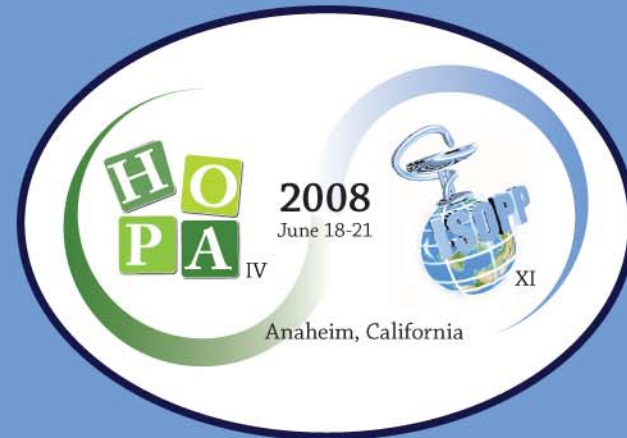


Now for the Encore: Following-up Transplant Survivors



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Disclosures

- Julie Wilkes has received assistance for conference attendance from Roche, Amgen, Pharmion, and Pfizer

Learning Objectives

- List the complications and risk factors associated with the long-term survival of patients who have received a hematopoietic stem cell transplant
- Formulate an appropriate plan for prevention and monitoring of long-term complications in survivors of hematopoietic stem cell transplants

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- Introduction
 - Case studies
 - Small group discussion
 - Management plan
 - Investigations
 - Therapeutic management
 - Group presentation, comments
 - Summary

Introduction

- Over 40,000 haematopoietic transplants performed per year worldwide
 - Follow-up care provided in a variety of locations, with health providers having differing **knowledge & expertise** in care
- Focusing on;
 - Post acute phase (6 months)
 - Allogeneic transplantation
- Graft versus Host Disease (GVHD)
 - Supportive Care
- Prevention and screening guidelines
 - Lack of evidence
 - Based on logical approach to prevention, monitoring of complications seen in these patient

Case Study 1

- Mr AS, 61 year old businessman
- Myelodysplastic syndrome, RIC (flu/mel) allo PBSCT 6 months ago
- Acute GVHD
 - Prophylaxis with cyclosporine and methotrexate
 - aGVHD (gut) grade 2
 - Treated with prednisolone 50 mg/d (plus CyA). Prednisolone tapered rapidly
- Presented with rising ALT, low platelets
 - “Presumed” GVHD liver (no biopsy)
 - Treated with cyclosporine, prednisolone 75 mg/d for 1 week, ALT worsened (5>ULN)
 - Referred to Home Cancer Care Service for IV methylprednisolone 2 mg/kg

Discussion AS

- Post transplant grade 2 aGVHD gut
 - What risk for chronic GVHD does the presence of G2 aGVHD confer?

Discussion AS

- Post transplant grade 2 aGvHD gut
 - What risk for chronic GVHD does the presence of G2 aGVHD confer?
 - The risk of cGVHD increases with the presence and grading of aGVHD. G2 aCGVHD confers a risk of 50-60% cGVHD
 - cGVHD occurs on average 150-200 days post transplant
 - Incidence increases with presence and grade of aGVHD
 - Most commonly occurs in skin, liver, eyes and mouth
 - Treatment of cGHVD involves a commitment to treatment for usually at least 2 years

Discussion AS

- 6 months post transplant AS presents to the outpatient clinic with an ALT 3 x ULN and a falling platelet count (from 130 to 50 x 10⁹/L). He is on cyclosporine 100 mg bd
 - What could be the cause of the falling platelet count?
 - What could be the cause of the rising ALT?
 - What other investigations would help you decide the etiology of the abnormal results?

Discussion AS

- Possible cause of the falling platelet count
 - Relapsed disease, drug therapy, immune disorders (ITP, TTP), GVHD
- Possible cause of the rising ALT
 - GVHD, viral hepatitis, iron overload, drug therapy (antifungal therapy, cyclosporine, any other implicated drugs)
 - If cholestatic may also be due to gallstones, fungus, or cancer
- Other investigations which could help decide the etiology of the abnormal results
 - Liver biopsy, radiological investigations (eg ultrasound), viral testing (Hb sAg, CMV), iron studies (ferritin)
 - FBP slides, bone marrow biopsy, ADAMTS13 (TTP only), LDH
 - Removing any drugs likely to be implicated if possible.

