E3. LATE COMPLICATIONS OF HEMATOLOGIC DISEASES AND THEIR TREATMENT.

Hortensia Ioniță[1], Ioana Ioniță[1]
1. University of Medicine and Pharmacy "Victor Babeş", Timişoara

There has been a marked improvement in survival for patients with hematologic malignancies over the past three decades, and the population of long-term cancer survivors continues to grow.

The disease- or treatment-specific subgroups of long-term survivors are at risk for developing adverse outcomes, including premature death, second neoplasms, organ dysfunction (cardiac, pulmonary, gonadal), reduced growth, decreased fertility, impaired intellectual function, difficulties obtaining employment and insurance, and overall reduced quality of life.

Complications observed after hematopoietic cell transplantation (HCT) have a multifactorial origin related to prior cancer therapy, intensity of the preparative regimen, graft-versus-host disease (GVHD), and other posttransplantation complications.

Cardiac Effects

Anthracyclines are causes of late-onset cardiomyopathy, characterized by increased afterload followed by development of a dilated, thin-walled left ventricle, which becomes poorly compliant. Among anthracycline-exposed patients, the risk for cardiotoxicity can be increased by mediastinal irradiation, uncontrolled hypertension, underlying cardiac abnormalities, exposure to chemotherapeutic agents other than anthracyclines and electrolyte imbalances. Risk is increased for survivors who are female, and those who were very young (<5 years old) at the time of therapy.

Chronic cardiac toxicity associated with radiation alone most often manifests as valvular abnormalities, coronary artery disease, pericardial effusions, or constrictive pericarditis, sometimes in association with pancarditis.

Late cardiac dysfunction after HCT is multifactorial in origin. The presence of the conventional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, increased body mass index, physical inactivity, and smoking) could increase the risk for cardiac toxicity in patients already exposed to cardiotoxic agents.

The prevention of cardiotoxicity is a focus of active investigation. Liposome-encapsulated anthracyclines have been explored for their propensity to result in a lower incidence of cardiotoxicity and biopsy results have confirmed a low early cardiotoxicity and the relative safety in clinical use.

Agents such as dexrazoxane, which remove iron from anthracyclines, have been investigated as cardioprotectants. The cardioprotective effects appear to be sex specific, with females showing the greatest protective effect.

Joint recommendations for monitoring long-term survivors of HCT by the European Group for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research/American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT) suggest that cholesterol and high-density-lipoprotein cholesterol (HDL-C) should be checked at least every 5 years for men starting by age 35 years and women starting at age 45. The screening for dyslipidemia should start at age 20 for smokers, patients with diabetes, or patients with a family history of heart disease.

Pulmonary Effects

Compromise of pulmonary function among survivors of hematologic malignancies has been reported after conventional therapy for Hodgkin lymphoma (HL) and leukemia and after HCT. Risk factors include exposure to certain chemotherapeutic agents (bleomycin), radiation to the chest, underlying lung disease, and a younger age at exposure to the pulmonary-toxic therapeutic agents. The toxicities involving the airway and lung parenchyma, including restrictive and chronic obstructive lung disease and bronchiolitis obliterans, are observed after HCT.

The Children Oncology Group Long Term Follow-Up guidelines (COG LTFU) recommend monitoring for pulmonary dysfunction in childhood cancer survivors that includes assessment of symptoms such as chronic cough or dyspnea on annual follow-up and respecting cumulative dosage restrictions of bleomycin and alkylators, limiting radiation dosage and port sizes, and avoidance of primary or secondhand smoke. Pulmonary function tests and chest x-ray examination are recommended for patients at risk.

Joint recommendations for monitoring long-term survivors of HCT by the EBMT/CIBMTR/ASBMT suggest routine clinical assessment at 6 months, 1 year, and annually thereafter; institution of active smoking cessation programs; and pulmonary function tests and focused radiologic assessment at 1 year after allogeneic HCT for patients with signs or symptoms of lung compromise.

Endocrinologic Effects

Thyroid – Patients with hematologic malignancies treated with cranial, craniospinal, or mantle irradiation are at increased risk for thyroid complications. Abnormalities including hypothyroidism, hyperthyroidism, and thyroid neoplasms, have been reported to occur at rates higher than those found in the general population.

Growth – Poor linear growth and short adult stature are complications after successful treatment of hematologic malignancies in childhood. The adverse impact of central nervous system (CNS) irradiation on adult final height among childhood leukemia patients, appear to be related to age and sex, with females and children younger than 8 years at the time of therapy being more susceptible.

