Management of iron overload in allogeneic BMT

Incidence and Impact of Iron Overload

Liver complications following BMT are common and often multifactorial and may result from medications, acute and chronic GvHD, metabolic syndrome, HSOS/VOD, viral hepatitis or iron overload.

BMT recipients develop iron overload largely as a consequence of RBC transfusions administered prior to transplant and post-transplant although ineffective erythropoiesis and hereditary haemochromatosis, if present, may also contribute.

Approximately 30-60% of allo-BMT recipients present with iron overload, either at the time of transplant or in the post-BMT period and 25-50% of long-term survivors of BMT have elevated liver iron concentration (LIC) on T2 MRI. (Majhail et al, 2008)(Rose 2007) While mild iron overload generally does not cause any problems and may reduce over time without treatment, more significant iron overload may be associated with increased morbidity and mortality post-BMT. (Inamoto and Lee, 2017)

Iron overload is a well-established adverse prognostic factor in patients undergoing allogeneic BMT for thalassaemia. Although the evidence is less clear in other conditions, studies including patients with AML, MDS and ALL suggest that iron overload (elevated pre-BMT ferritin) may increase the incidence and severity of a number of post-BMT complications including mucositis, hepatitis, bacterial and invasive fungal infection, progression of viral hepatitis, hepatic sinusoidal obstructive syndrome (HSOS/VOD) and GvHD. (Busca et al, 2014)(Armand et al, 2007) (Mahindra et al, 2009)(Tachibana et al, 2012)(Garcia-Vidal et al, 2008) There is some evidence that iron overload may also negatively impact transplant-related mortality (TRM), non-relapse mortality (NRM), overall survival and disease-free survival but the evidence for this is contradictory. (Trottier et al 2013)(Armand et al, 2014)

While there is limited data regarding the level at which elevated ferritin is associated with poorer post-BMT outcomes, the strongest associations are for patients who have a ferritin level >1000ng/ml. (Meyer et al, 2013)

Assessment of Iron Overload

Estimation of iron burden is primarily based on ferritin as a surrogate for iron overload. Many factors confound the use of ferritin as a marker of IO in BMT recipients as ferritin is an acute phase reactant and is elevated in infection, hepatitis and GvHD.

Estimation of LIC provides an accurate measure of whole-body iron levels as 90% of excess iron is deposited in the liver. While liver biopsy is the validated reference method for evaluation of LIC, given

the risks of bleeding, noninvasive measures are preferred in the BMT setting. Noninvasive measures for assessment of LIC include superconducting quantum interference device (SQUID) and T2 MRI (FerriScan). Given the limited availability and complexity of SQUID, MRI is currently the preferred method for assessment of LIC. (While FerriScan is TGA approved it is not currently reimbursed through Medicare and the out-of-pocket costs to patients may be in the range of $500-$700).

Management of Iron Overload

Given the detrimental effects of iron overload on early and late BMT outcomes there is a clear rationale for the idea that taking steps to reduce excessive body iron may be beneficial, both before and after transplant. While there is limited evidence that removal of iron pre-transplant improves outcomes following BMT there is a growing body of evidence supporting the removal of excess iron post-BMT. Defined criteria for when and how to treat iron overload post-BMT have not, however, been clearly established. (McDonald 2010)

Pre-transplant assessment and management of iron overload

All potential candidates for BMT should be assessed for iron overload. This assessment should include:

- Clinical assessment for risks of iron overload including history of hepatitis, myelodysplasia, thalassaemia, alcohol excess and family history of haemachromatosis.
- Blood transfusion history
- Laboratory investigation including ferritin, transferrin saturation and liver function studies.
- HFE gene studies in patients who have a persistently elevated ferritin and transferrin saturation and/or a family history of hereditary haemachromatosis.

Patients who are candidates for allogeneic BMT and who have a ferritin of >1000ng/ml should have phlebotomy pre-transplant to achieve a ferritin in the normal range if there is sufficient time to do so and the patient's haemoglobin and clinical situation allows for venesections to be performed. Iron chelation should be considered for paediatric patients with iron overload and in patients with iron overload who are unable to be venesected because they are transfusion dependent. Importantly, in all situations, treatment of iron overload should not cause a delay in transplantation.

Post-transplant assessment and management of iron overload.

Liver function tests should be done every 3 months post-transplant for the first year and then (at least) annually thereafter. (Mohty and Mohty 2011)

Ferritin should be measured at 1 year post-BMT and then annually until it is in the normal range.

Liver biopsy or MRI (FerriScan) should be considered in all patients with a consistently elevated ferritin (>1000ng/ml), particularly in patients with abnormal liver function studies, fatty liver or a diagnosis of haemachromatosis.

All patients with ferritin >1000ng/ml should be considered for venesection or iron chelation when clinically stable (generally 6-12 months post-BMT).