Discussion AS

- AS was “presumed” to have cGVHD (however no liver biopsy was done). He was treated with prednisolone 75 mg/d for one week (in addition to Cy A) as an outpatient
 - Presuming the diagnosis was correct, do you consider this a reasonable treatment option?
 - What monitoring and management would you recommend at this stage?
 - What prophylactic strategies would you consider in patients being treated for cGVHD?

Discussion AS

- Presuming the diagnosis was correct, do you consider this a reasonable treatment option?
 - Dose 0.5–1 mg/kg prednisolone appropriate
- What monitoring and management would you recommend at this stage?
 - Optimize current therapy
 - cyclosporine level (therapeutic range)
 - CyA toxicity; hypertension, tremour, increased creatinine &/or bilirubin
 - FBP, U&Es, LFTs
 - Check for any signs or symptoms which may affect oral steroid absorption (eg, gut GVHD)

Discussion AS

- Prophylactic strategies
 - Antibiotic prophylaxis – targeting encapsulated organisms (rate of pneumococcal infection 14% @ 10y in cGHVD), PCP
 - Antifungal – posaconazole (note inc Cy A levels, but by how much?) vs surveillance and preemptive therapy
 - CMV surveillance, HSV prophylaxis

Discussion AS

- One week later, his ALT had increased to $> 5 \times \text{ULN}$, and his platelet count had fallen to $26 \times 10^9/\text{L}$. He was started on methylprednisolone (MP) 2 mg/kg

Discussion AS

- How long would you treat him with IV MP before adding in additional therapy, and what would it be?

Discussion AS

- How long to treat and additional therapy
 - Timing difficult
 - Depends on rapidity of disease progression
 - Low platelet count ($<100 \times 10^9/L$) is a poor prognostic indicator, and may warrant faster escalation of therapy
 - Consider 3rd line agents
 - MMF, etanercept, anti-IL2 recp MAB, rituximab (B cells may present alloantigens and produce autoantibodies)

Outcome AS

- AS was treated with 1 week of MP with no improvement
- ALT continued to rise, and bilirubin and ALP started rising
- Platelets fell to $10 \times 10^9/L$
- He was admitted for further investigation
 - BMA/T was performed, and showed dysplastic changes consistent with relapsed disease
 - The abnormal LFTs were considered consistent with cGVHD though no biopsy was ever taken
 - Haemoglobin and white cell counts started falling
 - With relapsed disease in the setting of GVHD sadly the decision was made to withdraw active treatment, and palliative therapy was started

Case Study 2

- Ms RC, 22 yo student
- AML, Bu/mel allo PBSCT from sib 18 months ago
- Acute GVHD
 - Prophylaxis with methotrexate & tacro
 - Grade 2 aGVHD (gut and liver)
- Chronic GVHD
 - Liver (biopsy proven, raised bilirubin and ALP)
 - Treated with tacrolimus & methylpred/pred
 - Attempts to remove steroids have been unsuccessful (↑bili & ALP)
 - Tacrolimus ceased due to neurological toxicity
 - Remains on 12.5 mg prednisolone
- Presents to outpatient clinic with vaginal dryness

Discussion RC

- 18 months post transplant RC presents to outpatients clinic with vaginal dryness. On questioning she complains of never feeling like having sex anymore, and when she does it is quite painful
 - On physical exam the doctor reports a narrowing of the vagina with dryness and loss of elasticity, caused by cGVHD
 - You are asked for your advise re supportive management of this condition

Discussion RC

■ Supportive management

- Incidence of female genital cGVHD under intensive surveillance program at RMH was approx 50% (much higher with PBSC c/f BM)
- Oral hormone replacement, check hormone levels as amenorrhea almost universal after high dose busulphan
- Androgen therapy (for low libido if appropriate based on testosterone levels)
- **Topical** oestrogens
- **Topical** steroids
- **Topical** cyclosporine/tacrolimus
- Lubricants
- Vaginal dilators
- Counseling

Discussion RC

- RC has been amenorrheic since her transplant. She has read that this may result in an increased risk of osteoporosis.
 - What do you tell her about the risk of osteoporosis?
 - What therapeutic options are available for her?

