Biology of premature ageing in survivors of cancer

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ABSTRACT
Over 30 million cancer survivors exist worldwide. Survivors have an earlier onset and higher incidence of chronic comorbidities, including endocrinopathies, cardiac dysfunction, osteoporosis, pulmonary fibrosis, secondary cancers and frailty than the general population; however, the fundamental basis of these changes at the cellular level is unknown. An electronic search was performed on Embase, Medline In-Process & Other Non-Indexed Citations, and the Cochrane Central Register of Controlled Trials. Original articles addressing the cellular biology of ageing and/or the mechanisms of cancer therapies similar to ageing mechanisms were included, and references of these articles were reviewed for further search. We found multiple biological processes of ageing at the cellular level and their association with cancer therapies, as well as with clinical effects. The direct effects of various chemotherapies and radiation on telomere length, senescent cells, epigenetic modifications and microRNA were found. We review the effects of cancer therapies on recognised hallmarks of ageing. Long-term comorbidities seen in cancer survivors mimic the phenotypes of ageing and likely result from the interaction between therapeutic exposures and the underlying biology of ageing. Long-term follow-up of cancer survivors and research on prevention strategies should be pursued to increase the length and quality of life among the growing population of cancer survivors.

INTRODUCTION
Globally, there are over 30 million long-term survivors of cancer.1 By 2025, an estimated 19 million new cancer cases will be diagnosed each year, the majority of which will produce long-term survivors. Studies among long-term cancer survivors indicate numerous possible clinical complications resulting in considerable morbidity and mortality, related to chemotherapy, radiation therapy (RT) or both.2–6 Because of the elevated risk of chronic disease among cancer survivors, such as frailty syndrome, second cancers, psychosocial comorbidities and endocrinopathies, and because of the lack of standardised system-wide longitudinal medical follow-up, the Institute of Medicine has emphasised research in this area to establish guidance on survivorship care.7

A wealth of observational data on the development of late complications in cancer survivors are available, including our previous reviews on late complications in childhood cancer survivors8 and adults9 who undergo haematopoietic cell transplantation (HCT), but information documenting the pathological basis for development of these effects is sparse. To understand the biology of late effects better and provide a foundation for the development of interventions, it is important to characterise late effects at the cellular level. Cancer survivors, in general, appear to develop age-related diseases and phenotypes sooner than members of the general population. This is likely because damage to normal tissues from cancer therapies diminishes physiological reserve, accelerates processes typically associated with ageing or both. The roles of telomeres, senescent cells, epigenetic modifications and microRNA (miRNA) have been described in terms of their contributions to the pathobiology of accelerated ageing. However, published data linking clinical phenotypes seen in cancer survivors with processes of accelerated ageing at the cellular level is lacking. We do not wish to suggest that cancer therapies are not valuable or worthwhile; on the contrary, the advances made in cancer treatment have allowed many individuals to live long and healthy lives. However, the purpose of the current paper is to clarify the biological mechanisms by which the ageing-like sequelae cancer therapies occur. To do this, we conducted a comprehensive review of the pathogenesis of the accelerated ageing-like state in survivors of cancer.

DESIGN
A review of Embase, Medline In-Process and Other Non-Indexed Citations and the Cochrane Central Register of Controlled Trials was conducted by an experienced medical librarian resulting in 1259 articles by electronic search in December 2015. Only English language articles were searched.
The following medical subject heading terms were used: neoplasms, ageing, age factor, premature, survival, survival analysis, disease-free survival, telomere, telomere shortening, frail elderly, patients, randomised controlled trial, double-blind method, single-blind method, placebos, placebo effect, retrospective study, case report, animals and humans. The data were synthesised based on the publications pertaining specifically to the biological basis of late complications at cellular level. Translational studies on late complications of HCT were also included due to potentially similar mechanisms of tissue and cellular damage by chemotherapy or RT in HCT recipients. We first present data describing the current evidence for accelerated ageing due to cancer therapies and then detail the effects on premature ageing and senescence at cellular level by specific treatments.

