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REVIEW ARTICLE

Effects of smoking on outcomes of hematopoietic cell transplantation: a systemic review and future directions

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Abstract

Hematopoietic cell transplantation (HCT) survivors are at risk of increased mortality compared to the general population. Smoking by HCT survivors has been reported to impact a variety of health outcomes, resulting in an increased risk for infections, cardio-pulmonary diseases, and cancer. The purpose of our study was to conduct a systematic literature search to determine the relationship between tobacco smoking pre-HCT and post-HCT outcomes. We conducted an electronic literature search from all languages from multiple peer-reviewed databases of studies that evaluated the effects of tobacco smoking prior to HCT on clinical outcomes. Data were extracted from the studies according to a strict selection criterion. Due to differences in primary endpoint and different populations evaluated in different studies, a meta-analysis was not possible, and a descriptive quantitative analysis is provided. Out of the 447 publications fulfilling the selection criteria for the electronic search, 17 articles were included in the final sample. The studies varied in terms of study design, patient characteristics, and HCT type. Considerable variability in definition of smoking was observed. We found that smoking pre-HCT was associated with a higher incidence of cardiovascular diseases, new infections, pulmonary complications, and cancers in comparison to non-smokers. Moreover, smoking pre-HCT was significantly associated with increased risks of both relapse and non-relapse mortality, and inversely related to median overall survival. Smoking adversely affects mortality in all HCT survivors by increasing the risks of both malignant and non-malignant complications. Thus, guidelines are urgently needed to formulate lifestyle factor modifications for HCT survivors focusing on smoking cessation strategies and abstinence maintenance in former smokers. Given the strength of these findings, guidelines should include systematic definitions of smoking for use in clinical trials as well as in standardized data reporting.

Introduction

According to the World Health Organization (WHO), globally, complications from smoking tobacco kill more than 7 million people every year and second-hand smoke causes more than 890,000 deaths annually [1]. Complications related to smoking result in an estimated 300 billion dollars in annual health care costs in the United States alone [2, 3]. Approximately 16 million people live with serious disease caused by smoking, yet it remains the leading cause of preventable death in the world [4]. Smoking decreases the life expectancy by at least one decade compared to non-smokers, and smoking cessation before the age of 40 years decreases the risk of death associated with continued smoking by 90% [5].

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for many malignant and non-malignant disorders. Since its inception almost seven decades ago, improvements have significantly advanced the field permitting older patients and those with co-morbidities to safely undergo HCT. However, HCT is still associated with potential morbidity and mortality [6]. Hence, efforts to modify potential risk factors like smoking which can lead to adverse outcomes in

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HCT survivors are necessary. The prevalence of lifetime smoking has been documented to range from 10 to 62% among HCT candidates, noting variable quality of data collection [7]. The only known study of biochemically validated tobacco use found that 9.9% of HCT candidates were currently using tobacco [7]; post-HCT smoking prevalence 2–22 years post HCT has been documented as 17% by Bishop et al. [8]. Large database studies in HCT recipients have shown that tobacco smoking can significantly decrease overall survival (OS) [9] and lead to the development of solid cancers (particularly lung cancer) [10]. Despite convincing data concerning the harms of tobacco smoking on post-HCT outcomes, to our knowledge, currently none of the professional societies associated with HCT have specific health care delivery guidelines for providers who want to help their patients stop smoking pre- or post-HCT. Majhail et al. [11] provided general recommendations for education and counseling of all HCT recipients on a healthy lifestyle, including regular exercise, maintaining a healthy weight, following a healthy diet, and avoiding smoking. However, evidence-based methods of smoking cessation for HCT patients were not discussed.

Over the past decade, studies have noted associations of smoking with infections, cardio-pulmonary diseases, and cancers; however, the effect size among studies is variable given small sample sizes and different cohort selections. To address this issue, we conducted a comprehensive systematic review with the hypothesis that smoking leads to a significantly increased risk of mortality and morbidity.

Methods

Data sources

We conducted a systematic electronic literature search from 1998 to August 2017 from PubMed, Sage Journals, Science Direct, Springer Link, Amedo, ProQuest, OVID-MEDLINE, and Wiley-Blackwell for studies describing the association between smoking and HCT outcomes. The search focused on three themes of Medical Subject Headings (MeSH) terms and related exploded versions: smoking, tobacco or cigarette, blood and marrow transplantation (BMT) and HCT and studies with a prospective and retrospective design.

