Osteonecrosis after Allogeneic Bone Marrow Transplantation

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Abstract Osteonecrosis after bone marrow transplantation is usually severe. Most patients develop acute and chronic graft-versus-host disease requiring a high dose of steroids for a long period of time. Generally ineffective nonoperative treatment in the past has resulted in treatment primarily with total hip arthroplasty (THA). We asked whether THA (1) reliably improved functional status, (2) led to more complications, and (3) THA after bone marrow transplantation was as durable as THA for idiopathic ON. We retrospectively reviewed 77 patients (123 hips) with osteonecrosis. The mean age at surgery was 33 years (range, 15.7–56 years). We performed all arthroplasties with an alumina ceramic bearing coupled with an alumina head 32 mm in diameter. The minimum followup was 2 years (mean, 9.2 years; range, 2–26 years). We documented seven revisions: three for late septic loosening, four for late aseptic loosening. Considering loosening of any component as the end point, the survivorship was 74.8% (range, 58.7%–90.9%) at 10 years. In this difficult situation, we believe the results acceptable. Septic loosening affecting this specific population has to be considered a serious event.

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

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Introduction

Fatal hematologic diseases are now manageable and even sometimes curable with bone marrow transplantation. While a serious procedure for patients, acute and fatal complications are decreasing and bone marrow transplantation is considered an effective option by hematologists. Among the patients who were free of their primary disease 2 years after transplantation, Socié et al. [22] estimated the probability of surviving 5 more years was 89%. Patients surviving are then exposed to nonfatal complications. Among these complications, osteonecrosis (ON) occurs in between 3.9% and 19% of patients [7, 8, 11, 20, 22, 23, 25]. The two major risk factors for ON after bone marrow transplantation are acute and chronic graft-versus-host disease (GVHD) and its treatment with steroid therapy and total body irradiation [7, 8, 11, 14, 17, 20, 21, 23, 25]. (All patients in our series received total body irradiation hematological department protocol.) In a previous study [21], we reported a risk factor analysis: age of more than 16 years led to a relative risk of 3.87 and acute graft-versus-host disease requiring steroid therapy to a relative risk of 6.3. Young age seems to protect against ON [7, 8, 20, 21, 23]. We suspect the presence of the growth plate provides a vascular supply for the necrotic bone, which has the ability to reshape its structure.

Osteonecrosis after bone marrow transplantation leads to several specific problems for the orthopaedic surgeon: ON is characterized by multiple joint involvement, frequent bilateralism, and extensive involvement of the

Fig. 1A–C A 13-year-old boy with severe graft-versus-host disease (**A**) with bilateral hip involvement (**B**) underwent hip arthroplasty. (**C**) The aspect of the left femoral head at surgery is shown.

femoral head. Most patients are younger than 30 years old, and most are immunosuppressed (Fig. 1A–C). Since the late 1970s, we frequently managed these patients and have chosen to avoid conservative operative treatments, such as core decompression and cup arthroplasty, and have rather preferred THA.

We asked whether THA (1) reliably improved functional status for patients affected by ON after bone marrow transplantation, (2) led to a high rate of complications such as loosening, osteolysis, or sepsis, and (3) led to an acceptable survival rate at 10 years for patients with ON after bone marrow transplantation.

Materials and Methods

We retrospectively reviewed 77 patients (123 hips) with ON after bone marrow transplantation seen from January 1980 to October 2004. Hip ON was bilateral at the first examination in 31 patients (46%). Of the 77 patients, 61 (107 hips) had THA; the remaining 16 hips were treated medically and excluded from further analysis, leaving 61 patients. Of the 61 patients, 28 were women and 33 men. The mean age at transplantation was 28.8 years (range, 12.8–51.7 years). The hematologic disease was acute leukemia (myeloid and lymphoid) in 27 cases, chronic