RESULTS

Evidence for accelerated ageing in cancer survivors

Ageing is a natural and unavoidable process inherent to life. However, for many living creatures, ageing is associated with a variety of physical changes, hardships and illnesses. On a microscopic level, ageing is a consequence of gradual, lifelong accumulation of molecular and cellular damage and loss of physiological integrity. Hallmarks of ageing include genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, chronic low-grade inflammation and cellular senescence. 10

Although a great success, cure or control of cancer leads to a higher prevalence and earlier onset of multiple ageing-associated health problems; these include abnormal thyroid function, decreased bone mineral density and increased osteoporosis, infertility, compromised tissue regeneration, cardiotoxicity and decreased left ventricular function, pulmonary fibrosis and chronic sterile inflammation. 11–13 For example, at age 50, 45.5% of paediatric and adolescent/young adult Hodkgin’s lymphoma survivors have experienced at least one severe cardiovascular condition (defined using a modified common terminology for adverse events grading rubric). 13 Cumulative incidence of second malignant neoplasms at 30 years after childhood cancer diagnosis is nearly 8% 14; survivors of childhood cancer are 3.3–6 times more likely than age-matched individuals in the general population to develop a second malignancy. 14–16 The estimated life expectancy for this population is 30% less than that of the general population. 17 The prevalence of any chronic health condition among childhood cancer survivors at least 5 years post-treatment ranges from 66% to 88%. 6 Collectively, these epidemiological data suggest that cancer therapies may accelerate the biology of ageing.

Humans age at remarkably different rates, even in the absence of cancer therapies. 18 This separation between chronological age and biological age in part reflects an organism’s resilience to intrinsic (eg, reactive oxygen species) and extrinsic (eg, RT) stressors and capacity to restore cellular homeostasis. 19 Clinically, the increased vulnerability to stress and inability to restore physiological integrity is referred to as frailty. 20 Multiple and varied indices of frailty exist, 21 but all consistently show that those deemed frail are at significantly increased risk for adverse health outcomes, including morbidity, disability and death. 22 About 10% of individuals 65 years or older in the general population are considered frail, illustrating the link between frailty and ageing. 23

Frailty is a trait that is shared by many survivors of HCT as well. The Bone Marrow Transplant Survivor Study (BMTSS), including nearly 1000 survivors of HCT, aged 18–64, found that the risk of frailty among survivors was 10.8-fold higher than in siblings 4 and that the prevalence of frailty (8.4%) was comparable to that seen in individuals older than age 65 years. 24 Among survivors of HCT at least 10 years after transplant, the 15-year cumulative incidence of severe/life threatening/fatal conditions was 41%. 25 Frail health is often demonstrated in the population of childhood cancer survivors as well. Improvements in therapy and supportive care for children diagnosed with cancer have increased the overall 5-year survival rate from 20% in the early 1960s 26 to around 80% in recent years. 27 However, the risk of death of paediatric cancer survivors in 10 years can vary between diagnosis groups by at most 12% even up to 20 years postdiagnosis. 28 The Childhood Cancer Survivor Study (CCSS) compared the health status of 9353 adult long-term survivors of childhood cancer diagnosed between 1970 and 1986 to the health status of a randomly selected cohort of the survivors’ siblings. 29 Survivors were more likely to report poor general health, poor mental health, activity limitations and functional impairment. Forty-four per cent of survivors reported at least one adverse health status domain. Additionally, 20-year-old survivors of childhood cancer were found to have the same cumulative incidence of severe, life threatening and fatal chronic health conditions as 50-year-old siblings. 24 Furthermore, compared with sibling controls, childhood cancer survivors report poor general health with a prevalence ratio (PR) of 2.37 and adverse health status outcome in any domain with a PR of 2.10. 30 These studies provide a quantitative description of the phenotype of premature ageing in this population.