Obesity – An increased prevalence of obesity has been reported among survivors of childhood acute lymphoblastic leukemia (ALL). Obesity adversely impacts the overall health status in survivors and is associated with insulin resistance, diabetes mellitus, hypertension, and dyslipidemia. Growth hormone deficiency related to cranial radiation may predispose adult survivors of childhood ALL, particularly females, to abdominal obesity and metabolic syndrome.

Gonadal Dysfunction – Treatment-related gonadal dysfunction has been documented in male and female patients after therapy for hematologic malignancies. Radiation effects on the ovary are age and dose dependent. Reduced sperm production has been observed after testicular doses of 1 to 6 Gy and follows a dose-dependent pattern. Azoospermia has been reported among HL patients with calculated testicular irradiation exposures ranging from 1 to 3 Gy.

Ovarian and testicular damage can also result from chemotherapeutic agents, with alkylating agents showing the strongest association.

Pregnancy Outcomes – Offspring of survivors of childhood hematologic malignancies do not appear to be at increased risks for cancer or congenital malformations. The frequency of premature birth was not related to prior maternal exposure to alkylating agents, but prior exposure to doxorubicin or daunorubicin increased the risk for low birth weight independent of pelvic irradiation history.

Musculoskeletal Effects

Osteonecrosis is a painful and debilitating condition that develops when the blood supply to the bone is disrupted, usually in areas of terminal circulation; with resultant death of bone and cell tissues or disruption of bone repair mechanisms. Osteonecrosis has been reported after conventional therapy for hematologic malignancies, after exposure to dexamethasone between the ages of 10 and 20 years. Osteonecrosis is reported among HCT recipients. The hip joint was the most involved joint (80%); the knee, wrist, and ankle joints were also affected.

Osteopenia or osteoporosis is seen in survivors of hematologic malignancies. Risk factors include therapy with corticosteroids, methotrexate (at higher doses), and cranial irradiation with resultant pituitary insufficiency or gonadal dysfunction. Lifestyle factors that increase the risk for osteopenia include lack of regular weight-bearing exercise, inadequate calcium and vitamin D intake, smoking, and excessive alcohol consumption. Pain or a history of fractures may be the only indication of osteonecrosis or osteoporosis. The COG LTFU guidelines recommend a baseline dual-energy x-ray absorptiometry (DEXA) or quantitative CT scan for survivors 2 or more years following completion of treatment, with repeat studies as clinically indicated.

Neurocognitive Effects

Among survivors of childhood leukemia, neurocognitive late effects represent one of the more studied topics. These patients are prone to problems with receptive and expressive language, attention, and visual and perceptual motor skills, most often manifested as academic difficulties in the areas of reading, language, and mathematics.

The neuropathologic syndromes related to leukoencephalopathy may occur in survivors of childhood hematologic malignancies, including radionecrosis, necrotizing leukoencephalopathy, mineralizing microangiopathy and dystrophic calcification, cerebellar sclerosis, and spinal cord dysfunction, manifesting clinically as ataxia, spasticity, dysarthria, hemiparesis, or seizures.

Many survivors of adult-onset hematologic malignancies also experience impairments of neurocognitive function, including memory loss, distractibility, and difficulty performing multiple tasks. These patients may suffer from mood disturbances and symptoms that compromise their ability to function adequately, including fatigue and pain. HCT survivors are also at risk for neurocognitive late effects.

The adults patients are at risk for developing adverse sequelae related to neuropsychologic functioning, such as slowed reaction time, reduced attention and concentration, and difficulties in reasoning and problem solving; memory impairment; problems with executive functioning and processing spee; and cognitive impairment. Reduced memory function is associated with older age, longer interval since HCT, chronic graft-versus-host disease, and long-term cyclosporine use. Lower education level and poorer social functioning appear to impact cognitive performance.

Joint recommendations for monitoring long-term survivors of HCT by the EBMT/CIBMTR/ASBMT suggest that all recipients of HCT should undergo clinical evaluation for symptoms or signs of neurologic dysfunction at 1 year after HCT.

Other Toxicities

Ocular Effects – Survivors of hematologic malignancies are at risk for the development of cataracts as a consequence of therapy with corticosteroids, cranial irradiation TBI, or busulfan. Factors independently associated with an increased risk for cataract formation were older age (>23 years), allogeneic bone marrow transplantation, higher dose rate, and steroid administration for longer than 100 days. Xerophthalmia may also occur as a late complication because of decreased lacrimation resulting from damage to the lacrimal gland during radiation or, in HCT patients, from chronic GVHD.

