any evidence is found. The pathophysiology is barely known but decreases in bone turnover and vitamin D levels are potential reasons.[74,75] Bone and muscle atrophy, deformity, fibrosis, osteonecrosis and fractures may be associated with chemotherapy and especially RT. In a study on high-risk ALL patients, avascular necrosis developed in 3 years following the diagnosis in 111 of 1409 (9.3%) patients.[76]

RT is mainly responsible for late side effects in oral cavity (dry mouth) and teeth. These are never seen in patients treated with chemotherapy only. Patients receiving RT to head and neck region are at risk for maxillofacial abnormalities. Calcification, retarded development and caries in affected teeth are important problems. Younger age at diagnosis and higher dose of RT are known risk factors. Mandibular osteonecrosis related to biphosphonates is a relatively recent entity.[77]

Secondary Cancers

New secondary cancers are awaited in 20 years after diagnosis. The risk increases 10-fold in comparison with healthy individuals in the same age groups. Secondary cancers may be related to chemotherapy, RT or both.[78,79] Genetic predisposition and mutagenic effects of cancer treatment have a role in secondary cancer development together or independently. Genetic predisposition and point mutation of p53 gene are the most important causes. In addition, immunosupression, heredity, exposure to carcinogens (tobacco, alcohol) may play roles in the development of secondary cancers.[80,81] Secondary cancers are generally problematic in patients with once succesfully treated cancers with a good prognosis and long survival. Retinoblastoma, HL and soft tissue sarcomas are the most common primary cancers in patients who develop secondary cancers following treatment. Secondary cancer incidence is low in leukemias, especially following ALL. In the first 5 years, hematopoietic and lymphatic system cancers, then solid cancers (brain tumors and carcinomas) are most frequent.[82,83] When RT is added to therapeutic regimen, risk increases. Risk is especially higher in patients treated with higher doses and at younger age at diagnosis.[82] It has been shown that secondary cancers develop in 50% and 25% of patients with Rb gene carriers treated and not treated with RT, respectively.[84] Bone and soft tissue sarcomas, HL, non-Hodgkin lymphomas (NHL), brain, skin, breast and thyroid cancers and leukemias are the most frequent secondary cancers. The latent period in secondary leukemias is longer than the primary ones.

Alkylating chemotherapeutic agents may lead to dose-dependent acute myeloid leukemia (t-AML) and myelodysplastic syndrome (MDS). DNA damage is the direct mechanism. t-AML is very resistant to treatment and has a very low cure chance; its latent period may be 5-7 years. Risk makes a plateau after 10 years. Advanced age, history of splenectomy, concomitant RT, advanced disease, high dose alkylating agents and relapse are among the risk factors. Especially nitrogen mustard and chlorambucil increase AML risk. Using less leukomogenic agents instead of alkylating agents (e.g. nitrogen mustard) decrease t-AML risk.[13,85] In addition, epipodophyllotoxins (etoposide and teniposide) cause t-AML with different characteristics. They inhibit topomerase II and prevent DNA repair. Risk increases with increased total dose. Characteristically, latent period is short in this kind of t-AML and there is no prodromal period. Those leukaemias often belong to M4 or M5 subgroups. There is a translocation including MLL gene and 11q23 band. Risk increases especially with high (more than 5 mg/m^2) doses.[86]

Long-term immunosupression is another cause of cancer. Lymphoproliferative diseases following bone marrow or stem cell transplantation are the best examples. In addition, development of t-AML has been reported in these patients.

Solid tumors are less frequent in patients receiving RT. They develop later and frequently in irradiated parts of the body compared to leukemias. in secondary cancers. Using alkylating agents, especially using with RT, has been reported to cause secondary soft tissue and bone sarcomas. Risk is proportional to dose of alkylating agents. In addition, it has been reported that urothelial cancers are increased in patients treated with cyclophosphamide. Solid tumors related to RT are better characterized. Especially breast cancer following RT in HL is the most common solid tumor in these patients[13,86] and is related to radiation dose. Solid tumors are frequenty seen after a latent period of 8-25 years. Similarly, thyroid cancer is reported following RT in head and neck cancers.