The St Jude Lifetime Cohort Study (SJLIFE) compared patients who were treated for childhood cancer at St Jude Children’s Research Hospital between 1962 and 2003, at least 10 years prior, to age-matched controls in the general population. 31 Frailty, defined as ≥2 of low lean mass, weakness, exhaustion, low energy expenditure and slow walking speed, was found in 2.7% of male participants and 13.1% of female participants. None of the comparison population fulfilled criteria for frailty. Furthermore, survivors
of childhood acute lymphoblastic leukaemia exposed to cranial radiotherapy had reduced cognitive status and memory as well as reduced integrity by neuroimaging in neuroanatomical regions consistent with early onset mild cognitive impairment and dementia. The long-term health-related outcome among childhood cancer survivors has been compared between those who were treated with HCT and those who were treated with conventional therapy. Those who received HCT demonstrated significantly elevated risk for severe/life-threatening conditions (relative risk of 3). The higher than expected prevalence of frailty among HCT and childhood cancer survivors, their increased risk for adverse health outcomes and their shortened lifespan lend further evidence to the premise that cancer therapies may accelerate the fundamental biology of ageing.

The aforementioned childhood cancer therapies and HCT are vastly different from typical therapies used to treat adult cancers. Dose intensification occurs in the majority of standard regimens used to treat childhood cancer. Adult patients with cancer receive far less volumes of chemotherapeutics, in part due to the genetic complexity of childhood cancer tumours and in part due to the ability of children’s bone marrow to quickly recover. HCT conditioning regimens historically relied on dose intensification as well. While some regimens now rely on reduced intensity conditioning, most HCT survivors are faced with long-term immunosuppression and unique challenges like GVHD. Despite the relatively mild doses of chemotherapeutics used to treat adults with cancer, these individuals often develop features of accelerated ageing as well.

Among adult cancer survivors, various conditions that occur in normal ageing are seen prematurely as well. They include neurocognitive decline, osteoporosis, skin and ocular changes, sexual dysfunction, second cancers and chronic fatigue. Muscle dysfunction often occurs as a result of cancer therapy; prolonged bed rest decreases whole body protein synthesis and leads to wasting of skeletal muscle. Adjunct chronic corticosteroid treatment, which is used in many cancer treatment regimens, can induce cataracts, osteoporosis, proximal myopathy, thinning of the skin, infection and impaired wound healing. All of the aforementioned phenotypes occur during normal ageing (see figure 1).

We have demonstrated with clinical data that cancer survivors develop the health-related manifestations of ageing more quickly than their peers. While ageing prematurely is a better alternative to dying prematurely, a better understanding of what drives this process presents an opportunity for improvement.

**Mechanisms of cellular ageing induced by cancer therapies**

At the tissue level, the hallmarks of premature ageing can be further categorised into four interlinked processes that contribute to the ageing phenotypes of decreased resilience, geriatric syndromes and predisposition to age-related chronic diseases. These include telomere attrition, cellular senescence, stem and progenitor cell

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Figure 1  Diagram depicting age-related effects of respective cancer therapies. CHF, congestive heart failure; RT, radiation therapy.
Telomeres are regions of repetitive nucleotide sequences found on both ends of eukaryotic chromosomes that aid in chromosomal separation during mitosis and ensure that chromosomes are retained and properly inherited in chromosomal separation.\(^\text{10}\) Telomere shortening occurs with each cycle of cellular division until the cell reaches its ‘Hayflick limit’—a cultured human cell’s capacity to divide for a limited number of cycles before exiting the cell cycle in G1 phase and undergoing cellular senescence.\(^\text{41}\) Shorter telomeres have been linked to higher mortality rates in a meta-analysis.\(^\text{42}\) There is also a direct relationship between average telomere length and risk for developing de novo cancers,\(^\text{43}\) and telomere shortening during the natural process is thought to be a contributing factor to the increased rates of cancers among the population.\(^\text{44}\)

Ageing humans have an increased burden of senescent cells.\(^\text{45}\) Senescent cells exhibit specific characteristics that allow their identification in vitro and in vivo, including senescence-associated β-galactosidase.\(^\text{46}\) The senescence-associated secretory phenotype (SASP) comprises proinflammatory cytokines, chemokines, growth factors, extracellular matrix proteases and other factors that impact nearby and distant normal cells, leading to local and systemic consequences of senescent cells, such as frailty and insulin resistance.\(^\text{45,47,48}\)