Venesection:

Therapeutic venesection is the treatment of choice for iron overload in patients with full recovery of haematopoiesis after BMT. Venesection is generally well-tolerated and most adult patients are able to continue venesection until the target ferritin is reached. Venesection via a venepuncture is logistically more difficult in the paediatric population. Venesection may be considered in younger patients who have central access and in older patients who can tolerate repeated venepuncture.

In patients with ferritin >1000ng/ml venesection (6ml/kg - 450-500ml in most adult patients, 10ml/kg to a maximum of 350ml in children) should be performed every 4-8 weeks. Adult patients with a greater degree of iron overload (>2500ng/ml) may be venesected more intensively (every 2 weeks) if tolerated.

There is no consensus regarding the target ferritin for venesection post-BMT with some supporting a target ferritin of <1000 ng/ml, some a target of <500 ng/ml and some a ferritin in the normal range with a normal transferrin saturation <45%. In either case the target ferritin is a matter of clinical judgement and may differ depending upon whether the patient has haemachromatosis or has coincident liver disease due to fatty liver or viral hepatitis.

Where venesection is practically impossible, not tolerated or cannot be done because of poor venous access, hypotension (systolic BP <100) or Hb <120g/L, consideration should be given to iron chelation with deferasirox or deferiprone.

Iron Chelation:

While iron chelation is infrequently used post-BMT, chelation may sometimes be used to reduce the post-BMT complications associated with iron overload (Sivgin et al. 2013). The following chelating agents are available in Australia and New Zealand.

Deferasirox (Exjade Novartis)

Deferasirox is approved and on the PBS for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older as well as for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older. It has also been shown to be safe and effective following allogeneic stem cell transplant (Vallejo et al. 2014). For these reasons deferasirox is the most frequently used iron chelator post-BMT.

Dosing

20 mg/kg daily (maximum dose 40 mg/kg daily)

It is recommended that serum ferritin be monitored every month and that the dose of deferasirox is adjusted if necessary every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 5 to 10 mg/kg and are to be tailored to the individual patient's response and

therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 30 mg/kg (e.g. serum ferritin levels persistently above 2500 microgram/L and not showing a decreasing trend over time), doses of up to 40 mg/kg may be considered. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level. In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 microgram/L, an interruption of treatment should be considered. As with other iron chelator treatment, the risk of toxicity of deferasirox may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated

Adverse effects

Potentially serious adverse events, particularly in BMT recipients, may occur following administration of deferasirox include potentially fatal gastrointestinal hemorrhage, renal toxicity (including renal failure), and hepatic toxicity (including hepatic failure). More commonly observed adverse events include abdominal pain, nausea, vomiting, diarrhea, back pain, and skin rash; gastrointestinal adverse events are generally transient in nature, lasting not more than one week.

Monitoring

Renal

Consider dose reductions, interruptions, or discontinuation for increases in serum creatinine. For adult patients, the daily dose of deferasirox may be reduced by 10 mg/kg if a non-progressive rise in serum creatinine by >33% above the average of the pre-treatment measurements is seen at two consecutive visits, and cannot be attributed to other causes.

Hepatic

Although uncommon (0.3%), elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, have been observed in clinical trials. It is recommended that serum transaminases, bilirubin and alkaline phosphatase be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels – even in patients with GvHD or other possible causes of liver disease - deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of deferasirox treatment at a lower dose followed by gradual dose escalation may be considered.

Cytopenia

Cytopenias occur commonly in transplant recipients due to the effects of drugs, infection, graft loss, relapse or GvHD. As it is often difficult to determine the cause of cytopenia in BMT recipients, deferasirox should be ceased or dose-reduced in patients who develop unexplained cytopenia. Reintroduction of therapy with deferasirox may then be considered once the cause of the cytopenia has been elucidated.

Desferrioxamine (Deferoxamine)

Desferrioxamine is a clinically approved and effective iron chelator for long-term therapy in patients with beta thalassemia and other iron overload states. Desferrioxamine is indicated and on the PBS for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anaemias. Consequently it may be used to manage iron overload both pre- and post-transplant. Desferrioxamine is a relatively specific and nontoxic iron chelating agent. Although Desferrioxamine is absorbed orally, the pharmacokinetics of intermittent oral doses are unfavorable for effective iron chelation. Continuous intravenous or subcutaneous infusion is therefore necessary.

Dosing

In most patients average daily doses of 20 to 60 mg/kg body weight are adequate. Patients with a serum ferritin level of less than 2000 microgram/L require about 25 mg/kg/day. Patients with a serum ferritin level between 2000 and 3000 microgram/L require about 35 mg/kg/day. Patients with higher serum ferritin levels may require up to 55 mg/kg/day. It is inadvisable to regularly exceed an average daily dose of 50 mg/kg/day except when very intensive chelation is needed in patients who are no longer growing. If ferritin values fall below 1000 microgram/L, the risk of Desferal toxicity increases. Therefore, it is important to monitor these patients particularly carefully and to consider lowering the total weekly dose.

