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Cancer Survivorship Care

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ABSTRACT BOOK

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Achieving High-Quality Survivorship Care

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Over the past several decades, the number of cancer survivors has increased dramatically as a result of advances in early detection of first malignancies and effective therapies. The growing population of long-term (exceeding 5 years) cancer survivors is at increased risk for morbidity and premature mortality, related directly to the cancer itself, to preexisting comorbidities, and to exposure to cancer treatment modalities. Consequently, cancer survivors represent an important group that may benefit from risk assessment, disease prevention services, and health promotion counseling. Unfortunately, the lack of definitive guidance on what constitutes best practices in caring for long-term survivors contributes to wide variation in coordination of care, particularly as more individuals treated for cancer transition back to primary care. Further issues challenging the delivery of optimal survivor care is the fact that primary care providers are often unfamiliar with the consequences of cancer and its treatment and seldom receive explicit survivor care guidance about potential treatment effects from oncologists. Because no uniform standards for the care of survivors exist, significant efforts are required to understand the needs of survivors and to develop models of comprehensive, coordinated care that meet those needs.

A major clinical barrier to standardizing survivorship care is the lack of guidance on the management of survivors with diverse cancer types treated across an age spectrum with heterogeneous approaches and modalities that continue to evolve over time. Long-term follow-up of pediatric cancer survivors has led to an extensive evidence base linking specific therapeutic exposures with adverse outcomes as well as data to identify at-risk groups. This evidence base has been used by pediatric cooperative groups to develop guidelines for survivorship care that include systematic plans for screening, surveillance, and prevention. In contrast, survivorship care after treatment of adult-onset cancers more often focuses on surveillance for cancer recurrence and does not consistently address health promotion, primary or secondary cancer prevention, or symptom management of common long-term and late effects. Because of insufficient high quality evidence to inform

recommendations for follow-up care, previous efforts to develop guidelines have been unsuccessful. Organization of a codified set of best practices to guide providers in the follow-up care of adult-onset cancers is critical to optimize their clinical management. Alternatives to the exposure-based approach used to coordinate pediatric cancer survivor care include a disease-based approach that focuses on the therapeutic modalities and health concerns related to a specific malignancy (e.g., breast or prostate cancer), an organ-system approach that focuses on specific organs or organ systems affected by the cancer or cancer therapy (e.g., cardiovascular or pulmonary outcomes), and a symptom-based approach (eg, fatigue or sleep disturbances) that assesses common cancer treatment-related effects.

In addition to evidence-based guidelines, optimal survivorship care requires a comprehensive, multidisciplinary care infrastructure or model of care. A variety of models of survivorship care have been described across practice settings including academic models, community practice models, and shared-care models. Most academic programs offer either one-time consultative services or longitudinal survivorship care. Community practice models, most often supported by national funding, provide survivorship care services at community hospitals. The shared-care model features co-management of survivors by oncology and primary care providers. The shared-care model has been promoted for its facilitation of survivor access to cancer- and non–cancer-related preventive services. A risk-stratified approach has been recommended in defining the ideal model of follow-up care for specific survivors. Risk factors typically considered in these models include treatment intensity, risk of recurrence, persistence of moderate to severe toxicity of therapy, risk of serious physical late effects, and psychosocial status.

To ensure care coordination among oncologists and community providers, the IOM and other professional societies advocate the use of a written treatment summary and care plan that communicate the survivor's health status, provide a care roadmap to ensure survivor-appropriate services, and clearly delineate which provider is responsible for which aspect of care. However, adherence to this recommendation by oncology providers remains suboptimal because of the significant time and resource barriers involved in organizing survivorship care plans. Surprisingly, limited research supports their efficacy in improving survivor care outcomes, although most acknowledge the potential benefit of the care plan in

promoting communication among survivors and providers. Identification of the essential components of survivorship care plans, which may vary across health care settings, is important to facilitate its widespread adoption. The integration of automated, programmable applications within existing electronic health record systems may expedite the development of care plan summaries in the future.

Increased research is greatly needed to expand the evidence base required to define optimal care delivery, including the type or components of care delivered, the manner in which that care is delivered and by whom, and the efficacy of the various models of care. To enhance awareness of survivorship health issues, educational efforts must be expanded to target not only oncology providers, but also practicing clinicians, graduate medical trainees and survivors. In addition, for survivors to obtain the best follow-up care, they must collaborate with their providers in surveillance and management of cancer-related sequelae. Collectively, achievement of these initiatives aims to increase survivor access to high-quality survivorship care that includes screening, prevention, and post-treatment care coordination.

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Secondary malignancies in CML patients

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Increased overall survival in chronic myeloid leukemia (CML) requires closer long term observation of potential side effects. The development of secondary malignancies is regarded as a common risk of antineoplastic therapies and a potential carcinogenicity of TKI has been discussed. For imatinib it is known that in preclinical studies with rats neoplastic changes occurred in kidneys, urinary bladder, urethra, preputial and clitoral glands, small intestine, parathyroid glands, adrenal glands, and nonglandular stomach [1].
Several studies were published so far. An increased rate of prostate cancer was found in a French cohort of 189 patients treated with imatinib [2]. Data from the Novartis files of more than 9500 patients did not confirm this observation [3]. Analyses of patient cohorts from multiple phase I and II trials at the MD Anderson Cancer Center, who were treated with TKI for CML and other myeloproliferative neoplasms, showed a risk of secondary malignancies that was lower than expected [4]. In an analysis of a cohort of 1038 Czech and Slovakian CML patients treated with TKI the age adjusted incidence rate of secondary neoplasia was found to be 1.5 fold higher than of the normal population, but the difference was not statistically significant [5].
However, CML itself has been discussed as a risk factor for solid cancers and hematologic malignancies. Two epidemiologic studies that analyzed tumor registries for patients with CML in Sweden [6] and patients with chronic myeloproliferative neoplasms (MPN) including CML in Denmark [7], showed an increased risk of secondary malignancies in CML patients independent of treatment.
Data of the CML study IV show that the standardized incidence rate (SIR) for all malignancies is not increased in general. However, SIR for NHL was elevated for CML patients compared to the general population [8,9].
Long-term follow-up of CML patients is warranted, since the rate of secondary malignancies may increase over time.

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Risk and cause of death, with special focus on transformation to acute myeloid leukemia and myelodysplastic syndromes, in myeloproliferative neoplasms

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Background
In a recent population-based study, patients with myeloproliferative neoplasms (MPNs) had a shorter life expectancy than the general population. Although survival improved in MPN patients over time, an inferior survival was seen in all subtypes and during all calendar periods (I). To elucidate the underlying causes of the excess mortality and treatment-related risk factors for leukemic transformation we took advantage of high-quality population-based Swedish registries.

Patients and Methods
Based on a nationwide MPN cohort (II) we conducted a nested-case control study including 162 patients [110 polycythemia vera (PV); 26 essential thrombocythemia (ET); 15 primary myelofibrosis (PMF); 11 MPN not otherwise specified (MPN NOS)] with a subsequent acute myeloid leukaemia (AML; n=153) or myelodysplastic syndrome (MDS; n=9) and 242 matched control patients. For all patients we obtained clinical and MPN treatment data (III). To elucidate the underlying causes of the excess MPN-related mortality, we assessed the causes of death in a large cohort of patients diagnosed with MPNs in Sweden from 1973 to 2005 (IV). A total of 9,563 MPN patients and 37,643 matched controls were identified from Swedish Registers. Dates and causes of deaths were analyzed with follow-up until 2007. A flexible parametric model was used to estimate cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for six categories of causes of death. A competing risk analysis, based on the HRs, was performed and results are presented as cumulative incidence functions (probability of death).

