Seminars in Hematology 53 (2016) 209–215

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/enganabound

Hodgkin lymphoma: Late effects of treatment and guidelines for surveillance

Andrea K. Ng[a], Flora E. van Leeuwen[b,*]

[a] Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
[b] Department of Epidemiology, Division of Psychosocial Research & Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands

ARTICLE INFO

Available online 19 May 2016

Keywords:
Hodgkin lymphoma
Late effects
Second malignant neoplasms
Cardiovascular disease

ABSTRACT

Long-term survivors of Hodgkin lymphoma (HL) are at risk for a range of late effects, with second malignant neoplasm and cardiovascular diseases being the leading causes of death in these patients. The excess risks remain significantly elevated decades after treatment, and are clearly associated with extent of treatment exposures. Other late effects have also been identified, such as pulmonary dysfunction, endocrinopathies, muscle atrophy, and persistent fatigue. Systemic documentation of late effects and recognition of treatment- and patient-related risk factors are important, as they inform optimal surveillance and risk-reduction strategies, as well as guide therapeutic modifications in newly diagnosed patients to minimize treatment-related complications. As HL therapy evolves over time, with adoption of novel agents and contemporary treatment techniques, late effect risks and follow-up recommendations need to be continuously updated.

1. Introduction

After the introduction of modern radiotherapy (RT) and combination chemotherapy (CT) in the 1960s, Hodgkin lymphoma (HL) has become the prototype of a curable malignancy [1]. However, over the past decades it has been clearly demonstrated that both RT and CT can increase the risk of second malignant neoplasms (SMNs), cardiovascular disease (CVD), and other treatment complications [1–4]. Excess mortality from SMNs and CVD has been demonstrated to substantially reduce the life expectancy of HL survivors [5,6].

2. Risk of second malignancy

Increased risks of solid tumors in irradiated HL patients and of leukemia in CT-treated patients have been reported consistently in the literature [4,7]. In a recent study that included HL patients treated from 1965 to 2000 [8], the excess risk of second malignancy remains significantly increased beyond 35 years after HL treatment (Fig. 1), with a 40-year cumulative incidence of second cancer estimated at 43.6% (Fig. 2). The largest standardized incidence ratios (SIRs) are observed for leukemia (SIR 10–30), followed by connective tissue, pleura and thyroid cancer, and non-Hodgkin lymphoma (SIR 6–20) [8–10]. Moderately increased risks (SIR 2–7) are observed for a large number of solid tumors, such as cancers of the lung, breast, stomach, esophagus, colon/rectum, cervix, mouth and pharynx, and melanoma [8–12]. Absolute excess risk (AER) is the best risk measure to express burden of disease. HL patients experience an excess of about 85–125 malignancies per 10,000 patients per year, over and above the background rate. Solid tumors account for the large majority of excess cancers (60–100 per 10,000 patients per year), and, of those, breast and lung cancer account for the largest proportion of excess malignancies [4,6,8–13].

The SIR of solid tumors is minimally elevated in the 1- to 4-year follow-up period, but becomes significantly increased from 5 to >20 years since first treatment [8,11–14]. For several tumor sites (breast, thyroid, esophagus), the excess risk does not become apparent until after 10–15 years of observation. Hodgson et al [10] modeled relative risks (RRs) and found no indication for increasing or decreasing RRs beyond 10 years of follow-up. Due to the rising background incidence of cancer with age, long-term survivors experience strongly increasing AERs of solid malignancy.

The literature uniformly shows that the SIRs of various solid tumors increase strongly with younger age at first treatment [8–10,15]. The effect is strongest for breast cancer [11,12]. Both for breast and non-breast solid malignancies AERs strongly

* Corresponding author: Department of Epidemiology, Division of Psychosocial Research & Epidemiology Netherlands, Cancer Institute Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31-20 512 2483 / 2480; fax.: +31-20 512 2322.
E-mail address: f.v.leeuwen@nki.nl (F.E. van Leeuwen).

http://dx.doi.org/10.1053/j.seminhematol.2016.05.008
0037-1963/$/

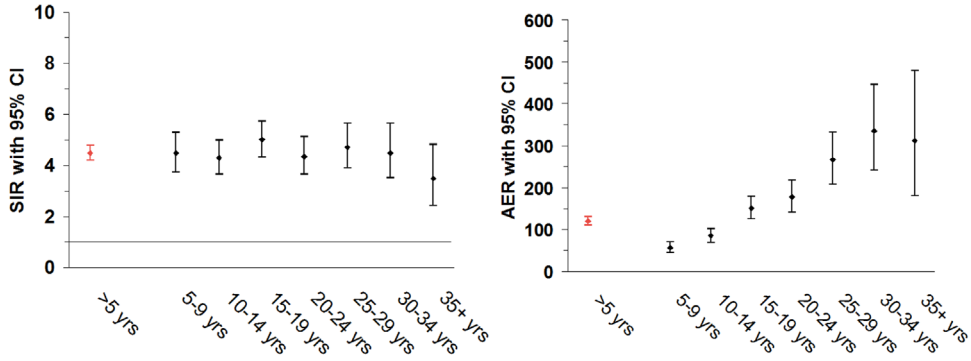

Fig. 1. Risk (SIR and AER) of new malignancies after Hodgkin lymphoma according to follow-up interval.

increase with older attained age, indicating the increasing burden of excess cancers with advancing age of HL survivors [8,10,11]. Thirty years after treatment, at attained ages of ≤51 years, the cumulative incidence of breast cancer in survivors treated before age 21 was as high as 26% [12,15].

