YL Kwong 鄺沃林
Y Wong 王　奕
KW Lie 李國維

Avascular necrosis of bone in patients with graft-versus-host disease after allogeneic haematopoietic stem cell transplantation and corticosteroid therapy: a magnetic resonance imaging study

Key Messages

1. Magnetic resonance imaging evidence of osteonecrosis occurs in about one third of patients who had received corticosteroid therapy for graft-versus-host disease after haematopoietic stem cell transplantation.
2. The only risk factor identified in this cohort of patients that predisposed to osteonecrosis was transplantation for acute lymphoblastic leukaemia.
3. The cumulative dose of corticosteroids was unrelated to the occurrence of osteonecrosis.
4. Patients with osteonecrosis were comparable to patients without osteonecrosis in symptomatology.

Hong Kong Med J 2008;14(Suppl 1):S17-20

Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China
YL Kwong, KW Lie
Department of Diagnostic Radiology, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China
Y Wong

RFCID project number: HA-CS-002b

Principal applicant and corresponding author:
Dr YL Kwong
Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China
Tel: (852) 2855 4597
Fax: (852) 2974 1165
E-mail: ylkwong@hkucc.hku.hk

Aims and objectives

1. To define the frequency of osteonecrosis, as detected by magnetic resonance imaging, in patients who had received corticosteroid therapy for graft-versus-host disease after allogeneic haematopoietic stem cell transplantation.
2. To define the risk factors for osteonecrosis.

Introduction

Osteonecrosis, or avascular necrosis, is the death of bone due to interruption of the vascular supply, resulting from traumatic or non-traumatic systemic causes.[1] In advanced osteonecrosis with infarction of bones, pain is the most important symptom, together with loss of function when joints are involved. By then the diagnosis is usually obvious on radiography and radionuclide bone scanning. However, early osteonecrosis can be asymptomatic. Magnetic resonance imaging (MRI) is more sensitive in detecting osteonecrosis during early stages and/or at asymptomatic sites.[2] The early diagnosis of osteonecrosis is important for two reasons. Firstly, advanced osteonecrosis severely limits the choice of therapy. Secondly, treatment results decline when the disease is advanced.[1]

Osteonecrosis is a main complication after haematopoietic stem cell transplantation (HSCT).[3-11] Predisposing factors include older age,[11] acute and chronic graft-versus-host disease (GVHD),[5,7] corticosteroid treatment,[3,6] HSCT for aplastic anaemia and leukaemia,[5,11] use of total body irradiation for conditioning,[6] and allogeneic source of haematopoietic stem cells.[9] However, not all of these risk factors have been consistently observed.

An important problem of past studies of osteonecrosis in HSCT is the inclusion of only symptomatic patients, often identified retrospectively from follow-up records at multiple centres.[5-7,9,10] Such an approach has several limitations. Firstly, asymptomatic patients with osteonecrosis could not be identified or included. Furthermore, as only symptomatic patients were studied, nearly 90% had involvement of the femoral head,[5,9] which gave the most symptoms in osteonecrosis. Hence, osteonecrosis affecting other sites, including the femoral condyles, humerus, and other bones,[2] has been grossly under-diagnosed. Finally, the impact of MRI, which is much more sensitive in detecting asymptomatic osteonecrosis, has not been fully evaluated in the setting of allogeneic HSCT.

To define the frequency and significance of subclinical osteonecrosis, we performed a cross-sectional study of a cohort of patients who underwent allogeneic HSCT.

Methods

This study was conducted from December 2004 to December 2005.

Table 1. Clinicopathological features of 52 patients studied by magnetic resonance imaging for osteonecrosis

Clinicopathological parameters	No. of patients
Male	23
Female	29
Diagnosis	
Chronic myeloid leukaemia	25
Acute myeloid leukaemia	8
Acute lymphoblastic leukaemia	8
Others	11
Conditioning regimen	
Total body irradiation (TBI) containing	25
Non-TBI containing	27
Donor	
Human leukocyte antigen–identical sibling	39
Others	13
Acute GVHD*	
≤grade II	35
≥grade III	17
Chronic GVHD of lung	
Present	2
Absent	50
Chronic GVHD of skin	
Present	29
Absent	23
Chronic GVHD of mouth	
Present	17
Absent	35
Chronic GVHD of eye	
Present	9
Absent	43
Chronic GVHD of liver	
Present	29
Absent	23
Chronic GVHD of gut	
Present	11
Absent	41
Significant weight loss	
Present	1
Absent	51
Reactivation of cytomegalovirus	
Present	29
Absent	23

* GVHD denotes graft-versus-host disease

Patients

A consecutive unselected cohort of patients, who underwent allogeneic HSCT with documented acute GVHD, were studied. There were no inclusion or exclusion criteria. All patients gave informed consent, and the study was approved by the Institutional Review Board of the Queen Mary Hospital.