Results
Risk factors for transformation in MPN. Forty-one of 162 (25%) MPN patients with AML/MDS development were never exposed to alkylating agents, radioactive phosphorous (P^{32}), or hydroxyurea (HU). Compared to MPN patients who were not exposed to HU, the odds ratios (and 95%

CIs) for 1-499 g, 500-999 g, >1000 g of HU were 1.5 (0.6-2.4), 1.4 (0.6-3.4), and 1.3 (0.5-3.3), respectively for AML/MDS development (not significant). MPN patients who received P^{32} >1000 megabecquerel and alkylators >1 g had a 4.6-fold (2.1-9.8; p=0.002) and 3.4-fold (1.1-10.6; p=0.015) increased risk of AML/MDS, respectively. Patients receiving two or more cytoreductive treatments had a 2.9-fold (1.4-5.9) increased risk of transformation. When analysis was restricted to PV and ET, results were essentially unchanged. Median survival after AML transformation was 3 months.

Risk and cause of death analysis. There was an excess mortality in MPN patients compared to matched controls; HRs of death from infection was HR 2.7 (95% CI 2.4-3.1) and hematological malignancy 92.8 (70.0-123.1). In patients aged 70-79 years at diagnosis HRs for death from cardiovascular disease were 1.5 (1.4-1.7), cerebrovascular disease 1.5 (1.3-1.8), from solid tumor HR=1.2 (0.99-1.3), and from other disorders HR=2.3 (2.1-2.6). In the same age group, the probability of dying from infections by 10 years were for male patients and controls 4.5% vs. 2.3%, from hematological malignancy 13.7% vs. 0.2%, from cardiovascular disease 16.8% vs. 15.0%, from cerebrovascular disease 5.5% vs. 5.1%, from solid tumor 9.7% vs. 11.5%, and from other disorders 24.9% vs. 14.9%, respectively.

Ten-year mortality decreased with time in both MPN patients and controls mainly due to a decline in the probability of cardiovascular death. The primary reason for the reduction in excess mortality in MPN patients over time were decreased probabilities of deaths from hematological malignancy during the first calendar period (1973-1982), infections, and in young patients, also cardiovascular disease.

Summary and conclusions

The risk of AML/MDS development after MPN diagnosis was significantly associated with high exposures of P^{32} and alkylators but not with HU treatment. Twenty-five percent of patients with MPNs who developed AML/MDS were not exposed to cytotoxic therapy, supporting a major role for nontreatment-related factors.

In this large population-based study, MPN patients had a higher 10-year mortality compared to matched controls and the excess mortality was mainly explained by hematological malignancy, infections, and other disorders. The probability of dying from hematological malignancies in MPN patients decreased over time. The overall decline in 10-year mortality, observed in both patients and matched controls over time, was

mainly explained by general advances in prevention and treatment of cardiovascular diseases. The improved survival over time is multifactorial and can only partly be attributed to improved management of the underlying MPN.

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Secondary malignancies in NHL

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Non-Hodgkin's lymphoma (NHL) include a group of malignancies that usually display high response to chemotherapy. The distinct chemo-sensitivity makes NHL a potentially curable malignancy and result in prolonged survival in most NHL patients. Moreover, novel drugs developed over the last decade have further improved the management of NHL **(1-5)**. These novel drugs are mainly monoclonal antibodies and they usually display potent anti-lymphoma activity along with reduced short-term toxicity. Unfortunately, long-term survival may bring about a progressive increase of secondary malignancy occurrence, particularly in patients previously treated with intensive chemotherapy schedules **(6-8)**. Recently, a large survey has been performed among NHL patients managed over the last three decades at two Hematology Centers, in Torino and Bergamo. Main objectives of the study were to define on a large series of NHL the overall rate of responsive patients following primary treatment and the actual long-term survival for those patients showing responsive disease; moreover, the main causes of deaths, namely lymphoma progression vs. secondary malignancies, has been investigated in order to clarify which is the ultimate outcome for the large group of long-term NHL survivors.

Data have been collected on 3,106 patients, referred at the University Hematology of Torino (S. Giovanni B. and Mauriziano Hospitals) (832 cases) and the Hematology Division of Bergamo (2,274 cases), between 1984 and 2012. There were 45% female patients, the median age was 59 yrs (range 15-94), B-cell NHL were 92%; main histological subtypes were Diffuse Large Cell (50.5%) and Follicular (19.2%) Lymphoma. There were 66.3% patients with advanced-stage disease, 41% had an intermediate-high IPI score. Overall, 48% received chemotherapy supplemented with rituximab. The criteria to identify primary refractory

NHL were: stable or progressive disease (fully refractory) or transient response with disease progression within 6 months (early relapse) **(9-10)**.

Overall, the study showed that 690 (22%) patients were refractory (12% fully refractory, 10% early relapse) to their primary treatment. The overall incidence of refractory NHL was similar in Torino and Bergamo Centers. The rate of refractoriness was 41.9% in the small T-cell subgroup. Besides T-cell histology, the following factors had the highest association with treatment response: i. *intermediate-high vs. low-grade histology* (OR 1.58, p=0.001); ii. *intermediate-high vs. low IPI score* (OR 3.53, p<0.001); iii. *female gender*, with a markedly lower incidence of refractoriness (OR 0.75, p=0.008); interestingly, the frequency of refractory disease was not influenced by age higher than 60 years. In addition, amongst B-cell NHL, the addition of rituximab was associated with a marked reduction of refractory disease (13.6% vs. 26.7% for non-supplemented chemotherapy, OR 0.35, p<0.001).

At present, 1,908 (61.4%) patients are known to be alive, and at a median follow-up of 7 yrs., the 5 and 10 yr. survival projections are 70.3% and 58.0%, respectively, with an overall median survival of 15 yrs. Patients with B-cell lymphoma had a much longer overall survival than those with T-cell subtypes, with median survival of 15.2 and 6.4 yrs., respectively. Among B-cell subtypes, the median survival was 20.6, 11.7, and 5.0 yrs., for FL, DLB-CL, and MCL, respectively (P<0.001). Moreover, B-cell NHL had a marked survival improvement since the addition of rituximab to chemotherapy, with a median survival of 12.3 yrs. for patients treated without rituximab, whereas the median survival has not yet been reached for patients treated with chemotherapy plus rituximab. For these latter patients, the 5 and 10 yr survival projections are 78.9% and 70.0%, respectively (data not shown). The survival was definitely prolonged in primary responsive compared to refractory patients. In fact, response to primary treatment was associated with a median overall survival of 19 years, compared to 1.3 years for refractory patients. Primary refractory disease was the most predictive factor for long-term outcome (HR 18.15, p<0.001).

As mentioned, the main causes of deaths were investigated among patients surviving at long-term. Overall, out of 555 deaths, 279 (50.3%) were due to lymphoma progression, whereas 154 (27.7%) were related to late toxic complications. These latter included secondary solid tumors

(93, 16.8% of all deaths), secondary myelodysplasia/acute leukemia (18, 3.2%), as well as other non-neoplastic fatal complications (43, 7.7%).

