PROTOCOL

Changes in body composition after allogeneic haematopoietic stem cell transplantation (HSCT) with total body irradiation (TBI) for treatment of leukaemia in children, teenagers and young adults (CTYA): a rapid review

Date of publication:
01/07/2019

Team
Dr Ava Lorenc, Prof Julian Hamilton-Shield, Dr Rachel Perry, Dr Alyson Huntley, Prof Michael Stevens

University of Bristol

Background

Leukaemia is the commonest type of cancer in children (0 to <16 years) and one of the most common diagnoses affecting teenagers and young adults (TYA, 16 to <25 years). Patients who fail primary treatment or those with very high risk factors at diagnosis, are commonly treated with allogeneic haematopoietic stem cell transplantation (HSCT) after conditioning (disease ablation and immune suppression) with high dose chemotherapy and total body irradiation (TBI)[1]. Survivors of HSCT with TBI conditioning experience long-term morbidity, impaired quality of life and reduced life expectancy. Endocrine disorders including growth hormone deficiency, hypothyroidism and gonadal failure are well-described but there is evidence of a phenotype emerging in early adult life that resembles accelerated ageing[2] with early post-transplant telomere shortening [3] and long term metabolic dysfunction [4], abnormal body composition [5,6], frailty[7] and fatigue [6]. Investigation has identified specific findings which incorporate features of the metabolic syndrome including hypertension, dyslipidemia, insulin resistance, visceral adiposity and a pro inflammatory state[8,9].

Screening for adverse adiposity that increases cardiometabolic risk in the general population is relatively easy using standard measures of obesity (raised BMI and/or waist circumference) but is less straightforward in HSCT/TBI survivors who may not be overtly obese by these criteria. In contrast, they are characterised by the presence of increased visceral but reduced subcutaneous fat and reduced lean mass, i.e. they also demonstrate sarcopenic and lipodystrophic phenotypes[10]. These changes seem casually linked to the increased risk of metabolic syndrome in this patient population[11]. Metabolic syndrome has six components that relate to cardiovascular disease risk (based on the ATPIII definition5): abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance ± glucose intolerance, proinflammatory and prothrombotic states[12].

Survivors of all forms of cancer diagnosed as children or as teenagers and young adults (CTYA), including leukaemia treated without HSCT/TBI, may also face long term morbidity in adult life depending on the nature of the treatment received; cardiovascular disease is the most common cause of early mortality in CTYA cancer survivors after the risk of death from second cancer[13] .

The incidence, severity, progression and outcome of changes in body composition/BMI in survivors of HSCT/TBI in the CTYA age range is unclear. Nor is it known how their risk compares with survivors of CTYA leukaemia treated without HSCT/TBI or with individuals without a history of cancer treatment with or without evidence of obesity.

Aims

The aims of this rapid review are to:

- collate evidence of changes in body composition/BMI in survivors of leukaemia treated in the CTYA age range (age 0 – <25 years) with HSCT with TBI;
- identify evidence that body composition is associated with change in metabolic status in survivors;
- describe dietary and exercise interventions used to ameliorate changes in body composition in survivors of leukaemia treated in the CTYA age range with HSCT with TBI;
- compare findings, where available, with studies of leukaemia survivors treated without HSCT with TBI and with the general population

Methods

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) 2015 reporting guideline. The review is registered on PROSPERO International prospective register of systematic reviews. If any amendments to this protocol are required when conducting the review, these will be clearly described in the review article when prepared for publication.

Eligibility criteria

Studies will be selected for inclusion in this review according to the following criteria:

Participants

We will include studies of people:

- treated for all types of leukaemia with the addition of cases of non-Hodgkin's lymphoma (NHL) and myelodysplastic syndrome (MDS) if included within a study of leukaemia patients
- treated with allogeneic HSCT and TBI (or both allogeneic and autologous if the allogeneic participants are analysed separately)
- aged up to and including 24years (i.e. to 25th birthday) at transplant
- any age at the time of evaluation.

We will include studies of multiple conditions if leukaemia patients make up ≥90% of the sample or if results for leukaemia are analysed separately. We will include studies of patients with and without TBI if those with TBI make up ≥90% of the sample or results are analysed for TBI vs no TBI.

Comparators

Studies with or without a comparator will be included. Comparators may include people treated for leukaemia without allogeneic HSCT and TBI, or age matched controls from the normal population with or without obesity.

Characteristics

We will include studies which measure changes in body composition (height, muscle or fat), specifically any of:

- Sarcopenia (including impaired muscle strength)
- Frailty
- Lipodystrophy (abnormal fat distribution)
- Changes in fat distribution e.g. increased visceral/central fat
- Changes in fat compartmentation/positioning
- Body mass index (BMI)

Intervention studies must use the intervention after the HSCT not before.

Study design

Completed studies, with or without control groups, with or without interventions (including case studies, feasibility studies, cohort studies). Literature reviews will only be included in order to identify primary studies in their reference lists.

No date or language restrictions will be applied.

Non-English papers will be translated where possible.

Information sources and search methods

Literature search strategies will be developed by an experienced systematic reviewer using a combination of Medical Subject Headings (MeSH) and keyword terms (see Appendix 1). We will search MEDLINE via OVID from its inception, and the first 20 pages of Google Scholar. We will contact key authors (lead authors on included papers and contacts known to the project team) to identify any work-in-progress or unpublished work.

To ensure literature saturation, reference lists of and citations to key full-text articles will be hand-searched for additional original publications. Update notifications from Medline will be set up for the searches for the duration of the project to identify any studies published since the initial search.

