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Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma

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The authors declare no competing financial interest related to this work.

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Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma

Despite high cure rates, life expectancy and quality of life of Hodgkin lymphoma (HL) survivors are often reduced by the occurrence of late adverse effects of treatment. Common late effects include second malignancies (Schaapveld *et al*, 2015), cardiovascular disease (Maraldo *et al*, 2015), thyroid dysfunction, reduced fertility, premature menopause, fatigue and psychosocial problems. Most HL survivors experience one or more physical and/or psychosocial effects. While HL generally occurs at young (adult) ages and survivors potentially have a long life expectancy, structured survivorship care for HL survivors is lacking. A well-organized survivorship care programme may prevent late adverse treatment effects or detect them early (McCabe *et al*, 2013; Barbui *et al*, 2014). In the Netherlands, the BETER consortium (*B*etter care after Hodgkin lymphoma: *E*valuation of long-term *T*reatment *E*ffects and screening *R*ecommendations) developed a nationwide structured survivorship programme for 5-year HL survivors with the aim to reduce morbidity and mortality from late effects. The consortium consists of haemato-oncologists, radiation oncologists, epidemiologists and nursing specialists from 31 hospitals throughout the country, as well as a general practitioner and patient representatives (Appendix S1). The following steps were taken.

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Table I. BETER consortium screening recommendations for late adverse effects after treatment for Hodgkin lymphoma

Late adverse event	Subgroup of HL survivors	Risk (Ng & Van Leeuwen, 2016)	Screening	Prevention	Treatment of late adverse effects
Breast cancer	Women treated with RT on chest and/or axillae before age 40 years	SIR 2–7	Age 25–30 years: annual clinical breast examination and MRI Age 30–60 years: annual clinical breast examination, mammography and MRI Age 60–70 years: biennial clinical breast examination and mammography Age 70–75 years: biennial mammography through population screening	Breast self-examination is optional Prophylactic mastectomy can be considered in very-high risk women (treated with RT on chest and/or axillae before age 20 years)	Take previous chest RT for HL into account Consider risk of cardiomyopathy when using anthracyclines
Cardiovascular disease	Cardiotoxic CTb: cumulative doses equivalent to doxorubicin ≥300 mg/m^2 RT to the mediastinum RT to the mediastinum in combination with cardiotoxic CTb, independent of cumulative dose	SIR 2–7	Every 5 years, up to age 70 years: Medical history Physical examination Blood tests: lipid spectrum, glucose, biomarkers (BNP or NTproBNP) as a reference for follow-up Cardiac ultrasound only once 15 years after diagnosis in case of RT to mediastinum and every 5 years in case of cardiotoxic CTb (with/without mediastinal RT) ECG (once as a reference)	Lifestyle recommendations	In accordance with general population
Thyroid dysfunction	RT to the thyroid region	AR 44–67% after 25 years	Every 1–3 years: palpation of the thyroid gland Annual laboratory examination: TSH; if abnormal FT4	None	In accordance with general population
Neck muscle complaints	RT to the neck and/or shoulders	AR 20–85% after 10–30 years	Every 3 years: physical examination	None	Options are limited
Fertility problems and premature menopause (women)	Alkylating CT before age 40 years RT on ovarian region before age 40 years	AR 25–50% after 5–25 years	During first visit, later if indicated: 1 Medical history 2 Physical examination 3 Blood tests: LH, FSH, oestradiol for menopausal status	Provide information about a possibly limited fertility span	Consider limiting use of hormone replacement therapy after RT on breast and/or axillae
Fertility problems (men)	Alkylating CT RT close to testicular region	AR 50–90% >5 years after alkylating CT AR 10% >5 years after RT on testicular region	During first visit, later if indicated: 1 Medical history 2 Physical examination 3 Blood tests: testosterone if hypogonadism is suspected	Provide information about limited fertility	Analyse semen Referral to a fertility clinic

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Table I. (*Continued*)

Late adverse event	Subgroup of HL survivors	Risk (Ng & Van Leeuwen, 2016)	Screening	Prevention	Treatment of late adverse effects
Osteoporosis	Alkylating CT RT on ovarian/testicular region Premature menopause	AR 21%, 5 years after premature menopause	During first visit, later if indicated: 1 Blood tests: vitamin D 2 DEXA scan	Lifestyle recommendations	In accordance with general population
Overwhelming post-splenectomy infections	Splenectomy Splenic RT (mean dose >20 Gy) Stem cell transplant	RR up to 20	None	Vaccinations: 1 Pneumococcus 2 Haemophilus Influenzae B: once 3 Meningococcus: once 4 Influenza: annual Medical alert cardTravel advice	Antibiotics on demand
Pulmonary disease	RT on chest CT (bleomycin, carmustine)	AR 10–45% after 5–18 years	None	No smokingPhysical exerciseUse high doses of oxygen with caution (anaesthesia, scuba diving)	In accordance with general population

AR, absolute risk; CT, chemotherapy; DEXA, dual energy X-ray absorptiometry; ECG, electrocardiogram; FSH, follicle-stimulating hormone; FT4, free tetra-iodothyronine; HL, Hodgkin lymphoma; LH, luteinizing hormone; MRI, magnetic resonance imaging; (NTpro)BNP, (N-terminal pro-) brain natriuretic peptide; RR, relative risk; RT, radiotherapy; SIR, standardized incidence ratio; TSH, thyroid-stimulating hormone.

