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Late treatment effects following bone marrow transplant: efficacy of implementing international guidelines

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Concise title: Efficacy of late effects screening

Abstract

An increasing cohort of haematopoietic stem cell transplantation (HSCT) survivors has raised awareness of long-term and late effects. Updated recommendations for HSCT late effects screening were published in 2012 (Majhail et al, 2012). We aimed to assess the clinical efficacy of a dedicated screening clinic to identify problems in HSCT survivors using the international guidelines. Clinic letters and test results of the first 59 consecutive patients attending the screening clinic were evaluated. 30 females and 29 males (mean age of 49 years, range 22-74) were included. The mean time since transplant was 6 years (0.5-18). 49/65 transplants were allogeneic. Primary indications for HSCT were myeloid (56%), lymphoid (37%), solid tumour (5%) and auto-immune diseases (2%). 134 complications were reported (mean 2, range 0-8), with 114 documented further actions/referrals. The most commonly reported concerns were pain 18/59(31%), fatigue 14/59(24%), sexual function 14/59(24%) and sleep disturbance 11/59(19%). Second primary malignancies were recorded in 5 cases. Implementation and audit of the international late effect screening guidelines confirm the need for systematic long-term physical and psychological screening and care, thus ensuring timely and efficient identification of problems and the opportunity to minimise morbidity effects and optimise health.

Keywords: Haematopoietic cell transplantation, Allogeneic, Autologous, Late effects, Screening, Prevention

Introduction

Autologous or allogeneic HSCT survivors have higher risks of developing medical complications compared with the general population or other cancer survivors. Life expectancy of HSCT patients is lower than that of an age, gender and nationality-matched general population. This lag in life expectancy decreases but continues to exist until at least 15-20 years after HSCT (Majhail & Rizzo, 2013). Disease relapse, however, is the dominant cause of mortality within two years post HSCT (Majhail & Rizzo, 2013; Wingard et al, 2011). Significant early treatment complications include the risk of severe infection and graft versus host disease (Syrjala et al, 2012). Non relapse and infection complications include secondary cancer, endocrine, pulmonary and sexual dysfunction, bone degeneration and cardiovascular complications (Tichelli et al, 2013). Other complications including xerostomia and dry eyes, may not directly impact mortality but could significantly reduce quality of life. Indeed any system can be affected with severity ranging from life-threatening to mild and reversible (Trotti et al, 2003).

Awareness of long term effects of HSCT and implication of long term follow-up ensures identification and treatment of complications thereby optimising survival rates (Sun et al, 2013). However, mortality rates are still increased even after 10-30 years post transplantation being 4-9 fold higher than reported in an age-matched general population (Tichelli et al, 2013). A systematic approach to screening guidance and recommendations, alongside specific and common late effects of HSCT, was published in 2012 (Majhail et al, 2012) and adapted for clinical use in our transplant centre with systematic screening coordinated through a nurse-led late effects clinic. Thus the aims of our clinical audit were:

1. To evaluate the clinical efficacy of the screening clinic to identify late effects following HSCT
2. To evaluate the number and nature of subsequent actions or referrals.

Subjects and Methods

Our centre implemented the internationally agreed guidelines in 2013 using a locally developed Standardised Operating Policy (SOP) through a nurse-led late effects screening clinic. 59 consecutive patients who attended the screening clinic for the first time during 1st Sept 2013 to 31st Aug 2014 were included in the audit. Suitable patients were referred into the clinic by the transplant physicians in the same institution. Patients were in remission, with no active GvHD and without infection. The late effects screening clinic was held in an out patients facility and run in parallel to the consultant led transplant clinics. Audit approval confirmation was given by the Clinical Effectiveness Unit of our hospital trust.

Data was extracted from the clinic letter annotated from the consultation and from results of the requested investigations as per the SOP. Presence or absence of each variable and investigation was coded and current results and actions were recorded in a spreadsheet. The accuracy of requesting investigations as per the departmental SOP was reviewed to check whether these results were deranged or within normal limits.

Results

Demographics

Thirty patients were female and twenty nine male. Fifty four patients received one transplant, 4 had two transplants and 1 had three transplants. 49/65(75%) of transplants were allogeneic. Primary indications for HSCT for audit participants are given in Figure 1. Mean age of patients at assessment was 49 years (range 22-74), mean years from initial diagnosis was 8 (range 1-28) and mean years since transplant was 6 (0.5-18).