In conclusion, this outcome research performed on a large series of 3,106 NHL patients allowed to conclude that: i. overall, primary refractory disease is variably observed in NHL, with the highest incidence in the T-cell subtypes; ii. among B-cell lymphoma, the introduction of rituximab has markedly reduced the risk of refractory disease, with an incidence of 13.6% in B-cell lymphoma patients receiving chemo-immunotherapy; iii. patients responsive to first-line therapy have a very prolonged life expectancy, with an overall median survival approaching 20 yrs.; iv. lymphoma progression remains the major cause of death, however secondary neoplasms account for approximately 20% of deaths; moreover, a non negligible group of long-survivors may ultimately die due to non-neoplastic toxic complications. Thus, response to primary treatment is crucial for overall survival in non-Hodgkin's lymphoma and this supports the necessity of ongoing studies aimed to identify early refractory disease, and to improve the therapeutic options for the front-line management of lymphoma patients. In addition, given the prolonged survival of lymphoma patients, efforts should be aimed not only to increase the anti-tumor efficacy but also to reduce any potential late effect in treatment options for NHL.

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Monitoring of late effects in long-term survivors after stem cell transplantation

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The long-term follow-up monitoring aims to provide care for childhood and adulthood survivors after hematopoietic stem cell transplant (HSCT). Long-term care includes screening and prevention of late complications after HSCT, education about the possible late consequences of the transplantation, and monitoring of health care needs according to risk profile of the survivor. For patients in remission from their primary disease and without active chronic graft-versus-host disease (GVHD) annual follow-up visits are considered as a standard. More frequent controls may be needed for survivors with active chronic GVHD, with recurrent infectious complications, or other posttransplant complications which need close guidance from experts in posttransplant care.

Health risk after HSCT is strongly depended on a number of factors: the patient's characteristics; the primary disease and the treatment received; the transplantation procedure itself. Since the magnitude of risk and the severity of the late complications for an individual patient may greatly vary, the follow-up care should be individualized on bases of the patient's history. The monitoring of late effects includes the establishment of a survivorship care plan, the organization of the annual visits, and the application of the recommendations for screening and preventive measurements of post-transplant survivors.

Survivorship care plan

The Institute of Medicine recommended that all patients completing primary cancer treatment are provided with a comprehensive treatment summary and a survivorship care plan, reviewed with the patient during an end-of-treatment consultation [1]. The survivorship care plan aims to assemble all relevant information, needed to prepare an individualized monitoring of the long-term survivor. It is intended for the health care provider as well as the transplant survivor and his family. A patient friendly version should be available for the survivor and his relatives.

The survivorship care plan includes demographics from the patient, details on his primary disease and treatment received before

HSCT, health relevant comorbidity, as well transplantation characteristics such as type of conditioning, extension of GVHD and the treatment received [2]. Based in this information, a detailed individualized description of anticipated risks of late effects as well as a follow-up plan is proposed. As an example, patients conditioned with total body irradiation with 12 Gy or more are prone to develop secondary non-squamous cell cancers, cataract formation, endocrine dysfunction and infertility. In contrast patients with an increased cumulative dose of anthracyclines and/ or etoposide received before HSCT are at risk for late congestive heart failure. During the presentation various risk profiles will be discussed.

Organization of the long-term follow-up visit

The annual long-term follow-up visit should last no longer than one full day; this will reduce cost for those patients coming from distant geographical areas and guarantee the attendance of long-term survivors socially integrated at school or employment. Beside the clinical visit, this follow-up visit includes a number of consultations by specialists as well as time-consuming, highly specialized investigations. Furthermore, time for special questions and for counseling of the patient should be allocated. As a consequence, this visit has to be prepared carefully before the scheduled date. The long-term follow-up visit can be divided into three different phases: the preparation for the clinic visit; the structured visit itself; the post-clinic follow-up [3].

The *preparation of the follow-up visit* begins with the reviewing of all documents and medical records available. The aim of this review is to visualize the individual risk constellation of the transplant survivor, the detailed treatment schedule and the current problems. It is recommended to share the information in a team meeting hold before the scheduled follow-up visit including the main participants of the multidisciplinary team.

The *clinic follow-up visit* includes the review of the history since last visit and the physical exam performed by the clinician. Important questions concerning the medical, family, social and psychological history have to be included. For particular examinations, the subspecialist, such as gynecologist, dermatologist, dentist, ophthalmologist or endocrinologist should be involved. These examinations by subspecialists as well as particular exams such as radiological exams, lung function tests, and cardiologic investigations have to be scheduled carefully for the visit. During the follow-up visit, comment on previous recommendation

and the concrete consequences drawn from them have to be considered. Finally, adequate time have to be dedicated for a general discussion and health counseling with the survivor, and, if desired, with relatives or a person of acquaintance.

The aim of *the post-clinic follow-up* is to summarize the patient's status and provide further recommendation for the health care provider. Therefore all clinical and biological information obtained should be available. The follow-up visit will be summarized in a single structured document. This document is a useful tool for the primary health care provider as well as for the long-term follow-up clinic.

Recommendation on screening and preventive practices

Recommendation on screening and preventive practices for long-term survivors after HSCT have been published for the first time by experts from the CIBMTR, the EBMT and the ASBMT in 2006. These guidelines have been updated in 2012, expanding the working group by including participants from most of the societies of HSCT worldwide [4]. These recommendations should represent the basis of the monitoring of long-term survivors after HSCT.

Conclusions

Life-long controls of survivors after HSCT by care providers who have knowledge about the potential long-term effects, and the causal relationship between transplantation and late effects are mandatory, but not sufficient. Convincing long-term survivors, their families, the general health care providers as well as the health authorities about the need of persuasive counseling and education on late effects surveillance is one of the challenges to face in the forthcoming years.

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Reproductive function, ovarian reserve and risk of premature menopause in female survivors of childhood cancer

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Background: Over the past 40 years there have been major improvements in the treatment of childhood cancer, dramatically increasing survival [1-3]. As a result, there is a rapidly growing population of young adult survivors of childhood cancer. However, cancer treatment during childhood can induce complications which may not become apparent until many years later.
In females, a compromised reproductive system is an important and frequently encountered late effect of treatment, which has a high impact on quality of life [4;5]. Treatment may damage the hypothalamic pituitary-
ovarian-uterine axis, clinically leading to delayed or arrested puberty, subfertility and adverse pregnancy outcomes [5-8]. However, it may also reduce fertile life span and induce premature menopause, since therapy may deplete or accelerate the decline of the non-renewable pool of primordial follicles in the ovary [9;10]. The issue of premature menopause has only gained attention in recent years since it is only now that the first generation of female childhood cancer survivors (CCSs) is reaching their forties. The available literature suggests that some female CCSs may enter menopause as early as the age of 32 [11]. The current Dutch trend to postpone childbearing to the thirties stresses the need for adequate information on fertility status in this group of females. In addition, CCSs who experience premature menopause are potentially at increased risk of developing a variety of menopause-associated conditions, including osteoporosis, death from cardiovascular diseases, and psychosexual dysfunction [11;12]. Evaluating the presence of these adverse health effects, in order to prevent or treat them, is essential.
Traditionally, ovarian function is assessed by menstrual history, pubertal staging and plasma hormone analysis. However, ultrasound-based antral follicle counts, measurement of ovarian volume and the use of the endocrine markers anti-Müllerian hormone (AMH) and inhibin B seem to offer additional clinical value [13-15] which can be useful to clinicians for counselling women about their chances for pregnancy. Based on the studies available we previously concluded that a future study should include a larger number of long-term CCSs and adequate control groups,

and focus on prolonged and complete follow-up of these CCSs. Furthermore, a panel of techniques should be used to assess ovarian function and reserve, including novel methods that are expected to be more accurate (ovarian volume, antral follicle count and AMH).
Therefore, we initiated the VEVO-study (VEVO is a Dutch acronym for *'Vruchtbaarheid, Eicelvoorraad en Vervroegde Overgang'*) a retrospective cohort study, performed within the nationwide collaborative group 'Dutch Childhood Oncology Group – Long-term Effects after Childhood Cancer (DCOG LATER)'.