†Cardiotoxic CT: doxorubicin, epirubicin, rubidomycin, daunorubicin, mitoxantrone.

‡Start with Prevenar-13, 2 months later followed by Pneumovax-23; repeat Pneumovax-23 once after 5 years.

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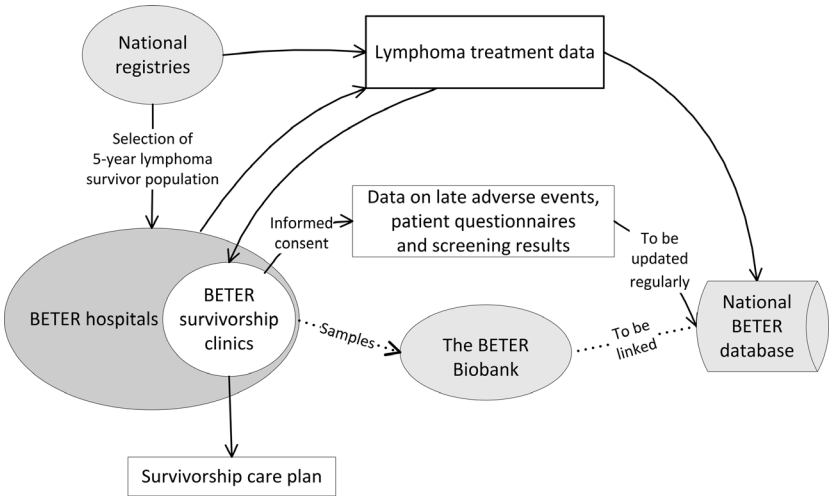

Fig 1. Data flow from and to different sources and its use. BETER, Better care after Hodgkin lymphoma: Evaluation of long-term Treatment Effects and screening Recommendations

The BETER consortium, cooperating with external experts, has developed guidelines for the most frequent adverse events after HL treatment, based on available scientific evidence and in line with other guidelines (Mulder *et al*, 2013; Armenian *et al*, 2015) (Table 1). When no evidence was available, recommendations were based on expert consensus. Each guideline provides an overview of the magnitude of the risks, risk factors, effectiveness of available screening methods, screening recommendations, and recommendations for treatment and lifestyle, where appropriate. These guidelines are published in the Dutch national database for medical guidelines for secondary care (richtlijnendatabase.nl). An English translation and patient versions will be published on our BETER website (www.beternahodgkin.nl). To facilitate the use of the guidelines, an online calculator generates risk-based screening recommendations based on gender, age at diagnosis and HL treatment.

In the Netherlands, regular surveillance for recurrence of HL ends 5 years after treatment. Therefore, 5-year HL survivors, aged 15–60 years at diagnosis and currently aged <70 years, are eligible for survivorship care in the participating centres. The so-called BETER clinics are spread throughout the Netherlands and are staffed by a haematologist, radiation oncologist, or both, and in some hospitals also nursing specialists. When necessary, HL survivors are referred to dedicated specialists, such as cardiologists, gynaecologists and psychologists. The BETER clinics pursue a close cooperation with the patients' general practitioner (GP); GPs particularly play a role in screening and treatment of cardiovascular risk factors, thyroid dysfunction and psychosocial issues. To facilitate this cooperation, a survivorship care plan intended for survivor and GP is being developed. It consists of a summary of relevant medical history and treatment data, observed adverse events, and recommendations for screening and treatment of adverse events.

Survivors were identified through the Netherlands Cancer Registry, which has national coverage of all cancer diagnoses since 1989. In order to identify HL survivors diagnosed 1965–1989, we used hospital tumour registries, the Dutch Pathology Database and HL research databases (Schaapveld *et al*, 2015). Around 9000 eligible 5-year HL survivors were identified, of whom approximately 5500 were still alive. For all eligible HL survivors, data managers collected detailed data on treatment and adverse events from medical records.

Survivors are invited to visit the BETER clinic in the hospital where they were treated for HL, but may attend another BETER clinic at their convenience. Survivors with the highest risks of late effects, e.g. young women treated with chest radiotherapy, are given priority. When inviting a previously discharged survivor (~50% of all eligible HL survivors), clinic personnel check whether he/she is still alive and collects his/her current address through the Netherlands Personal Records Database.