myeloid leukemia in 12 cases, aplastic anemia in nine cases, lymphoma in 11 cases, and other diagnoses in two cases. The mean time between transplantation and first symptoms was 2.1 years (range, 0.3–14.8 years), and the mean time between the first orthopaedic examination and the surgical procedure was 2.3 years (range, 0.08–20.6 years). The mean age at the time of the surgical procedure was 33 years (range, 15.7–56 years) (Table 1). THA was performed 53 times on the right side and 54 times on the left. Twenty-four patients underwent a bilateral one-stage procedure. Five hips had previous surgery: three had cup arthroplasty and two had core decompressions. During the followup period, nine patients (15 arthroplasties) died from a nonorthopaedic cause (mostly septicemia), two patients (three arthroplasties) moved to another country and could not be traced, and four patients (six arthroplasties) were lost to followup. Seven patients (13 arthroplasties) had followup less than 2 years; thus, 49 patients (70 hips) had complete followup for a minimum of 2 years (mean, 9.2 years; range, 2–26 years).

We (FZ, AR) used the Ficat and Arlet classification [9, 10] for ON staging which uses the anteroposterior and lateral radiographic appearance of the femoral head. At the first examination, six patients were classified Ficat 1 (normal standard radiograph, MRI positive signal), 35 were Ficat 2 (diffuse or localized osteoporosis, cyst of the

Table 1. Patient demographics

Hematological diagnosis	Number of patients	THA	Age at transplantation, mean years (range)	Age at surgery, mean years (range)	Time between transplantation and surgery, mean years (range)
Acute lymphoid leukemia	15	27	24.4 (12.8–46.6)	27.2 (15.7–49.3)	2.84 (1.3–5.6)
Acute myeloid leukemia	13	24	30.5 (14.2–48.1)	34.8 (17.5–52.3)	3.65 (1.33–12.5)
Chronic myeloid leukemia	12	18	35.7 (15.4–47.6)	40.1 (17.7–56)	4.7 (2.3–8.4)
Hodgkin's lymphoma	1	2	22.7	25.5	2.85
Lymphoma	9	15	35 (18.7–51.7)	38 (24–53.9)	4.6 (0.7–8.5)
Aplastic anemia	9	17	25.5 (19.5–33.5)	33.4 (22–52.8)	8 (1.8–21.3)
Promyeloid leukemia	1	2	24.3	27.6	3.3
Fanconi disease	1	2	19.5	20.5	0.98
Total and average	61	107	28.8	33 (17.5–56)	4.4 (0.73–21.3)

femoral head or crescentic subchondral line), 37 were Ficat 3 (sequestrum, break in articular cartilage, normal joint space), and 29 were immediately classified Ficat 4 (decreased joint space, collapse of the femoral head, acetabular osteoarthritic change). Preoperative Ficat staging showed three Ficat 2, 28 Ficat 3, and 76 Ficat 4 patients. The hip was the first necrotic location, but other joints were affected (Table 2). The mean necrotic joint number for this specific population at the last followup was three.

All procedures were performed by two senior surgeons (LS, RN) using a posterolateral approach. The prostheses were Ceraver-type (Ceraver Osteal, Roissy, France). Until 1998, the stem used was a cemented, collared, anodized stem of titanium alloy [18] (Osteal® Ceraver Osteal, Roissy, France) (43 stems). Since 1998, we have used the Cerafit® Multicônes H-AC (Ceraver Osteal, Roissy, France), a cementless tapered stem with hydroxyapatite coating (64 stems). Four types of acetabular components were used. At the beginning of our experience, 34 patients had bulky alumina cups (Cerapress®; Ceraver Osteal, Roissy, France) impacted into an acetabulum underreamed by 2 mm; 16 of them operated on at the initial phase were cemented. In all cases, we used high-viscosity gentamicin-loaded cement with finger packing. In 1990 we started to use a metal-back socket. Initially, 23 patients had a press-fit titanium alloy metal back covered with a titanium grid with an alumina core (Cerafit®), and since 1998, 50 had a press-fit cup with a hydroxyapatite coating (Cerafit HA®) with or

without the use of screws. All the implants were alumina ceramic bearing coupled with an alumina head 32 mm in diameter; the aim was to avoid osteolysis and to preserve the bone stock for possible revision.