Aim and methods: This aim of the study is to examines the effects of (different types of) treatment on the reproductive system of female CCSs using an adequate control group, a questionnaire, and a full panel of ovarian function and ovarian reserve tests. All adult female childhood cancer survivors treated in the Netherlands between 1963 and 2002, who are alive, not mentally retarded and able to read and/or speak Dutch will be invited to participate (n=2000). The study consists of two parts: a questionnaire and a clinical part which includes the provision of a blood sample from which values of several hormones are determined (such as FSH, AMH and inhibin B) and a transvaginal ultrasound measurement of the reproductive organs (from which, amongst others, the number of antral follicles in the ovaries was assessed). The control group consists of sisters of female survivors and women from the general population (n = 1687).

Preliminary results: Of the 1418 survivors invited so far, 83% responded to the study invitation, whereas 80% of the invited controls responded. So far, 920 female survivors (65%) and 800 controls (47%) have participated in the study. Preliminary results show that female survivors are, in general, at an increased risk for a diminished reproductive function compared to controls. Survivors more often have higher FSH values, whereas the average number of antral follicles in the ovaries is lower. With regard to the type of treatment, results showed that women who have been treated with alkylating agents, mitotic inhibitors, or anti-tumor antibiotics in the past are at the highest risk of a reduced ovarian reserve. Furthermore, the results of the questionnaire showed that survivors more often had irregular menstrual cycles, or no cycles at all. In addition, the proportion of women who were still a virgo was higher in the survivors group than in the control group. Finally, survivors appeared to more often use medications for menopausal symptoms.

In the upcoming year, more survivors and controls will be invited to participate in the study after which data will be further analysed taking into account age at time of treatment and the different doses of radiotherapy and chemotherapy on the risk of gonadal damage. In addition, the values of the hormonal markers inhibin B and AMH will be determined and related to treatment information.

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Patient perspectives in myeloma and the role of information and support

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Myeloma presents difficult challenges for everyone it touches: patients, their families, friends, doctors, nurses and other caregivers and providers. During its course, the failure of any of the above-named to understand the point of view of the other can lead to strains in their relationship that can be unpleasant and counter-productive to the situation at hand.

The purpose of this overview is to briefly explain certain interpersonal aspects, mostly from a patient's perspective and to suggest some coping mechanisms and to highlight the role of information and support, that will be helpful in enhancing the experiences of all those with myeloma and those involved in its treatment and care.

There are some very specific reasons about the nature of myeloma that makes a diagnosis especially difficult to come to terms with and to live as normally as possible with. What are these?

• Myeloma is a relatively rare cancer. Most people hear the word for the first time when they or a loved one are diagnosed

• Currently, there is no known cure, treatments need to be viewed in terms of how long they are able to control the disease or relieve symptoms and how they affect quality of life

• For some treatments, there is not enough clinical experience with patients to know what to expect. Further, no two patients are alike so that predicting results for any treatments is a mater of probabilities – there are no guarantees

• The complications and symptoms of myeloma can be traumatic and extremely debilitating and virtually all treatments have potentially serious side-effects. Indeed, some treatments can lead to complications that may prove fatal

Patients and family members dealing with a diagnosis of myeloma are confronted with a terrifying reality. It can be a wrenching confrontation with mortality. Very often, patients will present with debilitating physical symptoms, such as pathological fractures, anaemia or infection. At the same time, they may be dealing with a myriad of emotional, family and financial issues.

Generally, this is not an ideal circumstance to make the very important decisions one needs to make as a patient. Beyond this, the patient's state of mind can attenuate the stress attendant upon treatment and can also exact a physical toll.

Given these factors, attending to the psyche of the patient is a very important component of care and treatment.

Doctors and other healthcare professionals play an important part in helping patients and their families come to terms with this situation and to make treatment decisions.

Steps need to be taken to try and understand these emotional issues and to use this understanding to tailor the approach to delivering treatment and care. Emotional issues can be wide-ranging and can bee very bit as diverse as myeloma itself.

Patients too can be very different in their approach to treatment. Some patients want to bury their heads in the sand whereas others take a very aggressive action oriented stance and want to beat this thing no matter what it takes.
It is important to realise that the patient role in treatment decisions and the criteria they apply tend to be quite different and frequently patients do not necessarily share doctors' priorities in decision-making or place the same emphasis on different types of morbidity.

In addition, the impact of treatment on quality of life and the sense of well-being is a very individual equation for each patient. For example, hair loss due to chemotherapy can have a more devastating impact on some than neuropathy or nausea.

Treatments that require in-patient procedures can be an anathema to patients with active professional careers or young children. Many patients

look for treatments that allow them to self-administer much of the treatment (i.e. tablets) or receive home care.

Other patients much prefer to have things totally taken care of in the hospital. Where practical, doctors should be sensitive to these differences to achieve the best outcome and strengthen the doctor-patient relationship.

Doctors too face difficult issues in recommending diagnostic and treatment options for which results generally cannot be assured. They face formidable choices in deciding what to communicate to patients and how to convey it. The doctor is often in the position of having to persuade the patient to pursue what can be frightening procedures and treatments.

Thus, all parties face major challenges in dealing with myeloma. Understanding the different perspectives that foster communication and trust can be critical to achieving the best outcome.

The following is a brief outline of what can be done to improve the situation:

• Provide information – this can be a very powerful tool to strengthen the patient-familydoctor relationship. It can also serve to help people in negative emotional states get into more positive frames of mind

• Listen, listen, listen – stop talking and listen to the patient. It is important. By listening one is conveying interest, legitimising the patient's suffering, helping to simplify safe passage and demonstrating that you are taking the patient's problems seriously

• Be realistic and straightforward – this usually does not destroy hope nor increase fear

• Avoid giving up hope – try and maintain hope in the face of a patient's physical deterioration because there is almost always something that one can do or say to make the patient feel more comfortable. The key is to focus on comfort as opposed to cure and in doping so doctors will be less frustrated themselves

• Treat complications such as fatigue and physical discomfort such as pain energetically

• Try and understand patient denial, allow regression within certain bounds. Denial is often therapeutic and helpful. People face up to things in different ways and they do not always need to accept things. If they are able to, they will do so

• Support patient's strengths, this basically means to accommodate their personality rather than try and modify it

• It is essential to maintain continuity of care. Patients should be seen regularly because consistency and continuity of care are paramount to their well-being

• Facilitate the information needs of the family that may differ from those of the patient

• Correcting misconceptions on the part of the patient can improve the patient's quality of life as well as helping with compliance of treatment. It is always helpful to ask the patient 'What is your understanding of your illness?'