Forty four of 59 (75%) had chemotherapy treatment prior to transplant with 12 of these having further high dose treatments. The most widely used chemotherapy regimen was FLAG-Ida (n=8). Thirteen patients had TBI radiotherapy as part of their conditioning. Fifty one patients were given pre-transplant conditioning regimens with 8 patients not recorded as having conditioning. Thirteen of 59 received biological therapy, most receiving interferon (n=5) or rituximab (n=5). The most commonly identified health problems are given in Table 1.

Health problems by system

Skin

Nine patients reported skin concerns including dryness or rash. Seven had documented referrals for further review by the consultant in charge of the screening clinic or to the GP for monitoring of skin lesions.

Head, eyes, ears nose and throat

Ten patients suffered ocular complications mainly with dry eyes or 'gritty eyes'. Ocular action was documented for 16 people i.e. were recommended an optician appointment for routine eye testing or referred to an ophthalmologist for specialist review.

Thirteen patients reported oral complications mainly of xerostomia (dry mouth). Action or referral was documented in 11, 1 being advised a routine dental appointment, 2 needing no further action and 1 who had no action documented.

Respiratory

Seven patients reported respiratory problems, principally chest infections and coughs, and five further action documented. Fifty seven had recorded pulmonary function tests (PFTs) requested as part of routine post HSCT screening. Reported results indicated 21 had low TLCO, 3 low FEV1 and 4 with both low FEV1 and TLCO.

Cardiovascular

Thirteen cases of elevated blood pressure were recorded with 8 cases identified in clinic and 5 pre-existing. Three patients were found to have cardiac complications and all were referred to a cardiologist for specialist review. Fifty six had recorded echocardiogram reports, of which 49 were reported to have good systolic function with 22 reports of mild problems such as aortic regurgitation.

Thirty out of 47 patients who had lipids evaluated had deranged results, with 1 report of further action. Of these, 23 had elevated triglycerides but no recorded further actions.

GI

Two patients reported upper GI complications such as suspected silent reflux and excess gastric acid. Action was recorded for both patients. Six patients suffered lower GI complications, predominantly diarrhoea and urgent defecation- of these 5 had documented action. Forty one had liver function tests performed, 11 results were deranged, but no further action documented.

Genital

Fourteen patients reported problems with sexual function with 13 being referred for further investigation/specialist advice. Reports of 4 patients with early menopause as a result of HSCT were documented, 3 had documented action or referral. One man identified with testosterone deficiency, was referred to an endocrinologist.

Neurological

Six patients prioritised memory loss as a major concern, however no specific actions were documented. Fourteen patients reported persistent fatigue. Seven had documentation of further action such as referral to a specialist. All patients would normally have repeat bloods to exclude organic causes. Low energy, tiredness and sleep problems were the main concern of patients when

asked to prioritise concerns; 20 experienced difficulties with sleepiness and fluctuating energy levels, 11 reported problems sleeping at night of these- 7/11 had documentation of action.

Eighteen patients reported pain. The plan of action for pain management was documented although 2 patients had no further action documented.

Musculo-skeletal

DEXA scans results were available in 17/59 patients. Four patients were found to have low bone mineral density with further action being to evaluate specific problems and consider supplementation of Vitamin D. For others scanned, recommendations were given for time interval before repeat DEXA and lifestyle advice e.g. reducing alcohol consumption. Twelve patients had Vitamin D levels tested with 4 being below normal. 2 had actions reported of instigation of Vitamin D supplementation.

Haematological

Eighteen out of twenty four patients were found to have high ferritin levels. Two had reported evidence of further action (venesections) being taken. Twenty had Vitamin B12 levels tested, 2 of these were deranged but no action was documented.

Endocrine

TSH was measured in 48 patients, resulting in 12 deranged results and 1 documented referral/action.

Immunology

Thirty letters mentioned vaccination programmes with evidence of 23/30 having a reported plan such as recommending an annual flu jab or requests for GP reinstatement of vaccine programmes which may have been paused to manage GVHD. Five patients experienced complications from a compromised immune system- predominantly GVHD, recurrent chest infections and multiple

infections varying from sinusitis to UTI. All actions were documented- often the problem was already managed by other specialists but those with recurrent infections required further investigations.

Psychological

Six patients were referred to a psychologist with an additional one patient who was recommended to see a psychologist and 1 referred to a psychiatrist.

Malignancies

Six malignancies were recorded post transplantation of which 5 were recent onset primary skin lesions and the other new malignancy was liver metastases from previous colon cancer.

Figure 2 gives frequency of complications and frequency of documented action.

Discussion

To our knowledge this is the first time the new international late effect screening guidelines have been formally audited (Majhail et al, 2012). One hundred and thirty four new problems or concerns were identified in 59 consecutive transplant patients with 114 documented further action or referrals. The most frequently concerns were pain, fatigue, sexual function and sleep patterns. Second malignancy was reported in 5 cases.