Study selection

Titles and abstracts were screened to determine if publications met our inclusion criteria: (1) allogeneic and autologous HCT; (2) tobacco smoking; (3) retrospective and prospective observational cohort studies; (4) abstracts or unpublished work with sufficient information; and (5) cardio-pulmonary complications, infections, or secondary cancers. Case reports, abstracts, or unpublished work with insufficient information were excluded. We evaluated eligible articles first by screening titles or abstracts, followed by full-text reviews to ensure all included studies involved a prospective examination of smoking as a predictor of median survival in an HCT population. Two authors (SKH and MA) independently determined the eligibility of studies.

Data extraction and analysis

We extracted the following information using a predesigned collection form: study characteristics (authors, study type, and number of participants), smoking status, and patient characteristics (mean age and sex), transplant type, conditioning regimen, acute and chronic graft-versus-host disease risk, and transplant outcomes (cardiovascular diseases, infections, pulmonary complications, and secondary cancers), as well as the incidence of relapse, non-relapse mortality, and the OS (Table 1). Due to variability in definition of smoking, the HCT population, and outcome variables, a meta-analysis was not possible and hence a descriptive analysis was performed.

Definitions

Smoking dose: inhalation/exhalation of tobacco smoke. Definitions of smoking and exposure were searched in all articles.

Cardiovascular complications: these included ischemic heart disease (IHD), heart failure (HF), stroke, peripheral arterial disease, and atrial fibrillation.

Infections: types of infections included viral, fungal and bacterial. It included pneumonia, sepsis, and bacteremia.

Pulmonary complications: These included bronchiolitis obliterans (BO), idiopathic pneumonia syndrome, respiratory failure, interstitial lung disease (ILD), diffuse alveolar hemorrhage and adult respiratory distress syndrome.

Results

We identified 447 records from the literature search of which 17 eligible articles were included (Fig. 1). The results were divided into organ dysfunction and transplant outcomes. Different studies used different definitions of smoking and exposures (Table 1).

Organ dysfunction

Cardiovascular (CVS) complications

In the Chow et al. [12] study, smokers were found to be at a significantly higher risk of both IHD and HF. The

Table 1 Patient characteristic, NRM, Relapse, OS, and smoking dose

Author	Males	Smoking	Transplant type	Conditioning	NRM	Relapse	Median OS	Smoking dose	Smoking exposure
Marks et al. [9]	58%	22%	Allogeneic	Myeloablative	28% Non-smokers 50% smokers at5 years	8% Non-smokers 10% Low-dose smokers 6% High-dose smoker at 5 years	68% Non-smoker 62% Low-dose smokers 50% High-dose smokers at 5 years	High dose ≥10 pack-years or >1 pack per day) Low dose <10 pack-years or 1≤pack per day.	Medical records, self-reported
Mo et al. [24]	72%	22%	Allogeneic	NA	NA	NA	At 100 days HR 3.4	NA	NA
Chow et al. [12]	53%	44%	Allogeneic 57 Autologous 43%	Myeloablative	28.7%	28.7%	NA	Average smoking 22.3 pack-years	NA
Ehlers et al. [17]	54%	45%	Allogeneic 74% Autologous 26%	NA	19.8% Non-smokers 16.8% Previous 9.9% Current	25.7% Non-smokers 18.8% Previous 8.9% Current	42.9% Non-smokers 25.7% Previous 19.1% Current at 3 years	Previous smokers, more than 1 year from HCT Current smokers, 1 year or less from HCT	Medical records
Tichelli et al. [13]	57%	13%	Allogeneic	NA	NA	NA	With an arterial event was 48% ± 21%, 77% ± 3% for patients without an arterial event	NA	NA
Tran et al. [19]	57%	37%	Allogeneic	Non-myeloablative 38%, myeloablative 61%	37% Non-smokers 42% Previous 34% Current	20% Non-smokers 18% Previous 18% Current	NA	Former smokers quit smoking at least 1 year before the interview. Current smokers, actively smoke or quit in less than a year prior to the interview. Overall median numbers of pack-years smoked was 10	Self-reported at time of PFT
Hanajiri et al. [16]	NA	56%	Allogeneic	Non-myeloablative 23%, myeloablative 77%	20% Non-smokers 22% Low-dose smokers 24% High-dose smokers at 3 years	29% Non-smokers 25% Low-dose smokers 35% High-dose smokers at 3 years	48% Non-smokers 52% Low-dose smokers 38% High-dose smokers at 3 years	Low-dose BI 1–399, high-dose BI ≥400	NA
Qazilbash et al. [14]	62%	36%	Allogeneic	Non-myeloablative 63%, myeloablative 37%	LVEF <45%, 12.5% LVEF >50%, 14.9%	NA	LVEF <45%, 25% LVEF >50%, 38%	NA	NA
	60%	62%	Allogeneic	NA	NA	NA	NA	NA	NA