• The physical touch is important – a pat on the shoulder, a good firm handshake is reassuring to the patient

• The personal touch. A verbal or non-verbal expression of sadness or understanding at the patient's plight is often appreciated and therapeutic

Myeloma patients and the people who care for them are routinely dealing with serious medical and emotional issues. Modest investments of time and attention from doctors and other caregivers to understanding patient/family perspectives, interpersonal dynamics, education and the provision of appropriate information can significantly strengthen the therapeutic partnership. In addition, it can dramatically reduce stress levels for all concerned.

Screening for distress in cancer patients: A multicenter, nationwide study in Italy

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Several studies have demonstrated that 30% to 40% of patients with cancer report emotional distress symptoms both as a consequence of the disease and treatments (Mitchell et al., 2011a). Chronic stress not only impairs the quality of life of patients and their family, but also interferes with the disease in itself, with a worsening of the clinical outcome (Chida et al.,2008). A long lasting stress is strictly related to mood depression and pain with multiple mechanisms, both biological and psychological (Lee et al., 2010; Torta and Ieraci, 2013). From this point of view the relation between stress, mood and pain has a great implication for clinical practice, and provides strong rationale for assessing and treating stress from a bio-psycho-social perspective. One of the major biological component of the link between stress, mood and pain is represented by the hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis, with resultant hypercortisolism, glucocorticoid resistance, sympathetic over-activity and increased release of proinflammatory cytokines (e.g. TNF-alpha, IL-1, IL-6) (Thornton et al., 2010; Zunszain et al., 2011). The stress related proinflammatory cytokines increase is strictly linked to several clinical symptoms, observed in oncologic patients, such as pain, fatigue, cognitive impairment, mood depression, and anxiety (Felger and Lotrich, 2013). For these reasons distress has to be considered as the sixth vital sign and it is mandatory its monitoring in order to identify and treat stressed patients (Bultz and Johansen, 2011). Nevertheless only a third of patients with cancer related distress are recognized and treated in the oncology setting (Mitchell et al., 2011b).
A valid instrument for easily screening the level of stress is represented by the Distress Thermoter (DT) (NCNN, 2013) that is one of the most used tools in several clinical contexts and phases of the cancer disease. The DT is a visual analog tool that asks the respondent to rate his/her level of distress in the past week, on a scale from 0 (no distress) to 10 (extreme distress). The tool is integrated by a Problem List (PL) of 34 problems, grouped into 5 categories (practical problems, family problems, emotional problems, spiritual/religious concerns, and physical problems) that is rated in a yes/no format.

The validity of DT was confirmed in many countries by many studies, and recently also in Italy: Grassi and collegues (2013) evaluated the validity and acceptance of the DT, on 1108 patients (329 men [30%] and 779 [70%] women; mean age, 53.4 $\pm$ 9.3 years) in a nationwide validation study, carried out in 38 italian cancer centers, representative of the different regions of the country. In this study a cut-off score of 4 demonstrated that 47% of patients have possible stress, with a tendency to overstimate caseness as measured by HADs and BSI-18 (33% and 38% respectively), while a more conservative cut-off score of 5 indicated a significant distress in 33% of patients. In conclusion, a brief screening tool like the DT is a simple and effective screening instrument for detecting distress in Italian patients with cancer: the single item DT compares favourably with longer measures that are used to screen for distress and, when DT is combined with the PL, favours the identification of cancer-related problems. In a [18F]FDG PET study, about the relationship among DT and brain metabolism in cancer patients, we recently confirm that the DT correlates with brain areas typically involved in stress response: actually hypothalamus metabolism was found to be the best predictor of distressed patients according to DT scores (Castelli et al., 2013). Stress, mood depression and pain are reciprocally influencing aspects, that have to be constantly monitored in any patient. Biological, emotional and social components of the stress experience may strongly influence the course of the oncologic disease and stress must be diagnosed and treated, when interfering with the patient quality of life or causing a clinical worsening. The outcome of identifying distress in cancer patients in terms of both referral rates and, especially, treatments, is required.

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Long-term quality of life in patients with acute and chronic leukemia: what do we know?

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With continued improvements in medicine and public health and technological advances, the number of cancer survivors has increased in many countries. Worldwide in 2002, there were an estimated 22.4 million persons surviving from cancer who had been diagnosed in the previous 5 years, and an even greater number of persons were alive following the diagnosis of cancer at any time during their lives[1]. While Health-Related Quality of Life (HRQOL) research is now well integrated in oncology and the American Society of Clinical Oncology (ASCO), for example, has been supporting the use of HRQOL outcomes for a long time[2], the large majority of studies have been conducted in patients with solid tumors. For a number of reasons, the number of HRQOL based studies in patients with solid tumor is in sharp contrast with the paucity of robust evidence available for patients with hematological malignancies[3]. Still much has to be done to understand patient morbidity in many areas of hematological malignancies and in particular there is definitely lack of research in patients with leukemia. [3-5]

The potential late effects of cancer treatment can include second malignancies or other chronic conditions affecting physical and emotional well-being. There has been an increasing interest worldwide in evaluating the longer-term impact of cancer and its treatment and currently large cohort of patients enjoys disease-free survival of 5 years or longer.[6,7] However, it has to be noted that "disease-free status" does not necessarily translate into a life free of physical and psychosocial health problems related to the cancer and/or its treatment. Current evidence shows that cancer related health concerns may persist for several years after initial treatment. This has been shown in several cancer populations including prostate, testicular, breast cancer and lymphoma patients. Long-term cancer survivors can experience treatment-induced morbidity (e.g., cardiovascular damage due to chemotherapy or radiotherapy; infertility and second tumors), chronic disease- and treatment-related symptoms (e.g., pain and fatigue), functional impairment (e.g., sexual, cognitive)

and psychosocial problems (e.g., fear of disease recurrence, depression, work disability, educational deficits).

This presentation will focus on current evidence based knowledge on long-term leukemia survivors as defined by the American Cancer Society, that is surviving the initial diagnosis for more than 5 years.[8] The presentation will report concrete examples of studies conducted in patients with acute and chronic leukemias and will sought to highlight the value of conducting long-term studies in this area and the need to implement a systematic research agenda on this topic.

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Sexual and reproductive health: issues at the bedside

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Sexual and reproductive health issues are common consequences of cancer and its treatment. Whilst there is a moral and legal imperative to inform and discuss patients embarking on cancer treatment of potentially gonadotoxic consequences, sexual health consequences are not routinely addressed.

This short paper considers the impact of sexual and reproductive health on the quality of life of our cancer patients. We will consider common sexual problems experienced by cancer patients and barriers that contribute to the under provision of care in this area.

Frontline oncology staff can make an important contribution to patient care without having to be an expert. By adopting a holistic approach to screening, offering information and support about sexual dysfunction, much associated distress can be dissipated or resolved.

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Quality of life among long-term survivors of non-Hodgkin lymphoma: A follow-up study

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Purpose: Little is known about the change in quality of life (QOL) and post-traumatic stress disorder (PTSD) symptoms and over time among cancer survivors, despite the fact that such knowledge can guide treatment. In addition, existing literature raises concern that their informational and psychosocial needs are not being met. Therefore, these studies: 1) examined change in QOL and PTSD symptoms among long-term survivors of non-Hodgkin lymphoma; 2) identified demographic, clinical, and psychosocial risk factors for poor outcomes; and 3) assessed unmet informational and psychosocial service needs.