We (FZ, AR) graded patient activity level at the last followup according to the five-level system described by Devane et al. [6]. One patient was graded 1 (dependent sedentary), six were graded 2 (domestic activities), 16 were graded 3 (recreational activities), 36 were graded 4 (office work), and two were graded 5 (athlete, physical labor).

We (FZ, AR) graded the clinical results according to the d'Aubigné and Postel scoring system [4] with a maximum of 18 points based on three items (6 points for pain, 6 points for range of motion, and 6 points for walking ability); we considered a result excellent or very good if the score was 17 points or more, good if 16, fair if 14 to 15, and poor if 13 points or less. We examined radiographs for signs of loosening or implant migration. Radiolucent lines were recorded according to DeLee and Charnley [5] for the socket and Gruen et al. [12] for the stem. Loosening of the socket was defined as a cup migration exceeding 3 mm, angular rotation exceeding 3°, or a continuous radiolucent line wider than 2 mm. Loosening of the stem was defined according to the criteria of Barrack et al. [2]. A periprosthetic lesion exceeding 2 mm in diameter not noted on the immediate postoperative radiograph was defined as osteolysis [13]. To compare with previous results we then applied the Sedel et al. [19] global scoring system based on four grades combining the clinical and radiographic results. Group A had excellent or very good Merle d'Aubigné and Postel scores and no radiographic change. Group B had excellent or very good Merle d'Aubigné and Postel scores and radiographic change or impending radiographic failure. Group C had poor, fair, or good Merle d'Aubigné and Postel scores and no radiographic change or impending radiographic failure, and Group D had poor, fair, or good Merle d'Aubigné and Postel scores and radiographic change or impending radiographic failure.

Table 2. Other osteonecrotic locations

Osteonecrosis location	Number	Treatment
Shoulder	32	5 hemiarthroplasties
Knee	29	14 arthroscopies
Ankle	9	2 ankle fusions
Elbow	7	2 arthroscopies

Survival analysis was performed using the actuarial method [1] and 95% confidence interval (Xlstat 2006; Addinsoft, Paris, France).

Results

The mean preoperative Merle d'Aubigné and Postel score was 10.8 points (0–16) and the mean score at last followup was 17.1 (0–18). At the last followup, 62 hips (88%) were considered excellent or very good results, three hips good, three fair, and two poor. The two poor results are related to one patient waiting for a revision for acetabular component loosening (impacted alumina cup at 15 years) and one patient treated for a septic loosening by a resection arthroplasty because of persistent septicemia.

We observed one progressive socket migration without any functional impairment, two radiolucent lines around the socket less than 2 mm, two complete loosening of impacted alumina cups (cup migration > 3 mm) (one waiting for surgical revision), and two small regions of osteolysis in Gruen Zone 7 of the femur. We had 61 Group A hips, five Group B, no Group C, and four Group D. Three THAs (4.2%) underwent revision surgery of all components for late septic loosening (6.5, 7, and 9.4 years after the initial procedure). One of these three patients underwent a resection arthroplasty because of persistent septicemia and another had a vascular complication (superficial femoral artery injury due to a difficult dissection) leading to a two-stage procedure. Another patient had a single-stage revision leading to recovery. Septic