Adverse effects

Side effects of Desferrioxamine include visual and auditory neurotoxicity with chronic therapy and acute complications such as abdominal discomfort/pain, diarrhea, nausea, vomiting, hypotension, and anaphylaxis.

Visual loss and ototoxicity following the use of Desferrioxamine are directly related to the dose of deferoxamine and inversely related to the degree of iron overload. This risk can be minimized by adjusting the daily dose of deferoxamine to the patient's serum ferritin concentration.

Risk of infection

Administration may be associated with an increased risk of infection with mucormycosis (zygomycosis), *Yersinia*, and *Vibrio vulnificus*. The presumed reason for the susceptibility to these infections is that the Desferrioxamine-iron chelate, called feroxamine, is a siderophore for these species; the resulting increase in iron uptake stimulates their growth, possibly leading to clinical infection. For this reason many consider that deferoxamine should not be used post-transplant.

Deferiprone

Deferiprone is an orally active iron chelator indicated and on the PBS only for patients with thalassemia major. Deferiprone is currently not PBS-listed for pre or post-BMT use in other contexts and the cost for off-label use in these situations is approximately AUD$2500/month.

Dosing

The recommended initial oral dose of deferiprone is 25 mg/kg taken three times per day (initial total daily dose 75 mg/kg per day), and the maximum recommended total daily dose is 100 mg/kg per day.

Adverse effects

The most common adverse events included increased hepatic enzymes, gastrointestinal discomfort, and arthralgia. Incidences of neutropenia and agranulocytosis were 2.1 and 0.4 events per 100 patient-years, respectively; both were reversible upon interruption of therapy but would make this agent less desirable in patients who had undergone stem cell transplant.

References

1. Armand P, Kim HT, Cutler CS et al. 2007. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood,* 109;4586-88.

2. Armand P, Kim HT, Virtanen JM et al. Iron overload in allogeneic hematopoietic cell transplantation outcome: a meta-analysis. *Biol Blood Marrow Transplant*. 20(8):1248-51.

3. Busca A, Dellacasa C, Pecoraro C. 2014. Iron overload in patients receiving allogeneic hematopoietic stem cell transplantation. *Global Journal of Hematology and Blood Transfusion*. 1, 6-17.

4. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. 2008. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis*. 47:1041-50.

5. Inamoto Y, Lee SJ. (2017) Late effects of blood and marrow transplantation. *Haematologica.* 102(4):614-24.

6. Mahindra A, Sobecks R, Rybicki L et al. 2009 Elevated pretransplant serum ferritin is associated with inferior survival following nonmyeloablative allogeneic transplantation. *Bone Marrow Transplant*. 44:767-8.

7. Majhail NS, Lazarus HM, Burns LJ. 2008. Iron overload in hematopoietic cell transplantation. *Bone Marrow Transplant* 41;997-1003.

8. McDonald GB. 2010. Hepatobiliary complications of hematopoietic cell transplantation - 40 years on. *Hepatology*. 51(4):1450-60.

9. Meyer SC, O'Meara A, Buser AS et al. 2013. Prognostic impact of posttransplantation iron overload after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 19:440-4.

10. Mohty B, Mohty M. 2011 Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer J*. 1(4):p e16.

11. Rose C, Ernst O, Hecquet B et al. Quantification by magnetic resonance imaging and liver consequences of post-transfusional iron overload alone in long-term survivors after allogeneic hematopoietic stem cell transplantation (HSCT). *Haematologica.* 92(6):850-3.

12. Sivgin, Serdar, Suleyman Baldane, Gulsah Akyol, Muzaffer Keklik, Leylagül Kaynar, Fatih Kurnaz, Cigdem Pala, et al. 2013. The Oral Iron Chelator Deferasirox Might Improve Survival in Allogeneic Hematopoietic Cell Transplant (alloHSCT) Recipients with Transfusional Iron Overload. *Transfusion and Apheresis Science: Official Journal of the World Apheresis Association: Official Journal of the European Society for Haemapheresis* 49 (2): 295–301.

13. Tachibana T, Tanaka M, Numata A et al. 2012. Pretransplant serum ferritin has a prognostic influence on allogeneic transplant regardless of disease risk. *Leuk Lymphoma*. 53:456-61.

14. Trottier BJ, Burns LJ, DeFor TE et al. 2013. Association of iron overload with allogeneic hematopoietic cell transplantation outcomes: a prospective cohort study using R2-MRI-measured liver iron content. *Blood* 122(9):1678-84.

15. Vallejo, Carlos, Montserrat Batlle, Lourdes Vázquez, Carlos Solano, Antonia Sampol, Rafael Duarte, Dolores Hernández, et al. 2014. Phase IV Open-Label Study of the Efficacy and Safety of Deferasirox after Allogeneic Stem Cell Transplantation. *Haematologica* 99 (10): 1632–37.