Due to the numerous replicative cycles they undergo, cancer cells have shorter telomeres than cells in normal tissue.\(^\text{49}\) They can survive high numbers of replications by maintaining telomeres with telomerase, an enzyme expressed in over 90% of immortal cell lines and cancers but undetectable in most normal tissues.\(^\text{50}\) Inhibiting telomerase therefore limits the growth of human cancer cells.\(^\text{51}\) The properties of telomerase can be exploited to create targeted cancer therapies including telomerase inhibitors, telomerase-targeted immunotherapies and telomerase-driven virotherapies.\(^\text{52}\) Many cancer therapies impact telomere length by causing high proliferative demand for haematopoietic reconstitution.\(^\text{53}\) In addition to increasing replicative demand, some anticancer therapies (eg, cisplatin) directly impair telomeres.\(^\text{54}\) This telomere-initiated senescence reflects a DNA damage checkpoint response activated by chemotherapy-induced dysfunctional telomeres.

Short telomeres have also been associated with stem cell exhaustion in mice and humans.\(^\text{55}\) Stem cell lines are exhausted after a certain number of serial transplantations into successive recipients.\(^\text{56}\) Depletion of haematopoietic reserve is a major mechanism of normal ageing as ageing directly affects stem cells due to exhaustion proliferation.\(^\text{57}\) Patients receiving HCT from adult donors have shorter telomeres than patients receiving HCT from younger donors, likely due to telomere shortening in ageing.\(^\text{58}\) Clonal haematopoietic disorders occur more frequently in elderly individuals who are thus are more prone to developing cancer.\(^\text{59}\) In elderly people who are already predisposed to cancer, any further insult that can affect telomeres or induce senescence can increase the risk of development of new cancers significantly.

Additionally, many chemotherapeutic agents generate free-radical intermediates, which cause direct damage to DNA.\(^\text{60}\) DNA damage is also induced by alkylating agents, a process thought to introduce secondary malignancies.\(^\text{61}\) DNA repair enzymes are inhibited by some cancer therapies, such as topoisomerase I and topoisomerase I inhibitors.\(^\text{36}\)

Many epigenetic modifications occur as part of the normal cellular ageing process. Adult identical twins, despite identical genotypes, have different disease susceptibilities, largely attributed to the epigenetic changes that occur as they age.\(^\text{62}\) Overall, global hypomethylation, CpG island hypermethylation and changes in histone methylation increase with normal ageing.\(^\text{63}\)

The involvement of miRNAs has also been implicated in senescence and ageing.\(^\text{64}\) The most upregulated miRNAs are found in cells in states of stress-induced senescence, followed by those in replicative senescence, then by those in quiescence.\(^\text{65}\) It is likely through these primary mechanisms that adjuvant chemotherapy accelerates the development of age-related phenotypes and causes early onset frailty.\(^\text{36}\)

### Evidence of ageing at the cellular level due to specific cancer therapies

Tumour cells can be induced by chemotherapy to undergo senescence in both in vivo and in vitro models.\(^\text{66}\) One way by which this occurs is through allowing γH2AX to accumulate in telomeric DNA in cells undergoing senescence.\(^\text{67}\) γH2AX accumulation is an indicator for developing age-related disease.\(^\text{45}\) Various cytotoxic drugs (cyclophosphamide, doxorubicin, azidothymidine,
5-fluorouracil) have been shown to induce senescence directly in tumours via DNA damage. Many drugs act similarly, inducing ageing-related biological pathways.

Table 2 Specific therapies inducing/mitigating the development of an accelerated ageing-like state