Patients and Methods: Surveys were mailed to 682 lymphoma survivors who participated in an earlier survey and now were at least seven years post-diagnosis. Medical history, demographic variables, and standardized measures of QOL (SF-36), PTSD (PTSD Checklist), and perceptions of the impact of cancer (Impact of Cancer) were reported at both time points and examined using linear regression modeling to identify predictors of QOL[1] and PTSD[2] over time. Questions regarding interest in learning about late effects and health promotion strategies and receiving supportive services and care plans were included in the survey.[3]

Results: A total of 566 individuals participated (83% response rate) with a median of 12.9 years since diagnosis; respondents were 52% female and 87% Caucasian. One-third (32%) of participants reported persistently high or improved QOL yet a notable proportion (42%) reported persistently low or worsening QOL since the earlier survey. Participants who received only biologic systemic therapy reported improvement in physical health despite the passage of time. Older age, more comorbidity, and more or increasing negative and decreasing positive perceptions of cancer's impact were independent predictors of poor QOL.[1] In addition, while half (51%) of the respondents reported no PTSD symptoms, and 12% reported a resolution of symptoms, more than one-third (37%)

reported persistence or worsening of symptoms over five years. Survivors who reported a low income, stage ≥2 at diagnosis, aggressive lymphoma, having received chemotherapy and greater impact of cancer (both positive and negative) at the initial survey had more PTSD symptoms at follow-up. In multivariable analysis, income and negative impacts of cancer were independent predictors of PTSD symptoms.[2] Furthermore, the majority (83%) of participants reported a need for information related to late effects of their treatment and prognosis or risk of recurrence and 78% of participants did not report receiving a treatment summary, of which 62% cited that it would be helpful.[3]

Conclusion: Over one-third of long-term survivors of lymphoma report persisting or worsening PTSD and/or QOL symptoms. Providers should be aware of enduring risk; early identification of those at prolonged risk using standardized measures and treatments targeting perceptions of the cancer experience might improve long-term outcomes. Also, educational services and care plans may help to address the informational gaps related to diagnosis, treatment, potential late effects and other chronic conditions, and health promotion of long-term lymphoma survivors. Furthermore, the use of mobile technologies in delivering services to this survivor population should be considered, given the low-cost platform and potential for dissemination.

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Quality of life in survivors "EMPLOYMENT DISCRIMINATION"

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Besides the biological aspects of the sickness, cancer patients and their family suffer in most cases a form of social disease, which can be avoided and cured with success only by a cultural change in the direction of which Advocacy and Lobbying for the cancer patients are making great progress in recent times, promoting the assessment of the social rights of the patients and families. The latter can face hostility by an employer who believes that they have become unreliable either for their disease or for being involved in the assistance to their relative.
Thank to therapy improvements, many patients may become chronic patients, so that they can live an ordinary life. Sometimes they have to cope with difficulties in many fields (e.g. employment, school, family life, financial issues) for a disability, but also for the stigma of being affected by the disease.
A correct INFORMATION on the actual situation of the ill person, on his rights, and on the existing means of assistance and care is a main tool in relieving or preventing discrimination and social difficulties.
Until recent years, in Italy there were no specific social provisions for cancer patients, who have to rely on the provisions relevant to disabled people in general, subject to a certification of the percentage disability by a forensic medical commission. It used to take many months for the commission to issue a report, and financial assistance, if any, is only granted after a further delay. As of February 2006, as a result of a lobbying action by the Italian Federation of Volunteer-based Cancer Organizations (F.A.V.O.) new specific statutory provisions in favour of cancer patients were approved that speed up the temporary disability certification procedure down to 15 days. This means earlier release of any benefits such as economical indemnity, sick leave for disabled workers and relatives etc.
EMPLOYMENT is a main deal. In any enterprises employing more than 15 people, a quota of the positions is reserved by law to the handicapped people: patients who are able to work should be granted access to work opportunities as it is of utmost importance for their quality of life, in case they feel like, to be still an active member of society.

For many patients it could be of great help to have the opportunity to switch to part-time when they need time for cure or rest, and to be engaged again in their full time job when they have recovered. Back in 2003, the Italian cancer patients association AIMaC obtained from the Government, within the frame of a reformation of the labour market, that a substantive right to change from full time job to part time and reverse be granted specifically to cancer patients. Then in 2007, the joint action of advocacy of the Italian cancer patients association (AIMaC) and the Italian Federation of Volunteer-based Cancer Organizations (F.A.V.O.) succeeded in obtaining from the Italian Parliament to extend the reversible part-time job rule to family members who take care of a cancer patient.
It was the first time that legislation came out as a result of an agreement between a volunteers' association and the Government and, in Italy, this was the first specific law for employed cancer patients.

Hematopoietic Stem Cell Transplantation - Why long term follow up matters

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Transplantation of hematopoietic stem cells (HSCT) has become an established therapy for many congenital or acquired disorders of the hematopoietic system as well as for chemo- radio- or immunosensitive malignancies. Hematopoietic stem cells from bone marrow (bone marrow transplantation), peripheral blood (peripheral blood stem cell transplantation) or cord blood (cord blood transplantation) serve as stem cell source for autologus or allogeneic transplants. More than 60,000 transplants are performed annually worldwide; more than a million such procedures have been performed over the last four decades. This success is in part due to the rapid improvement in outcome in most recent years. Still, HSCT is a cost intensive medical procedure and remains associated with substantial morbidity and mortality due to early, late and very late complications. Potential complications are well described today and can in principle be attributed to the basic disease, the toxicity of the conditioning regimen or to immunological complications. Outcome after HSCT is not erratic; it can be assessed and factors associated with outcome are well described. Properties of the patients and their disease, the pretreatment, co morbidities, donor selection, transplant technique, supportive care measures, follow up as well as macroeconomic factors all contribute to the risk profile of HSCT. The likelihood of success or failure of HSCT, the choice of donor and the appropriate transplant technique has to be balanced against the likelihood of success or failure of an initial watch and wait or of any other non-transplant strategy. Ideally, HSCT should provide a better outcome measured as better overall survival, better quality of life and reduced costs.
Prerequisites for any such strategy is information on early and late outcome with HSCT or with non transplant strategies, detailed for individual patient populations and for specific transplant or non transplant techniques. HSCT is frequently associated with early mortality but reduced relapse incidence later on; specified techniques reduce early morality at the expense of delayed complications. Information on late outcome becomes essential in such a setting for correct and adequate risk assessment and patient counseling. The database of the European Group

for Blood and Marrow Transplantation (EBMT) provides such a framework and holds information on more than 300,000 patients transplanted over a 40 years period. No such comparable database is available for non transplant strategies, with the exception for aplastic anemia. Missing information will lead to inappropriate decision making. In addition, recent data from EBMT indicate that accreditation for the quality management system (QMS) JACIE (www.jacie.org) and adherence to internationals standards is associated with improved outcome after allogeneic HSCT. Data show as well that follow up of patients is significantly better for patients transplanted in an accredited center and for patients with and allogeneic compared to an autologous HSCT. Incomplete follow up might provide biased outcome data, hence trigger inadequate decisions. Mandatory data collection within a pre specified QMS can reduce such skewing, ideally within a supranational/European framework. The HSCT community has shown that such an approach is feasible. The JACIE QMS could be a role model for other cost intensive therapies in malignant diseases; ideally integrated from diagnosis to terminal care. Organizations such as the European Leukemia Net and the professional organizations such as the European Hematology Association are challenged to act.