Study records

Data management

EndNote reference management software package will be used to manage all the search results throughout the review period. Literature search results will be imported into an EndNote library and duplicates will be removed.

Selection process

Titles and abstracts will be assessed for eligibility by AL, with RP independently assessing a random sample of 10% of records. Articles that appear to meet the inclusion criteria will be retrieved in full and independently considered for inclusion by two reviewers (MS, JHS). The reviewers will resolve disagreements in opinion of studies for inclusion through discussion, and the reasons for excluding studies will be recorded in a table. Reference lists of included studies will be reviewed, and the full-text articles of any relevant studies identified will be retrieved and reviewed for inclusion by both reviewers.

Data collection process

Full-text articles for inclusion will be retrieved, and data will be extracted using a standardised data extraction template by AL, with RP independently extracting data from a random sample of 20% of articles and JHS and MS will also independently extract from a random sample of 10% of articles. Data to be extracted include: study methods (aim, setting, sample eligibility criteria, data collection methods and timing), participant flow (numbers eligible/recruited/followed up, reasons for non-participation), participant characteristics (diagnoses, treatment details, age at HSCT, age at follow up, sex, ethnicity), outcome data (for each outcome, subgroup comparisons). The primary outcome data to be collected are:

- Total fat e.g. BMI, whole body % fat

- Central adiposity e.g. waist circumference, abdominal fat
- Adipose tissue function e.g. adipokines, lipids
- Muscle mass e.g. sarcopenia, frailty, lean body mass, fat-free mass
- Muscle function e.g. muscle strength tests, frailty.

Secondary outcomes, to be collected only if body composition changes are also described:

- Measures of insulin resistance, glucose tolerance and metabolic syndrome

For studies which use interventions we will ensure adverse event data is extracted. The template will be piloted by both reviewers before starting the review and modified as required to ensure consistency. Disagreements in opinion of data extracted will be resolved through discussion.

Risk of bias/quality assessment

To assess the risk of bias of included studies two reviewers will use recognised checklists such as Cochrane RoB tool for trials[14], and Newcastle-Ottowa quality assessment scale[15] for observational studies. Risk of bias scores will be reported in a table. Any meta-analyses carried out will be conducted separately for studies at low and high risk of bias.

Data synthesis

A narrative review of the findings from the included studies will be presented, structured around the outcomes reported and the aims of the review (prevalence, diagnosis, severity, interventions). Meta-analysis will be performed only if the identified studies are comparable.

Sub-group analysis will be considered depending on the availability of data from sufficient numbers of comparable studies based on: time from HSCT (e.g. > < 5years); age at HSCT (e.g. > < 16 years); age at study (e.g. > < 25 years)

Results will be pooled for comparable sub-sets of studies only where possible.

Considerable heterogeneity between studies is anticipated.

Where there are sufficient studies deemed comparable, in respect the outcomes under consideration, their individual effect sizes will be illustrated using forest plots together with combined estimates, using random effect models. Sub-group analyses as outlined above will be undertaken together with meta-regression if indicated.

References

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3. Rufer N, Brümmendorf TH, Chapuis B, Helg C, Lansdorp PM, Roosnek E. Accelerated telomere shortening in hematological lineages is limited to the first year following stem cell transplantation. *Blood* 2001; **97**(2): 575-7.
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12. Huang PL. A comprehensive definition for metabolic syndrome. *Disease models & mechanisms* 2009; **2**(5-6): 231-7.
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Appendix 1: Search terms

Medline:

1. Lipodystro*.ti,ab.
2. Exp lipodystrophy/
3. (visceral adj1 fat).ti,ab.
4. (central adj1 fat).ti,ab.
5. Exp body fat distribution/
6. (fat adj1 distribut*).ti,ab.
7. (fat adj1 compart*).ti,ab.
8. Exp Abdominal Fat/
9. (abdominal adj1 fat).ti,ab.
10. (abdominal adj1 obes*).ti,ab.
11. (Body adj1 composition).ti,ab.
12. exp body composition/
13. exp Waist-Hip Ratio/
14. (waist adj1 hip adj1 ratio).ti,ab.
15. exp body mass index/
16. (body adj1 mass adj1 index).ti,ab.
17. BMI.ti,ab.
18. Frailty.ti,ab.
19. Exp Frailty/
20. Sarcopen*.ti,ab.
21. Exp Muscular atrophy/
22. (Muscle adj1 mass).ti,ab.
23. Body Height/
24. Height.ti,ab.

25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. HSCT.ti,ab.
27. HCT.ti,ab.
28. (h?ematopoietic adj1 stem adj1 cell adj1 transplant*).ti,ab.
29. (h?ematopoietic adj1 cell adj1 transplant*).ti,ab.
30. stem cell transplant.ti,ab.
31. (stem adj1 cell adj1 transplant*).ti,ab.
32. Exp Stem Cell Transplantation/
33. Bone Marrow Transplantation/
34. BMT.ti,ab.
35. (bone adj1 marrow adj1 transplant*).ti,ab.
36. h?ematocrit.ti,ab.
37. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
38. 37 NOT 36

39. 25 AND 38

40. exp Animals, Laboratory/

41. exp Animal Experimentation/
42. exp models, Animal/
43. Rodentia/
44. (rat* or mouse or mice).ti.
45. exp in vitro techniques/
46. in vitro.ti
47. pre-clinical.ti,ab.
48. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

49. 39 NOT 48

Google scholar:

(lipodystrophy OR fat OR waist-hip OR BMI OR body mass index OR frailty OR sarcopenia OR muscle OR height) AND (HSCT or stem cell transplant OR bone marrow transplant OR BMT)