In children of patients with long-term survival; cancers such as retinoblastoma, Wilms tumor, and Li-Fraumeni syndrome may develop; it has been thought that acquired hereditary abnormalities increase the secondary cancer risk but in a study, no difference was found compared to general population.[87]

CONCLUSION

Late side effects of cancer are increasingly seen due to increase in cancer incidence and successful use of combined modality cancer treatment regimens leading to long-term survival chance. These patients are frequently seen by physicians other than oncologists. We need objective guidelines to follow these patients to detect late side effects of cancer treatment. Thus, we can detect the complications of cancer treatment earlier, prevent sequelae with early treatment and improve the patients' QoL and long-term survival.

REFERENCES

1. van Dalen EC, van der Pal HJ, Bakker PJ, et al. Cumulative incidence and risk factors of mitoxantrone-induced cardiotoxicity in children: Asystematic review. Eur J Cancer 40: 643-652, 2004.
2. Carver JR, Shapiro CL, Ng A, et al. ASCO Cancer Survivorship Expert Panel. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 25: 3991-4008, 2007.
3. Ries LA, Percy CL, Berin GR. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program, 1975–1995. In: SEER pediatric monograph. Ries LA, Smith M, Gurray JA et al. NIH publication no: 99-464+9, MD National Cancer Institute; Bethesda, 1999, 1-5.
4. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. JAMA 290: 1583-1592, 2003.
5. Oeffinger KC, Eshelman DA, Tomlinson GE, et al. Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 88: 1687-1695, 2000.
6. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors CA Cancer J Clin 54: 208-236, 2004.
7. Stevens MC, Mahler H, Parkes. The health status of adult survivors of cancer childhood. Eur J Cancer 34: 694-698, 1998.
8. Dickerman JD. The late effects of childhood cancer therapy. Pediatrics 119: 554-568, 2007.
9. Atasoy BM, Unsal DK, Dincbas FO, et al. The results of questionnaire on assessing and reporting of side effects in Turkey: "Turkish Oncology Group (TOG) Early-Late Side Effects Working Party" study. Turkish Journal of Cancer 22: 13-19, 2007.
10. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 22: 4979-4990, 2004.
11. Ganz PA, Hussey MA, Moinpour CM, et al. Late Cardiac Effects of Adjuvant Chemotherapy in Breast Cancer Survivors Treated on Southwest Oncology Group Protocol s8897. J Clin Oncol 26: 1223-30, 2008.
12. 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 20: 3484-3494, 2008.
13. Hudson MM, Tyc VL, Srivastava DK, et al. Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: The protect study. Med Pediatr Oncol 39: 2-11, 2002.