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Quality of life in hematology: European Hematology Association theme of the year..and years to come

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Quality of Life (QoL) is an elusive concept and means a different thing depending on the setting in which it is used. The idea that we are treating patients and not illnesses is not a new one and the total care of patients is often referred to as 'holistic care'. Hippocrates believed in the holistic approach to patients; *'Whenever the art of Medicine is loved, there is also love of humanity*'. The idea that the patient is as important as the disease was eloquently stated by the 12th century Jewish Physician/Philosopher, Miamonides (Mūsā ibn Maymām or RaMBaM); *'The physician should not treat the disease but the patient who is suffering from it.'*

Before conducting a formal study on the effect of an intervention called 'Open Window,' I decided that a prospective, randomised clinical trial was necessary. The study showed significantly reduced levels of anxiety and depression in the group exposed to Open Window. Participants in the intervention (study) group also demonstrated a significantly better experience of the transplant when compared to the control group ($p=<0.001$).

How is it possible to evaluate the quality of the art intervention? Is it possible that any intervention could have a similar effect? The Open Window study, like Ulrich's, found for example, a preference for scenes of nature among patients. These are difficult questions and our study attempted to address the former. The randomisation was important to prevent bias on the part of the staff in choosing patients with an interest in art and also to make sure both groups were comparable. The curator of the project approached artists whose practise he thought would be amenable to our idea. Some artists refused, saying that their practise was unsuitable or that they did not want to make art for a specific environment.

We found that many patients treated Open Window as a personal 'art gallery' i.e. returning to images which they found reassuring or pleasant. 'Open Window' also opened up conversations between medical staff, patients and visitors rather than the usual medical problems associated with stem cell transplantation such as mucositis, hair loss etc. For some, Open Window allowed them to imagine being part of the

scenes that they viewed, to be 'somewhere else' other than their room and thinking about something else other than their illness.

What surprised us most was the positive difference in the experience of patients undergoing stem cell transplantation when exposed to Open Window, versus those who were not. Expectation is a profound form of reality. As we know the journey (in this case the stem cell transplant and all that it entails) and the destination are intertwined, one with the other. A destination (in this case discharge from the stem cell unit) without a journey would seem insignificant and a journey without a destination would be meaningless. The highly significant alteration in the experience and expectation of the transplant was a phenomenon that we feel is extremely important. The Open Window intervention had a direct beneficial effect on expectations and experience.

We do not suggest that an art intervention will necessarily influence the outcome of stem cell transplantation but that it makes the patient's time in hospital less difficult. Such interventions can be applied to many areas of medicine which have less rigorous restrictions than those of stem cell transplantation, and may significantly influence the QoL of patients. As Holm and colleagues pointed out; '*Interventions designed to increase a patient's expectations may be beneficial and should be examined in controlled studies*'. The 'Open Window' study has provided proof of principle that such an intervention has a definite place in an adult setting.

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Risk of cardiovascular disease after Hodgkin lymphoma

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Background: Late side effects after treatment are becoming increasingly important as modern treatments have led to improved survival of cancer patients. Radiotherapy (RT)-associated heart disease includes a wide spectrum of pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities. These diseases, except for pericarditis, usually do not present until 10-15 years after exposure, although non-symptomatic disorders may develop much earlier. Although the heart and vessels were considered to be relatively radioresistant, we know now that RT may damage the endothelium of blood vessels. This damage may lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism. For most cardiac toxicities a clear quantitative dose and/or volume dependence has not been shown yet, although the RT schedule, irradiated cardiac volume and irradiated structures are expected to be of great importance.
Chemotherapy (CT), especially anthracyclines, can also be cardiotoxic. The mechanism of damage from CT is different from that of RT. Although anthracyclines have long been known to induce acute cardiotoxicity, the long-term risks of CVD have hardly been examined. Anthracyclines generate oxygen-derived free radicals; increased oxidative stress results in cardiomyocyte apoptosis, thereby decreasing the number of myocardial cells. The wall of the left ventricle becomes thinner and the contractility of the myocardium decreases, leading to depressed overall function of the left ventricle. Reduction of the left ventricle ejection fraction leads to dilated and restrictive cardiomyopathy and may in the course of years result in congestive heart failure (CHF).
There are still many questions about possible interactions between CT and RT, especially concerning long-term effects. For instance, increased cardiotoxicity following anthracycline-containing CT and RT has been observed following Hodgkin lymphoma (HL) treatment. Established risk factors for CVDs are also of importance, especially because there are some indications that the effects of RT and smoking may be more than additive.

Results: We previously assessed CVD incidence in 1,474 5-year survivors of HL younger than 41 years at treatment (1965-1995). The risks of myocardial infarction (MI) and CHF were strongly increased compared with the general population (Standardized Incidence Ratios (SIRs) 3.6 and 4.9, respectively) resulting in 35.7 excess cases of MI and 25.6 excess cases of CHF per 10,000 patients/yr. SIRs of all CVDs combined remained increased for at least 25 years and were more strongly elevated in younger patients. The absolute excess risks (AERs), however, increased with longer follow-up duration, due to the increasing incidence of CVD with age. After a follow-up of 25 years or more, 7 excess cases of MI were observed per 1000 person-years. The persistence of increased risk over prolonged follow-up time is of concern.

Mediastinal RT significantly increased the risks of MI, angina pectoris, CHF and valvular disorders (2- to 7-fold). Our study was the first to examine the long-term effects of anthracycline-containing CT on CVD risk in HL patients. Anthracyclines significantly added to the elevated risks of CHF and valvular disorders from mediastinal RT (Hazard Ratios (HRs): 2.8 and 2.1, respectively). The 25-year cumulative incidence of CHF after mediastinal RT and anthracyclines in competing risk analyses was 7.9%.

Recently, we investigated in detail treatment-related risk for factors for ischemic heart disease (MI and angina pectoris), valvular disorders and CHF after HL in a case-control design. Patients are included in the studies as a case when they had at least grade 3 CVD according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Each case was matched to 2 controls on age at HL diagnosis, gender and year of diagnosis. Detailed data were collected from medical records and RT-charts. Furthermore, simulation films of radiation treatments were collected to perform radiation dosimetry (collaboration with Sarah Darby, Oxford).

For the valvular heart disease study we so far included 89 cases and 200 controls. Detailed radiation dosimetry has been performed by reconstructing the radiation treatment on surrogate Computed Tomography (CT) data sets using a CT-based treatment planning system, including estimation of dose to the individual heart valves. The mean dose to the affected valve in cases and to the same valve in controls in equivalent dose of 2 Gray fractions (EQD2) was higher for cases than controls (37 vs. 30 Gray, p=0.001) and risk increased with higher radiation doses. A linear model gave an excess odds ratio (OR) of 0.12 (95% confidence interval 0.02- 0.76) per Gray. However, this linear

model did not fit the data well as there was evidence for an upward curvature in the data (p=0.011).
In the case-control study of ischemic heart disease (IHD) we included 180 cases with IHD and 499 matched controls. Mediastinal RT (usually performed using parallel opposed fields) was associated with an increased risk of IHD (OR: 2.6, 95%CI: 1.5-4.6). Higher prescribed radiation dose to the lower mediastinum was associated with increased IHD risk. As compared to patients who did not receive mediastinal irradiation, we observed increased risks of IHD for patients who received 20-34 Gy (OR: 1.8, 95%CI: 1.02-3.2), 35-39 Gy (OR: 1.8, 95%CI: 1.4-2.4) or ≥40 Gy on the mediastinum (OR: 3.2, 95%CI: 2.2-4.6) (p<0.001). No associations or interactions were found with (anthracycline-containing) CT.
Preliminary analyses were also performed for the case-control study on CHF and cardiomyopathy. Patients who received a high dose of anthracycline-containing CT (251-600mg) had a significantly increased risk of developing CHF (OR: 4.3, 95%CI: 1.3-14.3) when compared to patients who did not receive anthracycline-containing CT. Patients who received lower doses of anthracyclines had an OR of 2.4 (95%CI: 0.6-9.6) for developing CHF RT to the mediastinum did not significantly increase CHF risk.

