Korean Journal of Pediatrics Vol. 53, No. 4, 2010
DOI : 10.3345/kjp.2010.53.4.477
■ Review article ■

Late physical effects of childhood cancer survivors

Young-Ho Lee, M.D.

Department of Pediatrics, Hanyang University College of Medicine, Seoul, Korea

= Abstract =

Advances in research and medical and supportive care have contributed to a growing population of adults formerly treated for childhood cancer. History of cancer and its therapy can have significant life-long health implications. Late effects of cancer therapy can be insidious on onset, occur outside the pediatric age, and contribute to premature morbidity and mortality. In this review, I have focused on the key long-term effects of pediatric cancer therapy, particularly on the metabolic syndrome, including cardiopulmonary complications, infertility, and secondary neoplasm. (Korean J Pediatr 2010;53:477-480)

Key Words : Late effects, Childhood cancer survivors

Introduction

With recent advances in medical care, including co-operative clinical trials and improved supportive care, there has been a remarkable improvement in the overall survival rates of children with cancer. Recently, the childhood cancer survival rate is approximately 80%[1]. Over time, after the completion of their treatment, cancer survivors are lesslikely to return to their initial cancer center for follow-up examinations[2, 3]. Childhood cancer survivors frequently lack detailed knowledge of their prior diseases do not undergo appropriate screening based on their prior exposures and ongoing risks[4]. However, according to the estimate of the Childhood Cancer Group in United States, 73% of childhood cancer survivors will develop at least 1 chronic physical health condition and 42% will develop a severe, life-threatening, or disabling condition or die from a chronic condition[2]. All childhood survivors should therefore have regular medical checkups throughout their lives. To provide effective care, a summary of treatments and a list of possible late effects need to be provided to survivors, their care-givers and primary health care providers once active cancer treatment has ceased.

Received: 7 March 2010, Accepted: 18 March 2010
Corresponding Author: Young-Ho Lee, M.D., Ph.D.
Department of Pediatrics, Hanyang University College of Medicine, #17, Haengdang-Dong, Seongdong-Gu, Seoul 133-792, Korea
Tel: +82.2-2290-8383, Fax: +82.2-2297-2380
E-mail: cord@hanyang.ac.kr
This work was supported by the research fund of Yuhan Pharmaceutical Company

In Korea, standardized and organized treatment for childhood cancer has been started from the late 1970s, and approximately 1,200 children have been diagnosed with cancer every year. We estimate that there are over 20,000 childhood cancer survivors alive today, with the prevalence increasing to nearly 1 in 800 young adults aged 16-45 years. Therefore, physicians as well as survivors and their families should have profound concerns regarding their physical health and social adjustment. This review focuses on the major long-term effects of pediatric cancer therapy, such as metabolic syndrome, cardiopulmonary complications, infertility, and secondary neoplasm.

Metabolic syndrome

Recently, the classification systems correspond with respect to the core components such as dyslipidemia, hypertension, central obesity, and insulin resistance. These could be important risk factors for developing cardiovascular diseases and type 2 diabetes mellitus. The most recently proposed criteria for metabolic syndrome emphasize the role ofcentral obesity and support the hypothesis that visceral adipose tissue is causally associated with the syndrome[5, 6]. In contrast with subcutaneous fat, visceral adipose tissue might directly lead to metabolic syndrome because of its hyperlipolytic stateand the contribution of excess free fatty acids to insulin resistance.

The increasing prevalence of obesity in the general population probably contributes to the increased prevalence of the metabolic syndrome in developed countries. At least

25% of adults in the Americas and Europe have the syndrome[7], which is associated with a two-times increased risk for cardiovascular events. It further raises the risk for type 2 diabetes by about 5-fold[8]. Trimis et al[9] found a 2-fold increased prevalence of the metabolic syndrome in patients treated with chemotherapy only and a 5-fold increased prevalence in patients treated with chemotherapy and radiotherapy, in comparison with the normal population. Otherinvestigators found metabolic syndrome is prevalent in 12.6-39% of childhood cancer survivors[10]. To date, very limited studiesin Korea have focused on the possible relationship between the treatment of childhood cancer and an increased risk of developing metabolic syndrome[11-13]. Moreover, most of these studies only include components of metabolic syndrome, such as obesity, or endocrine abnormalities.

A possible explanation for the increased risk of metabolic syndrome in cancer survivors might be a deficiency in growth hormone (GH). Children and adults who are GH deficient for other reasons are more likely to be obese. Moreover, increased total cholesterol, low-density lipoprotein (LDL)-cholesterol, apo-B, triglycerides and lipoprotein (a) levels, and normal or decreased high-density lipoprotein (HDL)-cholesterol and apo-A levels were found in GH deficient patients[14-18]. In addition, increased peripheral insulin resistance and impaired glucose tolerance were observed in these participants[19]. GH deficiency may be caused by direct pituitary or hypothalamic damage resulting from cranial irradiation. Hypothalamic damage may be a potential cause of insensitivity for leptin, a hormone involved in the regulation of appetite and metabolism. Subsequently, insensitivity for leptin can, in itself, cause obesity. GH deficiency could develop in survivors who had been treated with chemotherapy only. This phenomenon might be explained by the chemotherapy crossing the blood-brain barrier in combination with individual susceptibility[20].