Table 1 (continued)

Author	Males	Smoking	Transplant type	Conditioning	NRM	Relapse	Median OS	Smoking dose	Smoking exposure
Chang et al. [23]									
Mawardi et al. [21]	73%	42%	Allogeneic	Non-myeloablative 46%, myeloablative 54%	NA	NA	Invasive oral cancer 70%	NA	NA
Schlemmer et al. [34]	70%	43%	Allogeneic	Non-myeloablative 57.5%, busulfan based 25%, TBI 62.5%	33%	5%	Median survival 24 months after ILD is 61%	NA	NA
Shah et al. [22]	1 out of 3	NA	Allogeneic	NA	NA	NA	NA	NA	NA
Tomas et al. [35]	59%	35%	Allogeneic	Myeloablative 100%	NA	NA	NA	Median of 10 pack-years of smoking	NA
Ho et al. [20]	56%	38%	Allogeneic Autologous Syngeneic	NA	NA	NA	NA	NA	NA
Savani et al. [18]	58%	13%	Not specified	Myeloablative	Lung shielding 14.1% No shielding 3.3%	NA	Lung shielding 70% No shielding 52%	NA	NA
Miceli et al. [15]	61%	44%	Autologous	Melphalan high dose	NA	NA	NA	Active smoking regardless of the numbers of packs	NA
Majhail et al. [10]	53% AML, 58% CML	24% AML, 25% CML	Allogeneic	High-dose busulfan-cyclophosphamide	NA	NA	NA	NA	NA

NRM non-relapse mortality, *OS* overall survival, *NA* not applicable, *HR* hazard ratio, *HCT* hematopoietic cell transplant, *PFT* pulmonary function test, *BI* Brinkman index (the BI was calculated by multiplying the number of cigarettes smoked per day by the duration of smoking (years)), *LVEF* left ventricular ejection fraction, *TBI* total body irradiation, *ILD* interstitial lung disease, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia

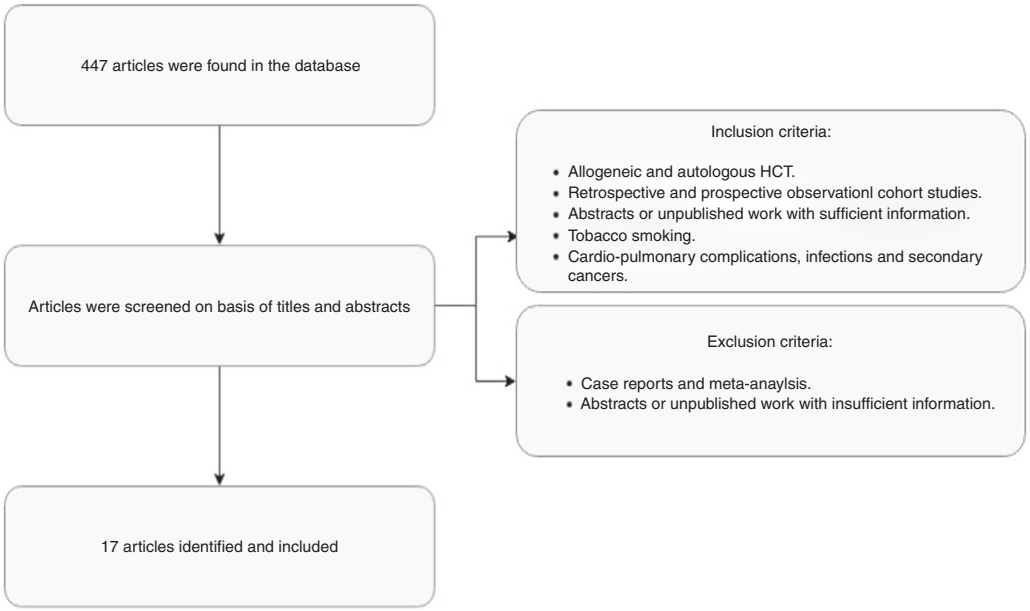

Fig. 1 Search and selection process

cumulative incidence of cardiovascular events in patients with high global cardiovascular score was higher in comparison to patients with low risk score, where patients with persistent smoking with CVS complications had a 15% risk (7–30%; $P = 0.0001$) of developing an arterial CVS outcome [13]. Cardiac complications were also higher among smokers (hazard ratio (HR) 3.9, 95% confidence interval (CI) 0.7–20.2, $P = 0.1$) compared to non-smokers as observed in the study by Qazilbash et al. [14].

Infections

In the study by Miceli et al. [15], a significant association between smoking and bacteremia was found ($P = 0.0296$). Smoking was a significant predictor of severe infection in myeloma patients after HCT [15]. Hanajiri et al. [16] reported that pneumonia occurred more in smokers than non-smokers [16]. In the Ehlers et al. [17] study, the mean number of infections in never, previous, and current smokers was 1.9, 1.8, and 2.2, respectively. People who smoked had a higher risk of bronchopneumonia in the study by Marks et al. [9].

Pulmonary complication

In the study of Marks et al. [9], the smokers were found to be at a higher risk of BO [9]. In a study by Savani et al. [18], smoking was an independent risk factor for pulmonary transplant-related mortality (relative risk (RR) ~5.0) [18]. The incidence of pulmonary complications was 46% among smokers in the study of Ehlers et al. [17]. In the study of Tran et al. [19], twofold increase in pack-years smoked was associated with a higher risk of early respiratory failure (HR 1.33, 95% CI 1.09–1.64, $P = 0.006$) [19]. In Hanajiri et al. [16], high-dose smoking was associated with higher risk of pulmonary complications in both univariate (RR 2.02, 95% CI 1.21–3.35, $P < 0.01$) and multivariate analysis (RR 1.78, 95% CI 1.06–3.00, $P = 0.03$). There was no association between smoking and severe pulmonary complications as observed in the study of Ho et al. [20]. Ehlers et al. [17] also documented decreased pulmonary function tests in current versus never smokers, including percent of predicted forced expiratory volume in 1 s (FEV1), diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin (DLCO), and forced expiratory flow at 25% to 75% capacity (FEF 25–75).

New cancers

Smoking was a risk factor for development of oral cancer in two studies by Mawardi et al. [21] and Shah et al. [22]. Majhail et al. [10] reported the risk of lung cancer was elevated in older patients with a smoking history prior to HCT. Of the 11 patients who developed lung cancer, 9 were smokers (RR 11.6, CI 1.4–96.0, $P = 0.02$) [10].

Transplant outcomes

Relapse

Smoking was significantly associated with higher rates of relapse in most of the studies. In Marks et al. [9], the risk of

relapse was higher in smokers than non-smokers (RR 1.67, $P = 0.003$). In Hanajiri et al. [16], the relapse incidence was higher in high-dose smokers than non-smokers at 3 years post HCT. Tran et al. [19] found that a twofold increase in pack-years smoked was associated with higher risk of relapse (HR 1.16, 95% CI 0.92 to 1.46, $P = 0.21$).

Non-relapse mortality

In the study of Marks et al. [9], the non-relapse mortality (NRM) at 5 years post HCT was higher among smokers. Ehlers et al. [17] found that, with 3.5 years of follow-up, current smokers were at higher risk of NRM in comparison to non-smokers. At 3 years after HCT, the NRM was higher among smokers in the study of Hanajiri et al. [16] ($P = 0.84$) [16]. In the study of Tran et al. [19], higher dose of smoking was not associated with a higher risk of NRM (HR 0.97, 95% CI 0.85–1.10, $P = 0.64$). The median numbers of days from HCT to NRM was 163 days. There was no clear association between the smoking and mortality after HCT in the study by Chang et al. [23].

Overall survival

Smoking was significantly associated with worse OS in all studies. OS was lower in the smoking group versus non-smoking group at 5 years after HCT ($P < 0.001$) in the study of Marks et al. [9]. The 100-day OS after pneumonia was lower in patients who smoked before HCT ($P = 0.002$) as observed by Mo et al. [24]. In Ehlers et al. [17], smokers had worse OS than non-smokers (HR 1.88, 95% CI 1.09–3.25).