Audiologic Effects – Survivors of hematologic malignancies who received platinum chemotherapy, those who had cranial irradiation at a young age, and those who required supportive therapy with aminoglycoside antibiotic are at risk for therapy-related hearing loss. Hearing loss associated with ototoxic agents is sensorineural in origin and is irreversible.

Dental Effects – Children whose teeth have not completely developed at the time of cancer treatment are vulnerable to dental complications, and treatment with chemotherapy during early childhood may result in qualitative problems with enamel and root development. The patients who received radiation therapy involving the head or neck are susceptible to dental complications, manifesting as increased susceptibility to dental caries and gingivitis as a result of diminished salivary gland function.

Hepatic Effects – Acute hepatic dysfunction may be seen with certain chemotherapeutic agents, including antimetabolites and anthracyclines, there has been a low reported incidence of delayed hepatotoxicity in patients receiving these agents.

Second and Subsequent Malignancies

Second or subsequent malignancies are defined as histologically distinct cancers developing after the occurrence of a first cancer. Second malignant neoplasms are one of the most devastating consequences of cancer therapy. Subsequent malignancies are categorized into two major types: therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML) or solid tumors. The latency between diagnosis and treatment of the primary cancer and the development of t-MDS/AML is short, whereas nonhematopoietic malignancies or solid tumors seem to have a longer latency. Female sex, older age at diagnosis, earlier treatment era, HL, and treatment with radiation were identified to increase the risk for subsequent malignancies.

Several host and clinical factors are associated with an increased risk for subsequent malignant neoplasms after HCT. These include age at HCT, pre-HCT exposure to chemotherapy and radiation, exposure to TBI as part of conditioning, infection with oncogenic viruses, prolonged immunosuppression after HCT, autologous versus allogeneic HCT, and original cancer. t-MDS/AML is the major cause of nonrelapse mortality in patients undergoing autologous HCT for patients with a primary diagnosis of HL or NHL.

CNS tumors, the most common second malignancy observed among survivors of childhood ALL, are associated with exposure to cranial irradiation. Secondary thyroid malignancies, typically papillary carcinoma, are associated with radiation exposure to the thyroid gland as part of CNS irradiation, either prophylactic or for treatment of CNS leukemia.

Survivors of HL represent one of the subgroups of cancer survivors who are at a very high risk for secondary cancer, especially for patients who received earlier regimens with predominantly radiation-based therapies.

Breast Cancer – Breast cancer is the most commonly reported second malignancy among female survivors of childhood HL treated with mantle field irradiation, and the risk remains elevated for many decades after exposure.

Thyroid Cancer – Secondary thyroid cancer, the second most common solid tumor reported among survivors of childhood HL, is strongly associated with radiation therapy, occurs more frequently in females. Sex, age at exposure, and time since exposure were identified to be significant modifiers of the radiation-related risk for thyroid cancer.

Central Nervous System Tumors – Radiation is the most important risk factor for the development of a new CNS tumor. There is the dose-response relationship between radiation exposure and development of new primary neoplasms of the CNS. Radiation exposure was associated with increased risk for subsequent glioma and meningiomas.

t-MDS/AML – Several studies have described an increased risk for t-MDS/AML with older age at HCT; Thus t-MDS/AML after autologous HCT is the result of cumulative toxicity that includes pre-HCT chemotherapy (alkylators and topoisomerase II inhibitors), topoisomerase II inhibitors used for stem cell mobilization, and transplantation-related conditioning. The COG LTFU guidelines recommend monitoring for t-MDS/AML with annual complete blood cell count for 10 years after exposure to alkylating agents or topoisomerase II inhibitors.

Most other subsequent malignancies are associated with radiation exposure. Screening recommendations include annual physical examination of the skin and underlying tissues in the radiation field. Screening for early-onset colorectal cancer (radiation doses of 30 Gy or higher to the abdomen, pelvis, or spine) should include colonoscopy every 5 years beginning at age 35 years or 10 years following radiation.

Psychosocial Effects

Survivors of hematopoietic malignancies are at risk for adverse psychosocial outcomes that may affect the overall quality of life, including anxiety, depression, posttraumatic stress disorder, and barriers to accessing the health care system due to problems obtaining health insurance coverage. The impact of cancer therapy on psychosocial functioning is dependent on many variables: intensity and duration of therapy, treatment-related complications, family functioning, developmental processes, and treatment-specific sequelae such as altered cognitive or physical functioning.