Thyroid dysfunction has been described after chemotherapy and radiotherapy. Decreased effect of thyroid hormone can cause increased levels of total cholesterol and LDL-cholesterol and a possible change in HDL-cholesterol owing to a change in metabolicclearance. In addition, hypothyroidism may result in insulin resistance as well as fatigue and loss of energy, contributing to the increase in weight. Gonadal dysfunction has also been described mainly after treatment with alkylating agents and gonadotoxic drugs or radiotherapy[21]. Gonadal hormone deficiency could also induce obesity, which subsequently induces insulin resistance and other components of the metabolic syndrome. Other factors of metabolic syndrome in long-term survivors are reduced physical activity or a sedentary lifestyle, which can contribute to obesity.

Therefore, the thorough and periodic investigations for endocrine abnormalities in childhood cancer survivors are essentialand very important for early prevention and treatment of the metabolic syndrome as well as associated sequelae. In addition, the treatment of metabolic syndrome should include weight loss by increased physical activity and an appropriate diet.

Cardiovascular effects

Cardiovascular disease can be a significant complication after chemotherapy and radiotherapy. While the metabolic syndrome could significantly increase the risk of cardiovascular disease in cancer survivors, most cardiovascular damage is the result of direct effects of chemotherapy, such as anthracyclines, or radiotherapy. The anthracyclines (e.g., doxorubicin, daunorubicin, idarubicin, epirubicin, etc.) are some of the most commonly used and effective agents for childhood cancers. Unfortunately, their effects upon the myocardium can be harmful, asymptomatic, and progressive. Cardiomyopathies may occur acutely or years after exposure and have been reported at any dose, however, the risk of congestive heart failure increases 11-fold at doses over 300 mg/m^2. The radiation delivered to the heart is also a risk factor for late onset cardiac disease. The risk of dying because of cardiac diseases was significantly higher in individuals who received an average radiation dose that exceeded 5 Gy to the heart. A linear relationship was found between the average dose of radiation administered to the heart and the risk of cardiac mortality[22]. These results of previous studies aimed at preventing anthracycline-induced cardiotoxicity in children can only advise care providers to monitor the cardiac function of children treated with anthracyclines carefully. The use of the cardioprotectant dexrazoxane may be justified in children if there is a high risk of cardiac damage[23].

Pulmonary effects

The risk of pulmonary conditions is more than 3 times higher in cancer survivors than in their siblings, as manifested by pulmonary signs (abnormal chest wall growth), symptoms (chronic cough, use of supplemental oxygen,or exercise-induced shortness of breath), or specific diagnoses (lung fibrosis, recurrent pneumonia, pleurisy, bronchitis, recurrent sinus infection, or tonsillitis). A number of chemotherapeutic agents (e.g., bleomycin, carmustine, etc.) together with radiation affect pulmonary function, usually with a restrictive disease. The lungs are particularly sensitive to radiation, and pulmonary problems occur most often in patients with malignant diseases of the chest treated with radiation. Clinically apparent pneumonitis with cough, fever, or dyspnea generally occurs only in survivors who received more than 30 Gy in standard fractions to more than 50% of the lung. The lungs receive some radiation even when they are not the target, such as in patients with malignant brain tumors, and this exposure can contribute to the development of lung disease, although these patients are likely to have no symptoms during day-to-day activities. Innovations in targeted radiation delivery (e.g., conformal radiation) should further limit damage to normal lung tissue. Although clinically apparent bleomycin pneumopathy is most frequent in older adults, interstitial pneumonitis and pulmonary fibrosis have been reported in children. Usually, the abnormalities began within 3 months of therapy and persisted or progressed. The alkylating agents such as carmustine, cyclophosphamide, melphalan, busulfan, and methotrexate have also been associated with chronic pneumonitis and fibrosis[24].

Fertility effects

Fertility outcomes are generally effective for boys treated for leukemias and most solid tumors. Radiation to the testes results in germinal loss with decrease in testicular volume and sperm production, and increase in follicle-stimulating hormone (FSH). Spermatogenesis can be recovered in patients treated with less than 3 or 4 Gy. Radiation therapy may also be toxic to Leydig cells, which results in delayed sexual maturation, at doses higher than those that are toxic to germ (Sertoli) cells. After exposure to alkylating agents in prepubertal boys, normal pubertal progression and normal adult levels of testosterone can be expected. However, it is important to remember that spontaneous progression through puberty does not equate to normal fertility[25]. Therefore, when indicated, the assessment of male pubertal development and fertility (semen analysis) is warranted.

Germ cell failure and loss of ovarian endocrine function occur concomitantly in females. Most girls who receive chemotherapy alone will retain their fertility. However, they may be at increased risk of a premature menopause and require hormone therapy. In contrast, after myeloablative doses of alkylating agents, including busulfan and cyclophosphamide, permanent ovarian failure can be expected at all ages[26].