Discussion

Smoking is one of the leading causes of preventable deaths in the United States. Smoking is associated with heavy economic burden all over the world [25]. The amount of health care expense due to diseases attributed to smoking is around 5.7% of global health expenditure. The economic cost of smoking reached $185 billion in 2012 [25]. To our knowledge, this is the first systematic review that examines the association between smoking and HCT clinical outcomes. Smoking was associated with an increased risk of cardiovascular disease in HCT recipients as observed in some studies. It was also associated with a heightened risk of infectious complications in HCT recipients. In addition, smoking was associated with an increased incidence of invasive fungal infections (IFIs) in allogeneic HCT recipients as observed in Mehdi et al. [26] study. In the heavy-smoking group, the incidence of IFIs was 27.5% (HR 2.54, 95% CI 0.98–6.58, $P = 0.06$). In addition, the OS and NRM were higher in the heavy-smoking group (HR 1.54 and 1.65, respectively). However, there was no significant difference in relapse or relapse mortality [26]. As observed in some studies, the pulmonary complications (both infectious and non-infectious) were strongly associated with smoking. The incidence of lung cancer was higher in smokers compared to non-smokers as expected. We found that the smoking was impactful for all HCT outcomes, being significantly associated with higher rates of relapse, NRM, and decreased OS in most of the studies. Our study has many limitations. One of the limitations is the absence of individual-level data and the absence of uniform endpoints. Another limitation is generally the poor quality of the studies. We could not find a single prospective study focusing on either the biology of late effects with respect to smoking, or on assessment of biochemically verified smoking exposure as a *predictor variable*.

Ehlers et al. [7] found that serum cotinine increased the smoking detection rate by greater than 50% over self-report, and thus documented impacts of smoking on HCT outcomes are based on under-reported use. Only one study examined health care utilization in HCT survivors; current smokers averaged 21 more hospitalization days than never smokers in an outpatient-based HCT program within 1-year post HCT [7]. In the Ho et al. [20] study, patients who underwent autologous HCT were at lower risk of severe pulmonary complications (SPCs) in comparison to patients who underwent allogeneic HCT. The incidence of SPCs was higher among patients with low FEV1 (≤80%). The risk of SPCs in patients who never smoked, quit smoking for more than 1 year, and actively smoked was 21%, 30%, and 29%, respectively [20]. In one recent publication, the risk of obstructive lung diseases was independently associated with smoking in lymphoma survivors post high-dose therapy with autologous stem cell transplantation [27]. Moreover, a large retrospective study was done in the United Kingdom to evaluate the impact of smoking on the development of many cancers. There was no association between smoking and skin cancer (HR = 0.74). However, smoking was positively associated with bladder cancer (HR = 2.32) [28]. Despite this wealth of data on tobacco-associated complications leading to both mortality and morbidity in HCT patients, currently, the professional organizations associated with HCT have not formulated health care delivery guidelines for smoking cessation before or after HCT. Other professional medical societies have developed recommendations and guidelines on smoking cessation based on the scientific evidence and have graded the summary via different tools (e.g., Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale). The National Comprehensive Cancer Network (NCCN) published an updated guideline for smoking cessation in cancer survivors in which they recommended combining

pharmacological and behavior therapy with medical therapy, a combination of nicotine replacement therapy and varenicline. In the smoking literature, attempt to quit and duration of quit are considered to be strong factors for smoking cessation. In a large smoking behavior study, the rate of the relapse was high within the quarter of a quit attempt (close to 80%). Of those who did not relapse within the first quarter of attempting cessation, almost 60% relapsed in the next quarter. However, after two quarters of abstinence, the relapse rate dropped below 20% and the cumulative relapse rate reached a plateau. In other words, the longer participants maintained abstinence, the less likely they were to relapse in the long term. Because smoking relapse is common, ranging from 75% to 80% after a quit attempt in the first 6 months [29], they recommended a focus on smoking "relapse prevention", discussion of relapse risk with patients, continuing smoking assessments, and support to encourage and maintain smoking cessation attempts. Smoking assessment and intervention should be integrated into treatment and survivorship care plans for smokers and those who report quitting within at least the past year if not longer [7]. All recommendations were grade 2A by the NCCN unless otherwise indicated [30].