| Agent modality                        | Agent                  | Cellular effects                                                                 |
|---------------------------------------|------------------------|----------------------------------------------------------------------------------|
| Radiotherapy                          | Ionising radiation     | Cellular senescence, changes to DNA repair genes, epigenetic alterations          |
| Hormonal                              | Tamoxifen              | Cellular senescence                                                              |
| Tyrosine kinase inhibitors            | Sunitinib              | Cellular senescence, Dasatinib→senolytic                                          |
| Anthracyclines                        | Doxorubicin, Daunorubicin | Free radical generation, DNA damage, telomere attrition, cellular senescence, stem cell exhaustion |
| Alkylating agents                     | Cyclophosphamide, Temozolomide | DNA damage, cellular senescence, epigenetic alterations                  |
| Topoisomerase inhibitors              | Anthracyclines, Epipodophyllotoxin (eg, etoposide), Camptothecin analogues (eg, irinotecan) | DNA damage, epigenetic alterations |
| Antimetabolites/cytotoxic drugs        | 5-Fluorouracil, Cisplatin | Cellular senescence, DNA damage                                                  |
| BRAF inhibitor                         | Vemurafenib            | Cellular senescence                                                              |
| Antitumor antibiotics                 | Mitomycin C            | Cellular senescence, epigenetic alterations                                       |
| Isoquinololine alkaloid                | Berberine              | Cellular senescence                                                              |
| Bcl-2 inhibitor                       | Navitoclax, Obatoclax  | Senolytic (apoptosis of senescent cells)                                         |
| HCT (includes conditioning regimen)   | N/A                    | Telomere attrition, stem cell exhaustion                                        |
| Telomerase inhibitors                 | GRN163L (Imetelstat), Vaccines (GV-1001, GRNVAC1, Vx-001) | Possible telomere attrition                                                    |
| Nucleoside analogue reverse-transcriptase inhibitor | Azidothymidine | Telomere attrition                                                             |
| DNA cross-linking agents              | Cisplatin              | Epigenetic alterations                                                           |
| Ribonucleotide reductase inhibitors   | Hydroxyurea, Methotrexate | Epigenetic alterations                   |
| Microtubule inhibitors                | Vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine), Taxanes (paclitaxel, docetaxel), Podophyllotoxin | Epigenetic alterations |
| miRNA                                 | miR-34a, miR-144, miR-21, miR-155 | Cellular senescence, telomere attrition |
| GVHD                                  | N/A                    | Telomere attrition                                                              |

BRAF, B-Raf proto-oncogene; Bcl-2, B cell lymphoma 2; GVHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; miRNA, micro RNA; N/A, not available.
of telomerase, hTERT, including small molecule inhibitors, antisense oligonucleotides, immunotherapies, gene therapies and G-quadruplex stabilisers. Preclinical studies with hTERT peptides have led to the creation of vaccines that target telomerase, including GV-1001, GRN163L and Vx-001. Normally, a self-antigen molecule, hTERT can stimulate specific cytotoxic T lymphocytes through major histocompatibility complex presentation, leading to tumour cell lysis.

Many epigenetic modifications occur during normal cellular ageing. Overall, global hypomethylation, CpG island hypermethylation and changes in histone methylation increase with normal ageing. While CpG hypermethylation is a component of drug-induced cytotoxicity that is damaging to cancer cells and thus advantageous in the treatment of cancer, it may also be a toxic side effect in normal cells of patients receiving such drugs. DNA hypermethylation at CpG islands is induced in human cells after exposure to each of the following commonly used cancer chemotherapy agents: topoisomerase II inhibitors, antibiotics, microtubule inhibitors, DNA cross-linking agents, hydroxyurea, antimetabolites and methotrexate. Clinically relevant drugs reported as DNA hypomethylating agents include azacitidine and decitabine, hydralazine and MG98. While these agents may be effective in making cancer cells more susceptible to cytotoxic damage, they may also accelerate ageing changes in normal cells. Furthermore, the same epigenetic alterations that are targeted by some anticancer drugs are likely involved in the development of new secondary cancers.

The involvement of miRNAs has been implicated in senescence and ageing. Inhibitors for oncogenic miRNAs and limitations of tumour suppressor miRNAs are being developed for potential use in various cancer treatments as correcting abnormal miRNA expression holds potential for overcoming resistance in certain types of cancer cells. miRNA-29 has shown promise in modifying lung cancer cells. While miRNA-29 has been shown promise in modifying lung cancer cells, expression profiles of miRNAs are different in lung cancer and normal lung. The enforced expression of miRNA-29 in lung cancer restores normal patterns of DNA methylation and induces expression of several tumour suppressor genes. miRNA-451 also holds potential to decrease cancer cells’ resistance to treatment. Transfection of breast cancer cells resistant to doxorubicin with this miRNA results in increased sensitivity to chemotherapy.