Secondary neoplasms

Among children treated for cancer, the cumulative incidence of a subsequent neoplasm has been estimated to be 3-5% at 20 years from the original diagnosis, a 3- to 6-fold increased risk over those without a history of cancer[27]. The more commonly reported second cancers in childhood cancer survivors are breast, thyroid, and bone cancers, and therapy-related myelodysplasia and acute myeloid leukemia[28].

Conclusion

Childhood cancer survivors are vulnerable to adverse health outcomes, which may not become apparent until years after therapy. These events may manifest well in adulthood when these individuals rarely return to their initial cancer center or seek preventive medical care. Risk- based follow-up can offer early detection and/or intervention and provides an opportunity to reduce cancer-related morbidity and mortality.

References

1) Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009; 8:784-96.
2) Oeffinger KC, Mertens AC, Hudson MM, Gurney JG, Casillas J, Chen H, et al. Health care of young adult survivors of

childhood cancer: A report from the Childhood Cancer Survivor Study. Ann Fam Med 2004;2:61-70.
3) Kadan-Lottick NS, Robison LL, Gurney JG, Neglia JP, Yasui Y, Hayashi R, et al. Childhood cancer survivors knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. JAMA 2002;287:1832-9.
4) Nathan PC, Greenberg ML, Ness KK, Hudson MM, Mertens AC, Mahoney MC, et al. Medical care in long-term survivorsof childhood cancer: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2008;26:4401-9.
5) Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition: A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469-80.
6) Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881-7.
7) Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008;28:629-36.
8) Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403-14.
9) Trimis G, Moschovi M, Papassotiriou I, Chrousos G, Tzortzatou-Stathopoulou F. Early indicators of dysmetabolic syndrome in young survivors of acute lymphoblastic leukemia in childhood as a target for preventing disease. J Pediatr Hematol Oncol 2007;29:309-14.
10) van Waas M, Neggers SJ, van der Lelij AJ, Pieters R, van den Heuvel-Eibrink MM. The Metabolic Syndrome in Adult Survivors of Childhood Cancer, a Review. J Pediatr Hematol Oncol 2010 Mar 11. [Epub ahead of print]
11) Ko MS, Kim JY, Lim YJ, Lee YH, An HS, Yoo JH, et al. Patterns of obesity during anticancer chemotherapy in children with acute lymphoblastic leukemia. Korean J Hematol 2008;43:77-82.
12) Lee YJ, Kim YH, Hah JO. Prevalence of obesity and cardiovascular risk factors in survivors of childhood acute lymphoblastic leukemia. Korean J Pediatr Hematol Oncol 2003;10:198-205.
13) Lee JH, Seo HJ, Kim JY, Ko CW, Lee KS. Late endocrine complications in childhood cancer survivors. Korean J PediatrHematol Oncol 2005;12:55-62.
14) Boot AM, Engels MA, Boerma GJ, Krenning EP, De Muinck Keizer-Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. J Clin Endocrinol Metab 1997;82:2423-8.
15) Binnerts A, Deurenberg P, Swart GR, Lamberts SW. Body composition in growth hormone-deficient adults. Am J Clin Nutr 1992;55:918-23.
16) de Boer H, Blok GJ, Voerman HJ, Phillips M, Schouten JA. Serum lipid levels in growth hormone-deficient men. Metabolism 1994;43:199-203.
17) Angelin B, Olivecrona H, Ericsson S, Rudling M. Growth hormone and low-density lipoproteins. Acta Endocrinol 1993;128(Suppl 2):26S8S.
18) Eden S, Wiklund O, Oscarsson J, Rosén T, Bengtsson BA. Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. Arterioscler Thromb 1993;13:296-301.
19) Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA. Growth hormone deficient adults are insulin-resistant. Metabolism 1995;44:1126-9.
20) Roman J, Villaizan CJ, Garcia-Foncillas J, Azcona C, Salvador J, Sierrasesúmaga L. Chemotherapy-induced growth hormone deficiency in children with cancer. Medical Pediatr Oncol 1995;25:90-5.
21) Stava CJ, Jimenez C, Vassilopoulou-Sellin R. Endocrine sequelae of cancer and cancer treatments. J Cancer Surviv 2007;1:261-74.
22) Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol 2010;28:1308-15.
23) van Dalen EC, Caron HN, Kremer LC. Prevention of anthracycline-induced cardiotoxicity in children: The evidence. Eur J Cancer 2007;43:1134-40.
24) Liles A, Blatt J, Morris D, Wardrop R 3rd, Sharma A, Sznewajs A, et al. Monitoring pulmonary complications in long-term childhood cancer survivors: Guidelines for the primary care physician. Cleve Clin J Med 2008;75:531-9.
25) Bhatia S, Constine LS. Late morbidity after successful treatment of children with cancer. Cancer J 2009;15:174-80.
26) Sanders JE, Buckner CD, Leonard JM, Sullivan KM, Witherspoon RP, Deeg HJ, et al. Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. Transplantation 1983;36:252-5.
27) Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: Findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27:2356-62.
28) Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkins disease. N Engl J Med 1996;334:745-51.