While alkylating CT is the main cause of acute myeloid leukemia after HL, elevated risks of solid cancers following HL have been largely attributed to RT [4,6,9,10]. For a number of solid malignancies (lung, breast, stomach, pancreas) the risk has been shown to increase strongly and linearly with higher RT doses [16–20]. For example, compared to a dose of less than 4 Gy to affected breast site, the relative risk of breast cancer rises from 4.1 for 7–23 Gy to an 8.0-fold increase for more than 40.5 Gy [17]. For lung cancer, the increased RRs from smoking appeared to multiply the elevated risks from RT (Table 1) [21], implying that there are large absolute excess risks for lung cancer among irradiated patients who smoke, while non-smokers experience little excess risk from radiation [19,22]. For breast cancer, it has been shown that smaller radiation volumes than mantle field are associated with substantially lower risk [8,13,15], which is important in view of the smaller field sizes currently used in HL treatment. Furthermore, alkylating CT and pelvic RT appear to reduce the risk of RT-associated breast cancer, due to the high frequency of premature menopause after CT [8,13,15–17]. A long versus short duration of intact ovarian function after radiation was a strong predictor of subsequent breast cancer risk. Women with less than 10 years of intact ovarian function after RT had a 70% decreased risk of breast cancer compared with women with 10–20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after RT had 5.3-fold increased risk of breast cancer [15]. These results indicate that ovarian hormones are a crucial factor to promote breast tumorigenesis once RT has produced an initiating event.

Several studies have observed that alkylating CT can also significantly increase the risk of solid malignancy, in particular

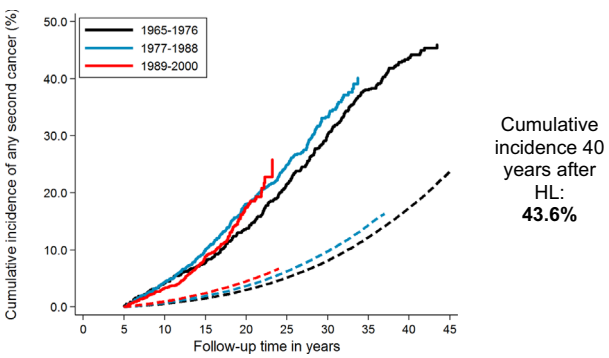

Fig. 2. Cumulative incidence of solid malignancy after Hodgkin lymphoma according to calendar period of treatment.

lung cancer risk [19,23] but also of stomach and pancreatic cancer [8,18,20]. While additive effects of CT and RT have been observed for lung cancer [19], supramultiplicative effects were recently reported for stomach cancer. RT doses to the stomach of ≥25 Gy combined with exposure to high-dose procarbazine (≥5,600 mg/m^2) were associated with a 78-fold increased risk of stomach cancer, compared to RRs of 2.8 and 1.2 for exposure to ≥25 Gy of radiation alone and exposure to high-dose procarbazine (≥5,600 mg/m^2) alone, respectively [18].

A recent study examined whether HL patients treated in the 1989–2000 period, when less toxic treatments had been introduced, had a lower risk of second malignancy than patients treated in the 1965–1988 [8]. While the cumulative incidence of leukemia was significantly lower in the most recent treatment era, no such decrease was observed for solid malignancies, even though smaller RT volumes were associated with lower risk, especially for breast cancer. The surprising absence of a declining overall risk of solid malignancy was attributed to a number of factors, such as later than expected wide application of changes in RT policy, screening for breast cancer, and changes in chemotherapy regimens.

3. Risk of cardiovascular disease

Both RT involving the heart and anthracycline-containing CT can increase the risk of CVD in HL survivors. Radiation-induced CVD includes coronary heart disease (CHD), valvular heart disease (VHD), myocardial dysfunction, electrical conduction abnormalities, and pericardial disease [2,24]. Anthracyclines can, depending on the cumulative dose, lead to both acute cardiomyopathy and chronic cardiac complications (especially HF) [25–27]. RT- and anthracycline-associated cardiac damage have a different pathogenesis, which also appears to differ from the general population. Radiation may damage the endothelium of blood vessels [28]. In large arteries this damage may lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism [29]. Animal studies have shown that radiation predisposes to the formation of unstable plaques, that are more likely to rupture and cause a fatal heart attack or stroke. Cardiotoxicity following anthracyclines is typically associated with loss of myocardial mass, leading to progressive cardiac remodeling and dysfunction [24].

Prospective screening studies among HL survivors demonstrate that clinically significant cardiovascular abnormalities, like coronary artery stenosis, coronary artery calcifications, reduced left ventricular dimensions, VHD, and conduction defects, are very common, even in asymptomatic survivors [30–33].

Large cohort studies of HL survivors show a two- to sevenfold increased risk of cardiac death (mainly myocardial infarction [MI]), depending on the age of the patients (stronger risk increases for RT at younger ages), treatment regimens used, and follow-up time [6,34–37]. Furthermore, three- to sixfold increased SIRs of CHD,