loosening in all cases was associated with serious chronic graft-versus-host disease requiring steroid therapy. For one case the origin of the hematogenous infection was a lumbar septic localization; for the two other cases the origin was not found. Four hips were revised for aseptic loosening (5.7%). One underwent revision surgery of all components for femoral and acetabular aseptic loosening at 10 years (a massive alumina cemented socket and a cemented stem); a press-fit hydroxyapatite-coated socket (Cerafit HA[®]) and an uncemented stem were used. We noted a femoral fracture on postoperative Day 15. We changed the stem for a larger one and used cerclage wire to stabilize the femoral fracture. At the last followup, the patient had a good functional result (Merle d'Aubigné and Postel score = 16). Two hips had an acetabular revision for aseptic loosening—one massive alumina cemented socket at 11 years and one impacted alumina cup (CeraPress[®]) at 14.5 years. Both were easily substituted by a press-fit cup with a hydroxyapatite coating (Fig. 2A–D). One hip underwent stem revision for aseptic loosening, a cemented stem at 5 years replaced by an uncemented stem (Cerafit[®] Multicônes H-AC).

Considering loosening of any component (aseptic or septic) as the end point, the survivorship rate was 74.8% (range, 58.7%–90.9%) at 10 years (Fig. 3). Using loosening as the end point survivorship of the 34 impacted and cemented plain alumina cups (CeraPress[®]) was 78.6% (range, 61.6%–95.6%) at 10 years (Fig. 4). The survivorship of the 73 metal back press-fit cups (Cerafit[®]) was 100% at 5 years. Survivorship of the 43 cemented stems was 88.9% (range, 78.3%–99.5%) at 10 years (Fig. 5) and

Fig. 2A–D A 28-year-old man with bilateral involvement was operated on the (A) right side 17 years ago and on the (B) left side 12 years ago. (C) Aseptic loosening of the right socket occurred after 16 years and (D) revision surgery was performed.

Fig. 3 Considering loosening of any component (aseptic or septic) as the end point, the survivorship rate was 74.8% (range, 58.7%–90.9%) at 10 years.

Fig. 4 The specific impacted and cemented plain alumina cup (CERAPRESS®) survivorship with loosening as the end point was 78.6% (range, 61.6%–95.6%) at 10 years.

Fig. 5 The specific metal back press fit cup (Cerafit®) survival was 100% at 5 years. The survival of the specific cemented stem was 88.9% (range, 78.3%–99.5%) at 10 years.

100% for the 64 cementless stems at 5 years (95% confidence interval).

One patient had a traumatic dislocation after a car crash (requiring a splenectomy) without any functional impairment after closed relocation under general anesthesia. There were two immediate nerve palsies, one femoral nerve palsy that partially recovered, and an ulnar nerve palsy that totally recovered. No ceramic implant failure was observed.

Discussion

The surgical treatment of hip ON after bone marrow transplantation is not described in the literature. Our experience in this field led us to believe THA is the appropriate treatment even if these patients are young and mostly immunosuppressed. To minimize particle-induced osteolysis we chose an alumina-on-alumina bearing couple with a 32-mm ceramic head. The initial weakness of the plain alumina socket fixation and the improvement of the material gave us the opportunity to use different types of acetabular components. The stem was cemented until 1998 and cementless thereafter. Our first report in 1996 [3] on THA in bone marrow transplant patients was a short-term study. We reported that among 46 THA with a mean follow up of 5 years, 96% had a good or excellent result. The authors noted the importance of the septic risk, the inadequacy of the acetabular fixation, and distinguished the ON after bone marrow transplantation as a particular entity. Ten years later, we wanted to know if the functional status of patients undergoing THA after bone marrow transplantation for ON was good, if the complication rate was high in regard to loosening, septic complications, and osteolysis and, finally, if the survival rate was acceptable. The data suggest THA is reliable for alleviating pain and restoring function, that septic complications must be considered as a serious event, and this procedure led to a durable survivorship.

We note several limitations. We used several types of acetabular and femoral implants. We could not follow all hips mostly owing to the population characteristic: patients are exposed to fatal complications even if they are considered cured. Despite these limitations, this single-center series is the largest dealing with THA for the treatment of ON following bone marrow transplantation. Furthermore, both clinical and radiographic results were analyzed by two independent observers. The followup of this study, however, is too short to demonstrate the potential long-term advantage of low wear of the ceramic-on-ceramic articulation.