14. Benekli M, Kars A, Guler N. Mitoxantrone induced bradycardia. Ann Intern Med 126: 409, 1997.
15. Gianni L, Herman EH, Lipshultz SE, et al. Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol 26: 3777-3784, 2008.
16. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart 94: 525-533, 2008.
17. Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 324: 808-815, 1991.
18. de Graaf H, Dolsma WW, Willemse PH, et al. Cardiotoxicity from intensive chemotherapy combined with radiotherapy in breast cancer. Br J Cancer 76: 943-945, 1997.
19. Mattioli R, Lippe P, Massacesi C, et al. Long-survival in responding patients with metastatic breast cancer treated with doxorubicin-docetaxel combination. A multicentre phase II trial. Anticancer Res 2004;24:3257-3261.
20. Von Hoff DD, Layard M. Risk factors for development of daunorubicin cardiotoxicity. Cancer Treat Rep 65: 19-23, 1981.
21. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 355: 1757-1770, 2000.
22. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol 20: 4517-4522, 2002.
23. Nuver J, Smit AJ, Sleijfer DT, et al. Left ventricular and cardiac autonomic function in survivors of testicular cancer. Eur J Clin Invest 35: 99-103, 2005.
24. Shan K, Lincoff AM, Young JB. Anthracycline induced cardiotoxicity. Ann Intern Med 125: 47-58, 1996.
25. Ganz WI, Sridhar KS, Ganz SS, et al. Review of tests for monitoring doxorubicin-induced cardiomyopathy. Oncology 53: 461-470, 1996.
26. Tripathy D, Seidman A, Keefe D, et al. Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer. Clin Breast Cancer 5: 293-298, 2004.
27. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. J Clin Oncol 23: 7820-7826, 2005.
28. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breastcancer: NSABP B-31. J Clin Oncol 23: 7811-7819, 2005.
29. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354: 809-820, 2006.
30. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 20: 1215-1221, 2002.
31. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344: 783-792, 2001.
32. Theodoulou M, Seidman AD. Cardiac effects of adjuvant therapy for early breast cancer. Semin Oncol 30: 730-739, 2003.
33. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 42: 743-749, 2003.
34. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 351: 145-153, 2004.
35. Cheng SW, Ting AC, Lam LK, et al. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 126: 517-521, 2000.
36. Haynes JC, Machtay M, Weber RS, et al. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. Laryngoscope 112: 1883-1887, 2002.
37. Villani F, De Maria P, Bonfante V, et al. Late pulmonary toxicity after treatment for Hodgkin's disease. Anticancer Res 17: 4739-4742, 1997.
38. Aisner J, Goutsou M, Maurer LH, et al. Intensive combination chemotherapy, concurrent chest irradiation, and warfarin for the treatment of limited-disease small-cell lung cancer: A Cancer and Leukemia Group B pilot study. J Clin Oncol 10: 1230-1236, 1992.
39. Sleijfer S. Bleomycin-induced pneumonitis. Chest 120: 617-624, 2001.
40. Read WL, Mortimer JE, Picus J. Severe interstitial pneumonitis associated with docetaxel administration. Cancer 94: 847-853, 2002.
41. Granena A, Carreras E, Rozman C, et al. Interstitial pneumonitis after BMT: 15 years experience in a single institution. Bone Marrow Transplant 11: 453-458, 1993.
42. McDonald S, Rubin P, Phillips TL, et al. Injury to the lung from cancer therapy: Clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 31: 1187-1203, 1995.
43. Wilczynski SW, Erasmus JJ, Petros WP, et al. Delayed pulmonary toxicity syndrome following high-dose chemotherapy and bone marrow transplantation for breast cancer. Am J Respir Crit Care Med 157: 565-573, 1998.
44. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 97: 663-673, 2003.