Protocol and treatment

The HSCT protocols, including conditioning regimens and prophylaxis against acute GVHD, have been previously described in detail.[12] Acute GVHD was diagnosed and graded according to standard criteria.[13] The initial treatment of acute GVHD comprised intravenous methylprednisolone (1-2 mg/kg/day) or oral prednisolone (1-2 mg/day). Patients responding to treatment would receive tapering corticosteroid therapy. Patients not responding to the steroid therapy would receive anti-thymocyte globulin or other additional therapy at the discretion of the attending physician. The total dose of corticosteroid used for the treatment of GVHD was calculated from the initiation of treatment to its successful tapering.

Magnetic resonance imaging

The use of MRI was according to standard protocols to the hip and knee region.[14] Osteonecrosis of the hip was graded according to the University of Pennsylvania System for Hip AVN Staging. Involvement of the knee was categorised according to number and size of the lesions. Intramedullary lesions were also enumerated according to their size and number.

Pain scoring

To assess if radiological findings correlated with symptoms, a Chinese version of the modified Arthritis Impact Measurement Scale 2 (CAIMS2) was used. The CAIMS2 has been previously validated in a Chinese population.[15] The questionnaire was self-administered.

Statistical analysis

To assess the correlation between osteonecrosis and various clinicopathological parameters, categorical data were compared with Fisher's exact test or Chi squared tests, where appropriate. For continuous variables, the median one-way analysis was performed. Stepwise logistic regression was performed to evaluate the impact of disease category and GVHD on osteonecrosis.

Results

Patients

A total of 52 patients were recruited. The clinicopathological features of the patients are shown in Table 1. Progression of acute to chronic GVHD involving the skin, gut, or liver occurred in 29 patients.

Magnetic resonance imaging findings

The MRI findings are shown in Table 2. Sixteen (31%) of the patients showed osteonecrosis, among whom there was involvement of the distal femoral condyles in 10 (63%), the hip in 5 (31%) and the proximal tibia in 2 (13%), whilst intramedullary lesions occurred in 7 (44%).

Clinicopathological correlations

Analysis of risk factors predisposing to osteonecrosis showed that HSCT for acute lymphoblastic leukaemia (ALL) was the only significant risk factor predisposing to osteonecrosis. Other potential risk factors, including the use of total body irradiation during conditioning, and the severity and extent of acute/chronic GVHD had no impact on the occurrence of osteonecrosis (Table 3). Interestingly, the time from HSCT to MRI, and the dose of corticosteroids (methylprednisolone, prednisolone, and total corticosteroids) were also unrelated to the occurrence of osteonecrosis (Table 4). Finally, an analysis of the CAIMS2 pain score showed that patients with or without MRI evidence of osteonecrosis reported comparable symptomatology with respect to joint pain and mobility.

Table 2. Magnetic resonance imaging findings of 16 patients with osteonecrosis after allogeneic haematopoietic stem cell transplantation