Conclusion: Cardiovascular toxicity is an important side-effect of RT and combined modality treatments. General risk factors for CVDs should be recognized and treated on indication. Modern RT techniques enable more accurate sparing of the heart. Further development of these techniques is of great importance because of the improved survival following many malignancies and the increased use of systemic treatment causing cardiovascular toxicity. Screening of HL survivors treated with cardiotoxic treatments is indicated.

The survivorship passport for childhood cancer survivors, and guidelines for long term follow-up

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Between 300,000 and 500,000 childhood cancer survivors (CCS) are now living in Europe and most of them have reached or are entering adulthood. Based on a conservative estimate that 75% of those treated on current protocols for childhood cancer will become long-term survivors (>5 years), then each year about 8,000 new long-term survivors are being added to the European population. Today their median age is estimated to be around 23 years and many are already well beyond the 50th year of age.

However, this success hase come at a price. Cancer or its treatment put survivors at increased risk of early mortality and/or of chronic health conditions that may severely affect their quality of life. Cumulative doses of chemotherapy and/or radiotherapy are the main risk factors for adverse events, but the individual risk may be modified by each subject's genetic susceptibility and/or lifestyle.

Clinical follow-up of CCS should be life-long and it is essential to minimize long term morbidity and mortality, and to improve patient care by providing important information for survivors and their families to enable them to become advocates for their own health. It is common clinical experience that the longer the interval from cancer diagnosis or end of treatment, the higher the probability that survivors become lost to follow-up. The risk of loss to follow-up increases as survivors transition from childhood into adulthood. Thus, it is critical that the network of care be expanded out from paediatric oncology to include family doctors, nurses and specialists from adult medicine. General practitioners and healthcare professionals who may come in contact with these patients should be aware of previous diagnoses, treatments received, hospital discharges and potential risks, in order to optimize prevention and care.

As part of the EU funded European Network for Research on Cancer in Children and Adolescents (ENCCA) the Survivorship Passport is under development, thanks to a joint effort between paediatric oncologists, cancer survivors and IT experts. The passport is generated through a secured web-based platform which is patient oriented, accessible in several European languages by all type of users (patients, clinicians, etc.) and can be integrated with national/hospital databases and clinical trials databases. Cancer-specific and treatment data can be

downloaded from clinical trials data bases through standard format files or can be imported by the paediatric oncologist. The information on the document is written in a simple and understandable way, and – on the basis of the personal data collected – the passport includes recommendations for a tailored follow-up.

The passport can be given to the individual patient at different time moments as most appropriate (e.g. at the elective end of therapies, or at 5 years since diagnosis, or at the moment of transition to adult care). In collaboration with PanCareSurFup, another EU funded project, and the International Guideline Harmonization Group for late effects of childhood cancer (IGHG) organ specific recommendations for surveillance are being developed. Guidelines are based on the best available evidence, and formulated after extensive literature review and consensus meetings.

The Survivorship Passport aims to harmonise the follow up on former cancer patients across Europe, by promoting homogeneous criteria and evidence-based guidelines from clinical practice for prevention, early detection and treatment of physical and psychosocial late adverse effects. In the age of personalised medicine, this simple and accessible tool can enhance an age-appropriate healthcare and address individual patient issues specific of paediatric cancer survivors, possibly leading to important breakthroughs in the monitoring and cure of childhood cancer survivors on the long-term.

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Scottish Intercollegiate Guidelines Network Long Term Follow Up Care for Survivors of Childhood Cancer

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Introduction

Cancer is diagnosed in 1,600 children each year in the UK, with a cumulative risk of 1 in 600 by the age of 15. Similar numbers of teenagers are also diagnosed – around 1,500 cases a year in the UK and, for teenagers, cancer is the leading cause of death after accidents. For all childhood cancers the five-year survival rate has improved over recent decades from 30% in the 1960's to 80% for children diagnosed between 2001 and 2005, due to advances in treatment regimens and better supportive care. This increased survival has led to a rapidly increasing population of adult survivors with an estimated 33,000 childhood cancer survivors now living in the UK. These survivors have higher premature death rates than the general population and are at increased risk of a range of physical and psychosocial problems. Late effects of treatment may occur soon after completion or many years later; it is possible that survivors may benefit from targeted screening, detection and treatment.

Methodology

SIGN recommendations are based on systematic reviews of best available evidence. The strength of the evidence is graded as A, B, C, or D. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based; it does not reflect the clinical importance of the recommendation. Recommended best practice ("good practice points"; GPP), based on the clinical experience of the guideline development group, is also indicated. The composition of the guideline development group will be discussed and the journey from formation of the group to the production of the guideline will be presented.

Results

One of the areas the SIGN guideline group addressed was the issue of subsequent primary cancers in survivors of childhood cancer and came up with the following recommendations.

Healthcare professionals should be aware that survivors of childhood cancer are at particular and lifelong increased risk of developing a subsequent primary cancer and that this may occur at any site on the body (C).

All survivors of childhood cancer who were treated with radiotherapy are at risk of subsequent primary cancer arising within the radiation field and healthcare professionals should adopt a high index of suspicion when assessing health concerns (C). The risk of a subsequent primary cancer increases through life.

Chemotherapy exposure is associated with increased risk of subsequent primary cancers in patients treated for childhood cancer. The effect is most consistently seen with alkylating agents (eg cyclophosphamide) and epipodophyllotoxins (eg etoposide) (C). There are reported increases in both leukaemia and solid subsequent primary cancers.

No studies were identified which explored any benefits or harms of specific screening programmes for survivors of childhood cancer, nor were any studies identified on outcomes for survivors of childhood cancer entering national screening programmes (eg mammography for breast cancer) at an earlier age than for general population groups. More research is required to determine whether those childhood cancer survivors who have received high doses of radiation to a field that includes the breast will benefit from early screening.

Summary

Guideline implementation requires investment in long term follow-up that is led by nurses with supervision from doctors. Lifelong follow-up of survivors will necessitate multidisciplinary collaboration between patients and their families, oncologists, and other health professionals (including primary care practitioners) for appropriate counseling, early diagnosis of late effects, and where possible, timely appropriate treatments.

To improve care of survivors of childhood cancer, the guideline recommends that each survivor has access to an appropriate designated key worker who will coordinate care, and that a training programme and career structure should be developed for nurse practitioners specialising in long term follow-up. A short summary of the full guideline SIGN 132 is available on the SIGN guideline app, and on the web at: http://www.sign.ac.uk/pdf/sign132.pdf

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