‘Stem cell exhaustion’ refers to the replicative stress of transplanted haematopoietic stem cells (HSCs) following haematopoietic reconstitution after HCT. Stem cells may effectively undergo the normal ageing process at an accelerated rate, leading to premature bone marrow failure. A single serial transplantation causes a large decline in HSC repopulating ability, and transplantation effectively causes an acceleration of the normal ageing process. The administration of doxorubicin to c-kit positive human cardiac progenitor cells (hCPCs) leads to the expression of the senescence markers p16INK4a and γH2AX, suggesting that anthracycline cardiomyopathy is caused by depletion of the hCPC pool (stem cell exhaustion).

After HCT, prevalence of myelodysplasia and secondary malignancies increases, likely induced by conditioning agents used in HCT and excessive proliferative stress following HCT. Newer non-myeloablative and reduced intensity preparative regimens for allogeneic HCT induce less toxicity and treatment-related mortality in recipients. While myeloablative conditioning is based on high-dose drug toxicity to haematopoietic stem cells, non-myeloablative conditioning utilises immunosuppression, resulting in a state of mixed chimerism (at least early after transplantation). However, telomeres are comparably shortened in recipients of both non-myeloablative and myeloablative conditioning, suggesting that the primary mechanism of telomere shortening is accelerated proliferation rather than the cytotoxic effects of myeloablative conditioning drugs.

Androgens have been used to treat various bone marrow failure syndromes, such as dyskeratosis congenita, since the 1960s. It has been used in patients who cannot undergo HCT. The proposed mechanism of sex hormone therapy is upregulation of telomerase gene expression. In a recently published clinical trial, patients with telomereopathies received daily doses of the synthetic sex hormone danazol for 24 months, and about 40% demonstrated a gain in telomere length from baseline. Additional study of sex hormones as potential mitigators of telomere attrition in patients at risk for acquired telomereopathy, including those receiving cancer therapies, is warranted. This study points towards potential future strategies with sex hormones to mitigate telomere attrition in patients at risk for telomeropathy, including those receiving cancer therapies.

As many cancer treatments appear to induce an accelerated ageing-like state, interventions that target fundamental ageing processes may have a role in cancer survivors. Since many cancer therapies induce cellular senescence, among the most promising agents are senolytics, drugs that selectively eliminate senescent cells and SASP inhibitors, which blunt local and systemic effects of the SASP. These agents alleviate frailty, restore progenitor function, reduce insulin resistance, rescue cardiac and vascular dysfunction, decrease adverse effects of RT and reduce osteoporosis in a variety of animal models of ageing and disease. Senolytics are effective when administered intermittently, potentially reducing toxicity, and resistance to these drugs is unlikely to develop as, unlike cancer cells or microbes, senescent cells that do not divide.

**DISCUSSION**

Despite the negative sequelae that many cancer therapies lead to or accelerate, it must be emphasised that these therapies are indeed valuable and worthwhile to countless patients with cancer. Ageing is a natural and in
some ways desirable phenomenon; however, we believe that a decline in health that mimics age-related illness is a negative consequence experienced by many recipients of cancer treatment. Recognising this phenomenon and understanding the mechanisms underlying it offer an opportunity for the development of alternative therapies and ameliorating medications. We believe that cancer survivors deserve long-term follow-up for mitigation of the late effects.

CONCLUSION
Our expert review of the associations of cancer treatments with accelerated ageing reveals that multiple ageing pathways contribute to late complications in cancer survivors. A variety of chemotherapeutic agents have been implicated in the pathogenesis of senescence and acquired telomereopathies, which culminate in morbidity and mortality due to frailty phenotypes and ageing-associated diseases. Our search also identified a paucity of long-term cancer survivorship studies evaluating ageing parameters (telomeres, p16\(^{INK4a}\) senescent cells, miRNA, methylomes) in the context of clinical outcomes. Future research to better understand mechanisms of accelerated ageing-like phenotypes is essential for oncology community as well as from a public health and health policy perspective. The ultimate goal of these studies will be to prevent late complications using early interventions including lifestyle changes and medications (eg, androgens, mTOR inhibitors and senolytic drugs).

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