Patient No.	Sex/ age (years)	Diagnosis*	Conditioning†	Time from bone marrow transplant (months)	Hip grade	Osteonecrosis					
						Distal femoral condyles		Proximal tibia		Intramedullary lesions	
						No.	Size (cm)‡	No.	Size (cm)‡	No.	Size (cm)‡
1	F/42	ALL	Cy+TBI	175	-	2	2.3, 2.3	-	-	-	-
2	F/23	ALL	Cy+TBI	176	-	2	1.3, 3.0	-	-	1	3.6
3	M/24	AA	Cy+TLI	168	Ia	-	-	-	-	-	-
4	M/16	ALL	Cy+TBI	162	-	2	2.5	-	-	-	-
5	M/28	AML	Bu+Cy+TBI	120	-	1	0.9	-	-	4	3.7, 4.1, 4.8, 5.2
6	F/35	ALL	Cy+TBI	101	Ib	3	1.5, 2.0, 3.5	-	-	4	4.1, 4.6, 5.6, 8.2
7	M/23	ALL	Cy+TBI	87	-	2	7.0, 15.0	2	7.1, 5.8	-	-
8	F/41	AML	Bu+Cy	66	-	-	-	-	-	1	3.3
9	M/48	ALL	Cy+TBI	61	-	2	3.5, 3.5	2	2.0, 2.0	-	-
10	F/45	MM	Bu+Cy	57	-	-	-	-	-	4	3.9, 4.3, 5.0, 5.1
11	M/46	CML	Bu+Cy	51	-	1	0.8	-	-	-	-
12	M/31	NHL	Cy+TBI	47	Ia/Ib	-	-	-	-	-	-
13	M/24	AML	Bu+Cy	46	-	6	0.9, 1.2, 1.5, 1.5, 2.2, 2.8	-	-	4	1.6, 2.2, 4.8, 5.1
14	M/44	ALL	Cy+TBI	44	Ia	-	-	-	-	-	-
15	M/52	MDS	Flud+TBI	40	IV	-	-	-	-	3	2.8, 3.0, 4.1
16	F/21	CML	Bu+Cy	34	-	1	1.0	-	-	-	-

* ALL denotes acute lymphoblastic leukaemia, AA aplastic anaemia, AML acute myeloid leukaemia, MM multiple myeloma, CML chronic myeloid leukaemia, NHL non-Hodgkin lymphoma, and MDS myelodysplastic syndrome
† Cy denotes cyclophosphamide, TBI total body irradiation, TLI total lymphoid irradiation, Bu busulfan, and Flud fludarabine
‡ The longest dimension was measured

Table 3. Correlations between clinicopathological features and osteonecrosis in 52 patients receiving corticosteroids for graft-versus-host disease

Clinicopathological features	Osteonecrosis		P value
	Present	Absent	
Gender			0.31
Male	10	18	
Female	6	18	
Diagnosis			0.001
Acute lymphoblastic leukaemia	6	2	
Acute myeloid leukaemia	3	5	
Chronic myeloid leukaemia	2	23	
Others	5	6	
Conditioning regimen			0.16
Total body irradiation (TBI) containing	10	15	
Non-TBI containing	6	21	
Donor			0.18
Human leukocyte antigen–identical sibling	10	29	
Others	6	7	
Acute GVHD*			0.49
≤grade II	9	13	
≥grade III	5	15	
GVHD of lung			1.00
Present	0	2	
Absent	16	34	
GVHD of skin			0.06
Present	12	17	
Absent	4	19	
GVHD of mouth			0.88
Present	5	12	
Absent	11	24	
GVHD of eye			0.43
Present	4	5	
Absent	12	31	
GVHD of liver			0.07
Present	6	23	
Absent	10	13	
GVHD of gut			0.46
Present	2	9	
Absent	14	27	
Reactivation of cytomegalovirus			0.58
Present	8	21	
Absent	8	15	

* GVHD denotes graft-versus-host disease

Table 4. Correlation of post–haematopoietic stem cell transplantation parameters with osteonecrosis

Clinicopathological parameters	Osteonecrosis		P value
	Present	Absent	
Median age at transplantation (years)	33.0	35.0	0.70
Median time from transplantation to magnetic resonance imaging (months)	63.5	70.0	0.55
Median dose of methylprednisolone (mg)	376.0	317.5	1.00
Median dose of prednisolone (mg)	1511.9	981.9	0.23
Median total dose of steroids (mg equivalent of prednisolone)	2270.0	1318.1	0.23
Median No. of days of antibiotics	21.0	22.0	0.87
Median No. of days of anti-fungal agents	0.0	2.5	0.31
Median No. of days of ganciclovir	1.0	3.0	0.55
Median CAIMS2* pain score	13.1	13.4	0.75

* CAIMS2 denotes Chinese version of the modified Arthritis Impact Measurement Scale 2

Discussion

There are a number of important findings in this study. With MRI, we showed a high frequency of osteonecrosis in almost a third of our patients who had received corticosteroid therapy for GVHD after allogeneic HSCT. Notably, none of our patients presented with conventional symptoms of osteonecrosis, which are mostly referable to the hip. Consequently, our study showed a much higher frequency of osteonecrosis particularly in the distal femoral condyles. Another interesting observation was the occurrence of intramedullary lesions in nearly one half of patients with osteonecrosis. As intramedullary lesions were not in close proximity to joints, they were unlikely to generate specific symptoms that would lead the attending physician to suspect osteonecrosis.