Pain is a well-recognised unmet need of cancer patients (Vogelzang et al, 1997) and also evident in HSCT patients (Niscola et al, 2008). Pain is often associated with fatigue with 30-42% of HSCT survivors troubled by fatigue in contrast to <20% prevalence of pain (Mosher et al, 2011). Interestingly, Vogelzang found that whilst oncologists believed that pain affected their patients to a higher degree than fatigue, patients believed that fatigue affected their lives more daily than pain (61% v 19%) (Vogelzang et al, 1997). The reported sources of pain are mainly due to the mucosal

tissue injury induced by the conditioning regimen but also include pain from infection, from acute or chronic GVHD as well as adverse drug reactions to GVHD drug prophylaxis. Furthermore, some late complications of the actual transplant may be associated with pain (Niscola et al, 2008). The management strategy of pain that is recommended is using the analgesic ladder- NSAIDs or paracetamol for mild pain, partial mixed opiate receptor agonists and mild opioids e.g. oxycodone for moderate pain relief and finally, the pure μ-opiate receptor agonists or strong opioids, e.g. morphine and fentanyl, are chosen for severe pain relief. With one third of our cohort reporting pain as an issue, there is a clear need for regular assessment and monitoring with implications for palliative and supportive care in addition to further investigation for cause.

Further detail as to whether physiological causes of fatigue such as anaemia or vitamin D deficiency were excluded or that it was confirmed as idiopathic with no identifiable cause. It is important to routinely screen for anaemia in this population of HSCT survivors.

Sexual function was also a highly prevalent concern in our cohort with 14 (7 male, 7 female) reporting problems- such as early menopause and testosterone deficiency. Psychosexual functioning has been found to be worse in HSCT patients compared with patients treated with chemotherapy alone and significantly worse compared with healthy subjects (Thygesen et al, 2012). The effect is long-lasting with survivors at increased risk of sexual function problems even 5-10 years after transplantation (Frey Tirri et al, 2015). The late effects guidelines (Majhail et al, 2012) suggest clinical and endocrinologic gonadal assessment at 1 year post HSCT in all women post-pubertal at transplantation with the frequency of subsequent assessments guided by clinical need. Women should have annual gynaecologic evaluation as part of general health screening to rule out for example atrophic vaginitis, a common problem after HSCT at which time HRT may be considered in those who are postmenopausal (Frey Tirri et al, 2015). In men, gonadal function (particularly FSH, LH and testosterone) should be assessed if symptomatic eg lack of libido or erectile dysfunction. It is

also important to rule out GvHD of the genital tract (Frey Tirri et al, 2015). Once again systematic enquiry is indicated, even for intimate topics to allow patients permission to open a conversation and be reassured, itself considered therapeutic (Yi & Syrjala, 2009).

HSCT survivors, particularly allogeneic patients, are at risk of developing secondary malignancies of the skin. In our cohort, 5 out of 6 of the malignancies reported post transplantation, were skin lesions. In terms of risk and prevention of secondary cancers, clinic letters gave detailed advice of the risks of UV exposure, smoking, alcohol and the importance of a healthy lifestyle. This identified that the post HSCT review is also a useful mechanism for health promotion. The late effects guidelines do have a section titled 'healthy lifestyle recommendations for all patients' which covers this.

We have demonstrated here that any system can be affected thus a complete systems review is indicated. Screening and taking a history of patient centred concerns such as pain, fatigue, sexual function and sleep are as important as ruling out physiological disorders to maximised health and recovery after HSCT.

This evaluation was limited by the decision to use conveniently available source data including the clinic letter, most recent blood test results and last ECHO, DEXA and PFT in the audit. This included DEXA scan reports which were only available if done within the previous 18 months gives scan reports within the last 18 months. Furthermore, data regarding initial diagnoses and treatment was inconsistently documented. Additional searching was required to retrieve more accurate information.

Conclusion

In summary, this study described the population of 59 new patients to the late effects screening clinic with a mean 6 years since transplant. We demonstrated a high prevalence of systematic

complications and evidence for further actions to assess these complications. This new nurse-led screening clinics demonstrates clinical efficacy in identifying late complications using holistic screening and confirms the need for long-term follow-up post-transplantation. Ultimately, screening clinics such as this aim to pick up complications earlier to prevent/reduce morbidity therefore playing a central role in optimising quality of life for HSCT survivors. Future evaluation should more accurately assess the severity of each concern using a scoring system such as the Common Toxicity Criteria (CTC) system (Trotti et al, 2003).