The American Society of Clinical Oncology (ASCO) has also published guidelines for smoking cessation. They encourage providers to talk to their patients about worse treatment outcomes for smokers regardless of whether the cancer was tobacco related. Because electronic cigarettes and smokeless tobacco are not evidence-based methods for smoking cessation, and have documented harms, they are not recommended by ASCO [31]. In September 2015, the United States Preventive Services Task Force (USPSTF) published an updated recommendation for smoking cessation. In non-pregnant adults, they recommended that all physicians should ask the patients about tobacco use, advise them to stop using it, and provide behavioral interventions as well as US Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to adults who smoke (Grade A). In addition, USPSTF recommends that physicians should ask all pregnant women about smoking, advise them to quit, and provide behavioral interventions for cessation (Grade A) [32] (Table 2). The American Society for Blood and Marrow Transplantation (ASBMT) provided a recommendation for screening and prevention of late complications in long-term HCT survivors. They recommended to assess for tobacco use and counsel against smoking to prevent secondary cancers, respiratory, and cardiovascular complications. In addition, they recommended to maintain the oral hygiene and avoid smoking before any dental procedure to decrease the risk of infective endocarditis [33]. A systematic review of the HCT literature clearly demonstrates a profound impact of tobacco smoking on long-term HCT outcomes. We encourage the transplant-related societies who develop clinical guidelines or recommendations (e.g., American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplant (EBMT), Asia Pacific Blood and Marrow Transplantation (APBMT), Latin American Bone Marrow Transplantation Group (LABMT), and Eastern Mediterranean Blood and Marrow Transplantation (EMBMT)) to develop consensus guidelines or position statements on smoking cessation post HCT (or pre-HCT at the time of referral if logistically possible) in the light of current evidence. Additionally, the results of this systematic review highlight important research questions, for which

Table 2 Current guidelines for smoking cessation

NCCN	➢A combination of pharmacologic and behavior therapy is the most effective method for smoking cessation.
	➢Smoking status should be updated at regular intervals (change in status of smoking, quit attempts, and interventions used).
	➢Providers should monitor smoking relapse.
	➢Clinicians should encourage continued smoking cessation attempts.
	➢Cessation of smoking should be offered during cancer treatment.
USPFTF	➢In non-pregnant adults, all physicians should ask the patients about tobacco use, advise them to stop using it, and provide behavioral interventions as well as US Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to adults who smoke (grade A).
	➢In pregnant women, all physicians should ask the patients about smoking, advise them to quit, and provide behavioral interventions for cessation (grade A).
ASCO	➢Ask every patient about their tobacco use at each clinic visit.
	➢Advise tobacco users to quit immediately.
	➢Assess patients' motivation to stop smoking.
	➢Assist tobacco users in their attempt to quit.
	➢Arrange for appropriate follow-up.

NCCN National Comprehensive Cancer Network, *USPSTF* United States Preventive Services Task Force, *ASCO* American Society of Clinical Oncology

Table 3 Questions on hematopoietic cell transplantation (HCT) survivorship with respect to smoking

Topic	Current evidence	Literature gap	Question
Smoking cessation pretransplant	Smoking status at the time of HCT affects post-HCT survival	No prospective or case control studies evaluating clinical outcomes	Should smoking cessation be a relative or an absolute contra-indication to HCT? And for allogeneic or autologous or both? In which conditions rapid quitting or cessation or taper should be instituted pre-HCT (e.g., those needing urgent HCT as in acute leukemias)
Timing of smoking cessation	Various studies have shown differential outcomes with respect to smoking cessation and late complications	Exactly timing of smoking cessation pre-HCT is unknown	When should active smokers quit smoking pre-HCT?
Smoking cessation strategies	None available in HCT survivors	No data available in HCT survivors	For smoking cessation, should behavioral or pharmacologic (or both) interventions be undertaken? Should smoking cessation strategies be different pre- and post-HCT?
Smoking and late effects	Ample observational data available on both malignant and non-malignant late effects	No data available on biology of accelerated aging due to tobacco in HCT patients	What type of prospective studies or nested case control studies should be undertaken to evaluate the biology of premature aging (p16 senescence, telomeres etc.) in HCT survivors with respect to tobacco exposures? What is the impact of smoking on the quality of life in HCT survivors?

scientific studies are needed to improve the care of HCT survivors (Table 3).

Author contributions SKH and MA wrote the first draft of the manuscript. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data for the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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