Bone Marrow Transplantation (2008) 42, 363–364

www.nature.com/bmt

LETTER TO THE EDITOR

Hypocalcaemic cardiac failure post BMT secondary to unrecognized vitamin D deficiency

Bone Marrow Transplantation (2008) **42,** 363–364; doi:10.1038/bmt.2008.178; published online 23 June 2008

Cardiac failure is not uncommon after BMT. It is usually multifactorial, contributed by chronic drug toxicity (anthracycline, BU, carmustine or cytarabine[1,2]), previous irradiation or pre-existing heart diseases.[1] Patients are particularly at risk in the immediate post transplant period because of the challenge from large volumes of intravenous fluid, and the additional risk of high-output cardiac failure precipitated by anaemia and infection. Given their known vulnerability to cardiac dysfunction, any potential precipitants should be minimized. Although electrolyte disturbances may occur post transplantation, hypocalcaemia resulting in cardiac failure has not been reported in BMT recipients. We report a case of decompensated cardiac failure post autologous stem cell BMT secondary to severe hypocalcaemia from unrecognized vitamin D deficiency, to highlight the importance of calcium homeostasis surveillance in BMT recipients.

A 60-year-old man with a past history of multiple myeloma was electively admitted for autologous stem cell BMT. He was previously treated with four cycles of chemotherapy with VCR, adriamycin (cumulative dose <250 mg) and CY, as well as monthly zoledronic acid infusion for 4 months (last infusion 1 month before transplantation) for myeloma-related vertebral fractures. Other medications included metformin 500 mg twice daily, simvastatin 40 mg daily and calcium carbonate 600 mg daily. The patient developed acute cardiogenic pulmonary oedema post transplantation, requiring bilevel positive airway pressure ventilation and diuretic therapy. Biochemistry demonstrated acute hypocalcaemia with an ionized calcium concentration of 0.8 mmol/l (3.2 mg per 100 ml) secondary to severe vitamin D deficiency (Table 1). Transthoracic echocardiogram showed severe global hypokinesis with a left ventricular fractional shortening (LVFS) of 16% (28–38) and an ejection fraction (EF) of 30%. Cardiac ischaemia and other structural causes of cardiac failure were excluded. High-dose cholecalciferol, as well as calcitriol, and calcium supplement were commenced, with gradual resolution of hypocalcaemia (Figure 1), paralleling improvement of cardiac function (LVFS = 25% 10 days later), and near-complete resolution of cardiac dysfunction 2 months later (EF = 55%).

Incidence of major cardiac events varies from 0.5 to 9% in several series.[3–5] Cardiac tamponade and cardiac arrhythmias are the most common life-threatening events. Although hypocalcaemia may cause arrhythmia, the incidence of cardiac dysfunction secondary to hypocalcaemia in BMT recipients is unknown. Because of the specific milieu of transplantation, BMT recipients are at significant risk of unrecognized hypocalcaemia, which may further compromise cardiac function in at-risk individuals.

Firstly, sun-avoidance to prevent skin malignancies, and reduction in time spent outdoors due to underlying chronic diseases, contribute to severe vitamin D deficiency in BMT recipients. Normocalcaemia is usually maintained from compensatory secondary hyperparathyroidism in patients with vitamin D deficiency, which leads to increased bone resorption and increased formation of 1,25-dihydroxy vitamin D to increase intestinal calcium absorption. However, bisphosphonate therapy used in the treatment of transplant-related osteoporosis or pathological fractures in myeloma, as in our case, frequently impairs such compensatory mechanism. Potent bisphosphonates, such as zoledronic acid, suppress bone resorption with great efficacy, and therefore eliminate an effective compensatory mechanism to correct hypocalcaemia by releasing calcium from the skeleton. Secondly, high-dose glucocorticoids, used immediately post transplant or for the treatment of relapse myeloma, can further precipitate hypocalcaemia due to hypercalciuria[6] and intestinal calcium malabsorption.[7] As vitamin D deficiency is common among patients with chronic diseases, vitamin D status should be evaluated before bisphosphonate therapy. Severe hypocalcaemia has been reported in patients with occult vitamin D deficiency who were administered zoledronic acid.[8] Decompensated cardiac failure as seen in our case has been reported in scattered case reports[9] in the non-transplant population.

Table 1 Baseline biochemistry of patients; SI units are expressed in parentheses

	Result	*Reference*
Sodium	137	137–147 mmol/l
Potassium	4.5	3.5–5 mmol/l
Chloride	99	95–110 mmol/l
Bicarbonate	25	24–31 mmol/l
Urea nitrogen	14.6 (5.2)	8.4–23.8 mg per 100 ml (3–8.5 mmol/l)
Creatinine	1.09 (96)	0.68–1.36 mg per 100 ml (60–120 μmol/l)
Corrected calcium	6.56 (1.64)	8.4–10.4 mg per 100 ml (2.1–2.6 mmol/l)
Ionized calcium	3.2 (0.8)	4.6–5.2 mg per 100 ml (1.15–1.3 mmol/l)
Phosphate	1.42 (0.46)	2.17–4.33 mg per 100 ml (0.7–1.4 mmol/l)
Magnesium	2.43 (1.0)	1.7–2.56 mg per 100 ml (0.7–1.05 mmol/l)
Parathyroid hormone	27.5	1–7 ng/ml
25-hydroxy vitamin D	6.8 (17)	>24 ng/ml (>60 nmol/l)