Clinically, the mean Merle d'Aubigné and Postel score of 6.3 points (to a postoperative range of 10.8–17.1), and

88% of the patients had an excellent or very good functional outcome. This result is important because the functional demand is especially high in this young population that wants to quickly recover a normal life after bone marrow transplantation. We believed THA was the only way to improve their functional status bearing in mind the risk of early loosening or major septic complications.

Radiographically the absence of osteolysis, with the exception of two small regions in Gruen Zone 7, is promising because one of the major long-term limitations of THA remains osteolysis. Four of our patients had aseptic loosening leading to implant removing, but none of these patients had osteolysis. Nich et al. [15] reporting a minimum 1-year followup of THA for ON using a metal-on-polyethylene articulation (Charnley-Kerboull THA) suggested the survival at 15 years was 88.5%. However they reported six revisions with osteolysis. In 2003, we studied the long-term results of alumina-on-alumina hip arthroplasty for ON [16]. We retrospectively reviewed 52 consecutive alumina-on-alumina THAs performed from 1978 to 1990. The stem was the same used in this study, a smooth and collared Ceraver-type made of anodized Ti alloy that was always cemented. The acetabular component was also a Ceraver-type: a plain alumina cup cemented in 39 cases and press fit later. The mean follow up was 16 ± 3.87 years. When considering revision surgery with implant removal for any cause as the end point, the cumulative survival rate was 84.5% at 10 years and 65% at 16 years. None of the THA reviewed had lytic lesions. None of the revisions underwent bone reconstruction for osteolysis. In this series the weak link was the acetabular fixation. Reasons for failure included an inadequate choice of alumina designs. Late loosening of cemented alumina cups could be explained by the high rigidity of bulky alumina, which created a mismatch between bone, cement, and ceramic. The improvement in socket fixation and the use since 1998 of a metal back press-fit cup that is hydroxyapatite coated (Cerafit HA[®]) led us to expect an appropriate survivorship rate (Fig. 6A, B). Moreover, no ceramic implant failure (fracture) or squeaking [24] was recorded.

The risk of septic complications must be taken into consideration. Among the seven revisions, three were performed for late septic loosening with a hematogenous origin. These three patients received steroids for chronic GVHDVVVV at the time of the revision. Septic loosening affecting this specific population must be considered a serious event. Indeed, one patient died 2 months after the revision from septic localization in the lumbar spine and another experienced a two-stage revision because of a vascular complication. Graft-versus-host disease is a bone-marrow-transplantation-specific complication that raises several problems, which distinguishes it from poststeroid

Fig. 6A–B Radiographic aspects (A) preoperatively and (B) 10 years after one-stage bilateral hip prosthesis implantation are shown. The patient can run, is pain-free, and has full range of motion.

ON and even ON after kidney transplantation. In GVHD, the donor's bone marrow attacks the patient's organs and tissues, impairing their ability to function and increasing the patient's susceptibility to infection. GVHD may play a part in some surgical difficulties because of fibrous tissue, vascular abnormalities, or preoperative neuropathy. Moreover, GVHD may also be an important cause of functional difficulties because of sclerodermatous skin, joint stiffness, and muscular dystrophy. We found 62% of the patients were affected by GVHD (all localizations and severity confounded). In a multicentric study [22], the incidence of chronic GVHD after allogeneic bone marrow transplantation was 43%.

The treatment of patients with ON after bone marrow transplantation requires close collaboration between the hematologist and surgeon. Hematologists treat all potential septic localizations. Surgeons must be very careful about aseptic conditions. The followup, the clinical and radiographic results, and the survivorship allow us to recommend THA as a treatment of choice. A longer-term followup is required to determine whether the ceramic articulation we used is superior to alternatives.

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