Evaluating Survivors for Potential Late Effects

The long-term complications of treatment for which an individual survivor is at risk are determined by several factors: the patient's diagnosis, age at treatment, specific chemotherapeutic agents received, specific radiation fields and doses, therapy-related complications, degree of psychosocial support received, genetic predisposition, and current health-related behaviors (diet, physical activity, tobacco, and alcohol use).

Therapeutic approaches to hematologic malignancies vary widely depending on the patient's age at diagnosis, biologic subtype and staging of disease, year (era) of diagnosis, initial response to therapy, and physician/institutional preference.

Conclusions.

As treatment for hematopoietic malignancies continues to improve, follow-up care for survivors of these diseases must be provided in a comprehensive manner. To minimize treatment-related sequelae and provide early intervention for identified late effects, the risks of long-term complications for each individual survivor must be evaluated.

References

1.Wendy Landier and Smita Bhatia: Late Complications of Hematologic Disease and Their Therapies. Hematology. Basic principles and practice – Ronald Hoffman. 2013; 1452:1469.
2. Fajardo L, Stewart J, Cohn K: Morphology of radiation-induced heart disease. Arch Pathol 1968; 86:512.
3. Prout MN, Richards MJS, Chung KJ, et al: Adriamycin cardiotoxicity in children. Cancer 1977; 39:62.
4. van Dalen EC, Caron HN, Kremer LC: Prevention of anthracycline-induced cardiotoxicity in children: The evidence. Eur J Cancer 2007; 43:1134.
5. 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 2004; 22:4979.
6. Rizzo JD, Wingard JR, Tichelli A, et al: Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: Joint recommendations of the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT). Bone Marrow Transplant 2006; 37:249.
7. Fulgoni P, Zoia MC, Corsico A, et al: Lung function in survivors of childhood acute lymphoblastic leukemia. Chest 1999; 116:1163.
8. Sklar C, Whitton J, Mertens A, et al: Abnormalities of the thyroid in survivors of Hodgkin's disease: Data from the Childhood Cancer Survivor Study. J Clin Endocrine Metab 2000; 85:3227.
9. Sanders JE: Growth and development after hematopoietic cell transplant in children. Bone Marrow Transplant 2008; 41:223.
10. Janiszewski PM, Oeffinger KC, Church TS, et al: Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab 2007; 92:3816.
11. Rowley MJ, Leach DR, Warner GA, et al: Effect of graded doses of ionizing radiation on the human testes. Radiat Res 1974; 59:665.
12. Blatt J: Pregnancy outcome in long-term survivors of childhood cancer. Med Pediatr Oncol 1999; 33:29.
13. Enright H, Haake R, Weisdorf D: Avascular necrosis of bone: A common serious complication of allogeneic bone marrow transplantation. Am J Med 1990; 89:733.
14. Vassilopoulou-Sellin R, Brosnan P, Delpassand A, et al: Osteopenia in young adult survivors of childhood cancer. Med Pediatr Oncol 1999; 32:272.
15. Matsumoto K, Takahashi S, Sato A, et al: —Leukoencephalopathy in childhood hematopoietic neoplasm caused by moderate-dose methotrexate and prophylactic cranial radiotherapyAn MR analysis. Int J Radiat Oncol Biol Phys 1995; 32:913.
16. Meyers CA: Neurocognitive dysfunction in cancer patients. Oncology (Williston Park) 2000; 14:75.discussion 79, 81, 85
17. Holmstrom G, Borgstrom B, Calissendorff B: Cataract in children after bone marrow transplantation: Relation to conditioning regimen. Acta Ophthalmol Scand 2002; 80:211.
18. Matz GJ: Aminoglycoside cochlear ototoxicity. Otolaryngol Clin North Am 1993; 26:705.
19. Castellino S, Muir A, Shah A, et al: Hepato-biliary late effects in survivors of childhood and adolescent cancer: A report from the Children's Oncology Group. Pediatr Blood Cancer 2010; 54:663.
20. Neglia JP, Friedman DL, Yutaka Y, et al: Second malignant neoplasms in five-year survivors of childhood cancer: Childhood cancer survivor study. J Natl Cancer Inst 2001; 93:618.

21. Padovan CS, Yousry TA, Schleuning M, et al: Neurological and neuroradiological findings in long-term survivors of allogeneic bone marrow transplantation. Ann Neurol 1998; 43:627.