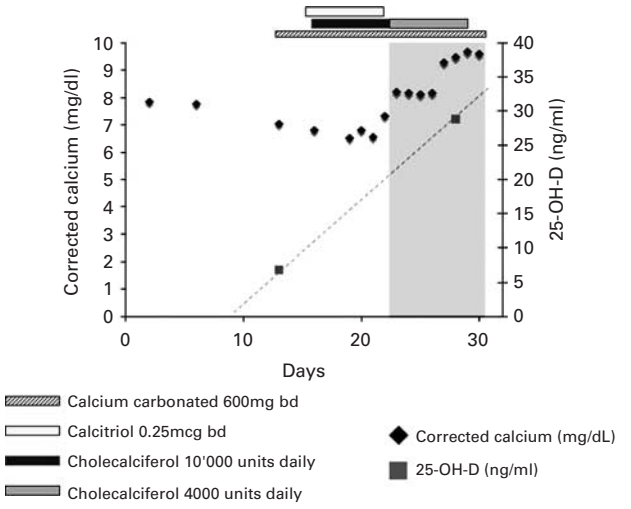

Figure 1 Normalization of serum calcium concentration with vitamin D metabolites and calcium supplements. Shaded area indicates correlation of achievement of normocalcaemia with vitamin D sufficiency (30 nmol/l).

Less severe hypocalcaemia may compromise cardiac function in at-risk BMT recipients with pre-existing cardiac diseases, and may increase their risk of decompensated cardiac failure in the post transplant setting when exposed to large volumes of intravenous fluid, anaemia or infection.

Treatment of hypocalcaemia secondary to severe vitamin D deficiency necessitates high-dose cholecalciferol replacement. Figure 1 demonstrated normocalcaemia only after 25-hydroxy vitamin D concentration reached at least 30 nmol/l (12 ng/ml) following high-dose replacement (10 000 U cholecalciferol daily). Standard replacement with 1000 U daily is inadequate. Calcitriol may be used initially, although it may not be as effective in the treatment of hypocalcaemia secondary to severe vitamin D deficiency.

In conclusion, although vitamin D sufficiency is now emphasized to prevent transplant-related osteoporosis,[10] hypocalcaemia is a dangerous, but under-recognized complication of vitamin D deficiency. BMT recipients are particularly at risk of hypocalcaemia-related cardiac dysfunction due to unrecognized vitamin D deficiency. Monitoring of calcium and vitamin D homeostasis can be easily neglected in the complex medical management of BMT. Vitamin D sufficiency should now be emphasized not only for bone protection, but also for the prevention of hypocalcaemia-related cardiac dysfunction in BMT recipients.

P Lee[1,2], S Milliken[3] and JR Center[1,2]
[1]*Department of Endocrinology, St Vincent's Hospital, Sydney, New South Wales, Australia;*
[2]*Garvan Institute of Medical Research, Sydney, New South Wales, Australia and*
[3]*Department of Hematology, St Vincent's Hospital, Sydney, New South Wales, Australia*
E-mail: p.lee@garvan.org.au

References

1 Buja LM, Ferrans VJ, Graw RG. Cardiac pathologic findings in patients treated with bone marrow transplantation. *Hum Pathol* 1976; **7**: 17–45.
2 Vaickus L, Letendre L. Pericarditis induced by high-dose cytarabine therapy. *Arch Intern Med* 1984; **144**: 1868–1869.
3 Hertenstein B, Stefanic M, Schmeiser T, Scholz M, Göller V, Clausen M *et al*. Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplant. *J Clin Oncol* 1994; **12**: 998–1004.
4 Jain B, Floreani AA, Anderson JR, Vose JM, Robbins RA, Rennard SI *et al*. Cardiopulmonary function and autologous bone marrow transplantation: results and predictive value for respiratory failure and mortality. *Bone Marrow Transplant* 1996; **17**: 561–568.
5 Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977–1997. *Bone Marrow Transplant* 2001; **28**: 283–287.
6 Suzuki Y, Ichikawa Y, Saito E, Homma M. Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. *Metabolism* 1983; **32**: 151–156.
7 Kimberg DV, Baerg RD, Gershon E, Graudusius RT. Effect of cortisone treatment on the active transport of calcium by the small intestine. *J Clin Invest* 1971; **50**: 1309–1321.
8 Rosen CJ, Brown S. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. *N Engl J Med* 2003; **10**: 1503–1504.
9 Hurley K, Baggs D. Hypocalcemic cardiac failure in the emergency department. *J Emerg Med* 2005; **28**: 155–159.
10 Ebeling PR. Transplantation osteoporosis. *Curr Osteoporos Rep* 2007; **5**: 29–37.