45. Liversey EA, Hindmarsh PC, Brook CG, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 61: 622-625, 1990.
46. Nandagopal R, Laverdiere C, Mulrooney D, et al. Endocrine late effects of childhood cancer therapy: a report from the children's oncology group. Horm Res 69: 65-74, 2008.
47. Lannering B, Marky I, Mellander L, et al. Growth hormone secretion and response to growth hormone therapy after treatment for brain tumour. Acta Paediatr Scan 343: 146-151, 1998.
48. Hancock SL, Cox RS, McDougall IR, et al. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325: 599-605, 1991.
49. Brennan BM, Rahim A, Mackei EM, et al. Growth hormone status in adults treated for acute lymphoblastic leukemia in childhood. Clin Endocrinol (Oxf) 48: 777-783, 1998.
50. Swerdlow AJ, Reddinguis RE, Higgins CD, et al. Growth hormone treatment of children with brain tumours and risk of tumour recurrence. J Clin Endocrinol Metab 85: 4444-4449, 2002.
51. Clayton PE, Shalet SM, Gattameni HR, et al. Does growth hormone cause relaps of brain tumours? Lancet 1: 711-713, 1987.
52. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of hodgkin's disease. N Eng J Med 325: 599-605, 1991.
53. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. Journal of Clinical Endocrinology and Metabolism 85: 3227-3232, 2000.
54. Rao SD, Frame B, Miller MJ, et al. Hyperparathyroididm following head and neck irradiation. Cancer 140: 205-207, 1979.
55. Sklar C, Whitton J, Mertens A, et al. Changes in body mass index and prevelance of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol 127: 91-95, 2000.
56. Talvensaari KK, Lanning M, Tapanainen P, et al. Long term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab 81: 3051-3055, 1996.
57. Santoro A, Bonadonna G, Valagussa P, et al. Lomgterm results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: Superiorty of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 5: 27-37, 1987.
58. Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow-up of testicular fuction following radiation therapy for early stage Hodgkin's disease. J Clin Oncol 7: 718-724, 1989.
59. Narayan P, Lange PH, Fraley EE. Ejaculation and fertility after extended retroperitoneal lymph node dissection for testicular cancer. J Urol 127: 685-688, 1982.
60. Bryne J. Infertility and premature menapouse in childhood cancer survivors. Med Pediatr Oncol 33: 24-28, 1999.
61. Madan-Swain A, Brown RT. Cognitive and pshycosocial sequelae for children with acute lymphoblastic leukemia and their families. Clin Psychol Review 11: 267-294, 1991.
62. Packer RJ, Zimmerman RA, Bilanuik LT. Magnetic resonance imaging in the evoluation of treatment-releated central nervous system damage. Cancer 58: 635-640, 1986.
63. Bottomley SJ, Kassner E. Late effects of childhood cancer therapy. J Pediatr Nurs 18: 126-133, 2003.
64. Recklitis CJ, Lockwood RA, Rothwell MA, et al. Suicidal ideation and attempts in adult survivors of childhood cancer. J Clin Oncol 24: 3852-3857, 2006.
65. Jones DP, Spunt SL, Gren D, et al. Renal late effects in patients treated for cancer in childhood: A report from the Children's Oncology Group. Pediatr Blood Cancer 51: 724-731, 2008.
66. Erdlenbruch B, Nier M, Kern W, et al. Pharmacokinetics of cisplatin and relation to nephrotoxicity in paediatric patients. Eur J Clin Pharmacol 57: 393-402, 2001.
67. Cohen EP, Robbins ME. Radiation nephropathy. Semin Nephrol 23: 486-499, 2003.
68. Rossi R, Kleta R, Ehrich JH. Renal involvement in children with malignancies. Pediatr Nephrol 13: 153-162, 1999.
69. Smith GR, Thomas PR, Ritchey M, et al. Long-term renal function in patients with irradiated bilateral Wilms tumor. National Wilms' Tumor Study Group. Am J Clin Oncol 21 :58-63, 1998.
70. Fairchild WV, Spence CR, Solomon HD, et al. The insidence of bladder cancer after cyclophosphomide therapy. J Urol 122: 163-164, 1991.
71. Perry MC. Hepatotoxicity of chemotherapeutic agents. Semin Oncol 9: 65-74, 1982.
72. Ducrey N, Nenadov-Beck M, Spahn B. Update of orbital rhabdomyosarcoma therapy in children. J Fr Ophtalmol 25: 298-302, 2002.
73. Hoover DL, Smith LE, Turner SJ, et al. Ophthalmic evaluation of survivors of acute lymphoblastic leukemia. Ophthalmology 95: 151-155, 1988.
74. Arikoski P, Kroger H, Riikonen P, et al. Disturbance in bone turnover in children with a malignancy at completion of chemotherapy. Med Pediatr Oncol 33: 455-461, 1999.
75. Kaste SC, Jones-Wallace D, Rose SR et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their devolepment. Leukemia 15: 728-734, 2001.
76. Mattano LA Jr, Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: A report from the Children's Cancer Group. J Clin Oncol 18: 3262-3272, 2000.

77. Kucukzeybek Y, Gourumlu G, Cengiz E, et al. Bisphosphonate (zoledronic acid) associated adverse events: single center experience. UHOD 20: 135-140, 2010.
78. Cecen E, Bolaman Z. Ikincil kanserler. UHOD 20: 190-200, 2010.
79. Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 27: 2356-2362, 2009.
80. Cardous-Ubbink MC, Heinen RC, Bakker PJ, et al. Risk of second malignancies in long-term survivors of childhood cancer. Eur J Cancer 43: 351-362, 2007.
81. Ganz PA. Late effects of cancer and its treatment. Semin Oncol Nurs 17: 241-248, 2001.
82. Demirci U, Bugdayci F, Cakir A, et al. Bilateral breast cancer in a survivor of acute lymphoblastic leukemia: a case report. Med Oncol 27: 481-483, 2010.
83. Neglia JP, Maedows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 325: 1330-1336, 1991.
84. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278: 1262-1267, 1997.
85. Pui C-H, Riberio RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epidophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 325: 1682-1687, 1991.
86. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 25: 1489-1497, 2007.
87. Mulvihill JJ, Myers MH, Connely RR, et al. Cancer in offspring of long-term survivors of childhood and adolescent cancer. Lancet 1: 813-817, 1987.

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