Discussion RC

- Risk of osteoporosis
 - Measurable
 - Bone densitometry testing to predict likelihood of osteopenia/porosis
 - Check gonadal function (as per previous discussion) and TFTs if bone density low
- Therapeutic options
 - Treatment with oestrogen, Vitamin D, Ca, and bisphosphonates
 - Weight bearing exercise

Outcome RC

- RC was treated with oral and vaginal oestrogens and vaginal steroids, with improvement in her symptoms
- Hormone levels showed she was “post menopausal”
- Her t-score on bone densitometry was -2.0, and she was started on zoledronic acid 4 mg 3 mthly
- TFTs were normal

Case Study 3

- Mr AP, 52 year old labourer
- Refractory CLL
 - Previously treated with FCR, prednisolone
 - Flu/TBI MUD PBSCT 8 months ago
- Acute GVHD
 - Prophylaxis with tacrolimus and methotrexate
 - Grade 4 aGVHD (liver, skin) treated with tacrolimus, methylprednisolone 2 mg/kg, basiliximab (20 mg x 3), etanercept 25 mg sc 2x/weekly
- cGVHD (lungs)
 - Remains on tacrolimus, etanercept and prednsiolone (weaning dose)
- Patient presents to outpatient clinic with sinus pain

Discussion AP

- AP required treatment for Grade 4 aGVHD, and cGVHD using highly immunosuppressive drugs. He still works as a tiler and smokes (though he is trying to cut down!)
 - Whilst on immunosuppressive therapy, what management including prophylactic antifungal therapy and/or surveillance would you recommend?

Discussion AP

- Management, prophylactic antifungal therapy and/or surveillance
 - Posaconazole versus surveillance and preemptive therapy
 - Stop smoking
 - High risk occupation because of environmental contamination

Discussion AP

- He presents 8 months post transplant with sinus pain, after being heavily immunosuppressed for GVHD. He had been on voriconazole as secondary prophylaxis (previous pleicomyces of the lip during transplant)
 - What could be causing AP's symptoms?

Discussion AP

■ Symptoms

- Sinusitis – bacterial, fungal (mucor), hayfever, CI mucosal hypertrophy
- Risk factors for fungal infection include him still working as a labourer in the building industry, smoking, and highly immunosuppressed

Discussion AP

- After ENT review, biopsy samples grew a zygomycosis. Radiology showed localized fungus, amenable to surgical debridement
 - What treatment options are available to him?

Discussion AP

■ Treatment options

- Surgery
- AmBisome[®] – dose? Up to 10-15 mg/kg?
Combination therapy
- Change to posaconazole when?
- TDM of posaconazole
- Don't forget to adjust tacrolimus dose and monitor levels

Discussion AP

- Post transplant immune reconstitution occurs over time, and is delayed in patients with GVHD
 - What education does this patient need with regards to his immune status and prevention of infectious complications?
 - What laboratory tests could be used to monitor his immune status?
 - What therapeutic interventions could be used to reduce his risk?

Discussion AP

- Education
 - Warning symptoms and signs of infection
 - Stop smoking
 - Work - ?? how do you minimize the risk
- Laboratory tests to monitor immune status
 - CD4 counts, CD4/CD8 ratios, IgG levels (IgG infusions if hypogammaglobulinemic)
- Therapeutic interventions to reduce risk
 - Immunization
 - All other prophylaxis as per case study 1

Outcome AP

- AP went on to have surgical debridement of the fungal lesion in his sinus
- He was subsequently treated with AmBisome 5 mg/kg for 3 weeks, and then converted to posaconazole 400 mg bd
- His symptoms have not returned

Summary

■ Knowledge and resources

- NMDP, long-term survival guidelines – recommended post transplant care
 - Long term screening
 - *Rizzo JD, et al. BMT. 2006;37:249-61*
 - Screening for cGVHD
 - *Filipovich AH, et al. BBMT. 2005;11:945-55*
- Guidelines for preventing opportunistic infections among HSCT recipients, MMWR 2000
- General recommendations on immunization, MMWR 2006
- NIH ancillary therapy & supportive care guidelines
 - *Couriel D, et al. BBMT. 2006;12:375-96*

Summary

- Female genital cGVHD
 - *Zantomio D, et al. BMT. 2006;38:567-72*
- Osteoporosis monitoring and treatment
 - *Tauchmanova L, et al. J Clin Endocrinol Metab. 2007;92:4536-45. (Review)*
 - *Kananen K, et al. J Clin Endocrinol Metab. 2005;90:3877-85. (Randomised trial +/- pamidronate)*
 - *D'Souza A, et al. Int Med Journal. 2006;36:600-3. (Small study with zoledronic acid)*
- Expertise
 - Thank you for participating and sharing!