Previous studies have identified a number of risk factors for osteonecrosis. In our study, we found that HSCT for ALL was the only significant factor predisposing to osteonecrosis. Interestingly, the severity and extent of GVHD, and also the use of corticosteroids (dosages of methylprednisolone, prednisolone, and cumulative dose of corticosteroids), which was an indirect reflection of the degree of GVHD, were unrelated to the occurrence of osteonecrosis.

Finally, patients with and without osteonecrosis reported similar symptomatology on CAIMS2 scoring. This reflected the fact that after HSCT, patients reported non-specific symptoms at a high frequency, so that symptoms alone might not help the attending physician suspect osteonecrosis.

Several limitations may confound the interpretation of the results of this study. It was a retrospective study, and some of the clinicopathological data were obtained by review of the case records of the patients instead of being collected prospectively. Patients with serious GVHD who had died were not included. Furthermore, patients who had ALL would have received corticosteroids before HSCT. It is therefore possible that the total cumulative dose of corticosteroids before and after HSCT might also be important. These potential caveats will have to be addressed by future prospective studies.

Conclusions

In our patients receiving corticosteroids for GVHD post-HSCT, a high frequency of osteonecrosis was found on MRI. However, its occurrence was not related to the total cumulative dose of corticosteroids. This suggested that in addition to the use of corticosteroids, other underlying factors might also have a role in the occurrence of osteonecrosis. Finally, patients with MRI evidence of osteonecrosis were no more symptomatic than those without such lesions, which emphasises the importance of MRI rather than symptomatology in the diagnosis of subclinical osteonecrosis.

Acknowledgements

This project forms part of a series of studies commissioned by the Food and Health Bureau of the Hong Kong SAR Government and funded by the Research Fund for the Control of Infectious Diseases (Project No. HA-CS-002b). The authors thank Ms Eva LH Tsui for statistical analysis.

References

1. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002;32:94-124.
2. Saini A, Saifuddin A. MRI of osteonecrosis. Clin Radiol 2004;59:1079-93.
3. Enright H, Haake R, Weisdorf D. Avascular necrosis of bone: a common serious complication of allogeneic bone marrow transplantation. Am J Med 1990;89:733-8.
4. Mascarin M, Giavitto M, Zanazzo GA, et al. Avascular necrosis of bone in children undergoing allogeneic bone marrow transplantation. Cancer 1991;68:655-9.
5. Socie G, Cahn JY, Carmelo J, et al. Avascular necrosis of bone after allogeneic bone marrow transplantation: analysis of risk factors for 4388 patients by the Societe Francaise de Greffe de Moelle (SFGM). Br J Haematol 1997;97:865-70.
6. Fink JC, Leisenring WM, Sullivan KM, Sherrard DJ, Weiss NS. Avascular necrosis following bone marrow transplantation: a case-control study. Bone 1998;22:67-71.
7. Socie G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. Blood 2001;98:3569-74.
8. Torii Y, Hasegawa Y, Kubo T, et al. Osteonecrosis of the femoral head after allogeneic bone marrow transplantation. Clin Orthop Relat Res 2001;382:124-32.
9. Tauchmanova L, De Rosa G, Serio B, et al. Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review. Cancer 2003;97:2453-61.
10. Kaste SC, Shidler TJ, Tong X, et al. Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. Bone Marrow Transplant 2004;33:435-41.
11. Ades L, Mary JY, Robin M, et al. Long-term outcome after bone marrow transplantation for severe aplastic anemia. Blood 2004;103:2490-7.
12. Leung AY, Suen CK, Lie AK, Liang RH, Yuen KY, Kwong YL. Quantification of polyoma BK viruria in hemorrhagic cystitis complicating bone marrow transplantation. Blood 2001;98:1971-8.
13. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18:295-304.
14. Griffith JF, Antonio GE, Kumta SM, et al. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. Radiology 2005;235:168-75.
15. Chu EM, Chiu KY, Wong RW, Tang WM, Lau CS. Translation and validation of Arthritis Impact Measurement Scales 2 into Chinese: CAIMS2. Arthritis Rheum 2004;51:20-7.