Conflict of Interest

There are no conflicts of interest.

Acknowledgements

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References

Frey Tirri B, Häusermann P, Bertz H, Greinix H, Lawitschka A, Schwarze C-P *et al*. (2015) Clinical guidelines for gynecologic care after hematopoietic SCT. Report from the international consensus project on clinical practice in chronic GVHD. Bone Marrow Transplan*t*, 50(1), 3–9.

Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C *et al*. (2012) Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Biology of Blood and Marrow Transplantation, 18(3), 348–71.

Majhail NS, Rizzo JD. (2013) Surviving the cure: long term followup of hematopoietic cell transplant recipients. Bone Marrow Transplant, 48(9), 1145–51.

Mosher CE, DuHamel KN, Rini C, Corner G, Lam J, Redd WH. (2011) Quality of life concerns and depression among hematopoietic stem cell transplant survivors. Support Care Cancer, 19(9), 1357–65.

Niscola P, Romani C, Scaramucci L, Dentamaro T, Cupelli L, Tendas A *et al*. (2008) Pain syndromes in the setting of haematopoietic stem cell transplantation for haematological malignancies. Bone Marrow Transplant, 41(9), 757–64.

Sun CL, Kersey JH, Francisco L, Armenian SH, Baker KS, Weisdorf DJ *et al*. (2013) Burden of morbidity in 10+ year survivors of hematopoietic cell transplantation: report from the bone marrow transplantation survivor study. Biology of Blood and Marrow Transplantation,19(7), 1073–80.

Syrjala KL, Martin PJ, Lee SJ. (2012) Delivering care to long-term adult survivors of hematopoietic cell transplantation. Journal of Clinical Oncology, 30, 3746-51.

Thygesen KH, Schjødt I, Jarden M. (2012) The impact of hematopoietic stem cell transplantation on sexuality: a systematic review of the literature. Bone Marrow Transplant, 47(5), 716–24.

Tichelli A, Rovó A. (2013) A clever person solves a problem; a wise person avoids it. Biology of Blood and Marrow Transplantation, 19(7), 1004-5.

Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V *et al*. (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Seminars in Radiation Oncology, 13(3), 176–81.

Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D *et al*. (2011) Long-Term Survival and Late Deaths after Allogeneic Bone Marrow Transplantation. Journal of Clinical Oncology, 29(16), 2230-2239.

Vogelzang NJ, Breitbart W, Cella D, Curt GA, Groopman JE, Horning SJ *et al*. (1997) Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Seminars in Hematology, 34(3), 4–12.

Yi JC, Syrjala KL. Sexuality After Hematopoietic Stem Cell Transplantation. (2009) The Cancer Journal, 15(1), 57–64.

Figure legends

Figure 1:

Primary indications for HSCT for audit participants

Figure 2:

Frequency of identified problems/concerns and documented actions/referrals

Figure 1

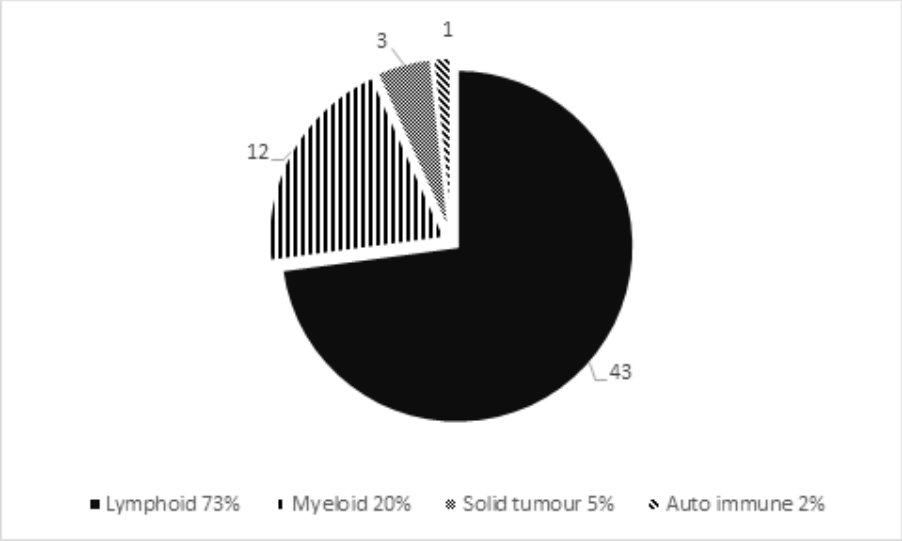

Figure 2