Prior to visiting, all survivors are asked to complete a questionnaire on their current health status, medication, medical history, family history and lifestyle, as well as psychosocial and socio-economic problems. This helps the healthcare providers to focus on actual symptoms of late effects and lifestyle.

The BETER board negotiated reimbursement of the survivorship care with the responsible authorities, because reimbursement can constitute a major obstacle for implementation (Barbui *et al*, 2014). An adapted care product was approved in 2016.

In collaboration with the Dutch Haematology Patient Federation, we developed a website for HL survivors with information about late effects of HL treatment (www.beternahod

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gkin.nl). Visiting HL survivors expressed high user satisfaction and were shown to have increased knowledge of treatment-related adverse effects (G.C.C. Sombroek, unpublished data).

Data from medical records and questionnaires will be combined after written informed consent in a national database, together with data on screening results, diagnosis and treatment of late adverse events, and data from national registries (e.g. second malignancies) (Fig 1). This database will facilitate future research and may lead to the discovery of unrecognised late adverse treatment effects. The database will also be used to evaluate the effectiveness of the BETER clinics, including guideline adherence and reasons for non-attendance.

Funded by the Dutch Cancer Society, we are setting up a national HL biobank (serum and DNA) for research purposes.

Only 57% of the first 584 invited HL survivors attended a BETER clinic (Aleman *et al*, 2017), similar to the attendance rate in a UK programme on radiation-related risk of breast cancer (Howell *et al*, 2009). Survivors who were not under regular medical surveillance in the BETER centre were less likely to attend. The most common reasons not to attend were surveillance or treatment for adverse events elsewhere and unwillingness to attend (e.g. due to emotional burden). As Dutch healthcare insurance entails a mandatory deductible sum of €385 (2016–2019), personal financial circumstances also hamper participation.

In conclusion, we expect that implementation of the BETER programme will lead to improved life expectancy and quality of life for HL survivors. The experience gained with the BETER programme may be used to develop effective, evidence-based survivorship care for lymphoma survivors in other countries and for survivors of other malignancies.

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Competing interests

The authors have no competing interests.

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AN, ND, BA, MvtV, FvL, and JR wrote the first draft of the manuscript. All authors critically reviewed the draft and approved the final version for publication.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Members of the BETER consortium in addition to the authors.

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Role of MFHAS1 in regulating hepcidin expression via the BMP/SMAD and MAPK/ERK1/2 signalling pathways

Malignant fibrous histiocytoma amplified sequence 1 (MFHAS1 or MASL1) is a member of the human ROCO protein family, characterized by a Ras of complex proteins (ROC) and a C-terminal of ROC (COR) domain that is ubiquitously expressed in various human tissue (Sakabe *et al*, 1999), as well as erythroid-lineage cell populations (Kumkhaek *et al*, 2013a) and macrophages (Ng *et al*, 2011). MFHAS1 has been shown to play a role downstream of Toll-like receptor-dependent signalling in innate immunity (Ng *et al*, 2011) and macrophage polarization (Zhong *et al*, 2017). Importantly, *MFHAS1* was originally identified in a human 8p23.1 amplicon detected in malignant fibrous histiocytomas (Sakabe *et al*, 1999). It has also been found to be a potential oncogene for oesophageal/gastro-oesophageal carcinoma, gastric cancer and B-cell lymphoma. Although these findings suggest that regulation of MFHAS1 is important for normal function, the precise mechanisms that regulate MFHAS1 remain to be determined.

We previously demonstrated that MFHAS1 is upregulated in terminal erythropoiesis through the Raf/MEK/ERK pathway (Kumkhaek *et al*, 2013b). Further, downregulation of MFHAS1 expression in macrophages has been reported to strongly enhance interleukin (IL) 6 production following their lipopolysaccharide or polyinosine-polycytidylic acid stimulation (Ng *et al*, 2011). IL6 is one of the negative regulators of erythropoiesis that inhibits the release of iron from macrophages and mediates hepcidin expression rather late in erythroid maturation (Nemeth & Ganz, 2006). However, the role of MFHAS1 in regulating hepcidin expression has not yet been explored. Based on our earlier work, we hypothesize that MFHAS1 could directly (or indirectly) influence hepcidin expression. Methods are detailed in Appendix S1.

The BMP/SMAD and JAK/STAT3 pathways are important transcriptional regulators of hepcidin expression. To examine the contribution of MFHAS1 to the regulation of hepcidin expression, we determined whether MFHAS1 affects the BMP/SMAD or JAK/STAT3 pathways in the human hepatoma cell line HuH-7 and in normal primary human hepatocytes. Because both of these types of cells express low endogenous levels of MFHAS1, we overexpressed *MFHAS1*

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