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# Advances in treatment for chronic granulomatous disease

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**Abstract** Chronic granulomatous disease (CGD) is a rare congenital disorder resulting from a failure of neutrophils to produce oxidases. Patients are therefore prone to recurrent infections from various organisms including fungi and atypical bacteria. The mortality in patients with the X-linked form of CGD, the most common type, ranges from 3% to 5% per year and although management of infections has improved with advances in antimicrobial therapies, better methods are needed to be able to cure these patients. Peripheral blood stem cell or bone marrow transplantation, while curative, is not widely used due to the episodic nature of the infections and the belief by many that conservative management is preferable to the risks of transplantation. Still, as will be discussed, improvements in the field are making allogenic transplantation more desirable and tilting the risk benefit ratio in favor of this modality. Additionally, gene therapy, which has been a long touted method to cure CGD, has within the last 5–10 years become more and more of a reality and may be realized by the end of this decade.

**Keywords** Chronic granulomatous disease · Gene therapy · Allogeneic transplantation · Autoimmune complications · Antibiotic prophylaxis · Interferon gamma

## Background

Chronic granulomatous disease, or CGD, is a congenital disorder with an estimated prevalence of 1/200,000 in the United States, but ranges to as low as 1/450,000 in other countries. [1, 2]. The disease arises from a defect in one of the four NADPH oxidases necessary for microbicidal oxidant production. As a result, patients are highly susceptible to catalase-positive infections including fungi, as well as developing granulomata and autoimmune complications.

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The most common form of this disease, consisting of 65–75% of cases, arises from mutations in the gp91 phox gene located on the X chromosome. The autosomal forms affect the p47 phox gene (about 20% of the cases) or either the p67 phox or the p22 phox genes (remaining 5%), found on chromosomes 7, 1, and 16, respectively. The level of oxidase production appears to correlate with morbidity and mortality and patients with the X-linked form have a death rate estimated at 3–5% per year. The p22 phox mutations are biochemical isomorphs of the X-linked form. In both cases, the entire heterodimeric cytochrome b558 is missing or defective and the mortality rate is thus similar. Patients with the p67 deficiency also seem to have higher mortality compared to the p47 phox patients who have the best mortality rate estimated at 1–2% per year [3].

## Presentation

Patients typically present at an early age with a soft tissue infection or osteomyelitis with Serratia being the most common isolate. In older patients, the diagnosis is usually made after a pulmonary, lymph node, bone, or skin infection with cultures positive for the typical CGD pathogens of Burkholderia, Nocardia, and/or Aspergillus. These infections can be difficult to diagnose as the patients often present with vague or mild symptoms, belying the amount of infectious burden. Fungal infections, which constitute approximately 50% of all CGD infections, are frequently indolent with patients presenting with malaise or being diagnosed only after a routine radiographic study. Liver abscesses are the second most common severe deep tissue infection in CGD patients with 90% of these abscesses due to *Staphylococcus aureus* [4].

## Autoimmune sequelae

Not only do patients with CGD suffer from recurrent infections, but as the name implies, they are also prone to granuloma formation. Fifty percent of patients will develop gastrointestinal granulomata, which may be large enough to be obstructive. Less commonly, granulomas can form in the bladder, ureters, or even retina, also leading to obstruction in some cases. Additionally, patients with CGD are prone to various types of autoimmune diseases. Twenty percent have or develop a condition that resembles Crohn's disease with identical endoscopic and histologic findings and associated arthritides. There have also been reports of patients with lupus like symptoms, sarcoid, and other autoimmune manifestations such as IgA nephropathy and rheumatoid arthritis. Patients often develop significant pulmonary dysfunction due to their recurrent pneumonias and non-infectious inflammatory granulomas. Almost 10% of patients eventually require oxygen supplementation due to hypoxia [5–13].

## Treatment

Standard treatment for patients with CGD consists of close medical management including routine CT screening, to rule out asymptomatic infections, as well as prophylactic antibiotics. Trimethoprim sulfamethoxazole, due to its broad spectrum including activity against Nocardia and Burkholderia, and the antifungal itraconazole are the agents of choice. At the National Institutes of Health (NIH), a randomized placebo controlled study of itraconazole

prophylaxis demonstrated a reduction in fungal infections and was well tolerated [14]. Interferon gamma therapy has also been shown in a number of studies, but not all, to decrease the incidence of infection in patients with CGD and the current recommendation is to treat patients with thrice weekly injections at a dose of 50 μg/m$^2$ [15–18]. In a randomized placebo study, investigators at the NIH demonstrated a reduction in the total number of infections from 56 to 20 per year using interferon gamma in a group of 127 patients divided equally between placebo versus treatment group ($P < 0.00001$; a more than 60% reduction in infection rate) regardless of age, mode of inheritance, and use or non-use of prophylactic antibiotics [19]. However, a recent informal survey of more than 70 patients, representing respondents from less than half of the total cohort of patients followed long term at the NIH, indicated that less than 25% of patient respondents with CGD are continuing to take prophylactic interferon injections (E Kang and H Malech, personal communication). Furthermore, many of these patients are only intermittently compliant or take the interferon gamma with reduced frequency or at lower dosing because of unacceptable side effects, cost issues, or phobia of injections. During this same informal survey, patients were asked how many severe infections they experienced during the previous 6 months (a reliable time frame for accurate response) requiring either prolonged hospitalization or more than 16 days of outpatient antibiotic treatment. The infection rates in patients either being treated with interferon gamma or not, are similar to those of the patients during the 1990 interferon gamma study [15]. That is to say, despite advances in the actual treatment of infections, the rate of infection itself has not changed since 1990.

For patients with granulomata, a short course of corticosteroids is the treatment of choice. Corticosteroids are also useful in patients with pulmonary dysfunction, ameliorating the symptoms in a number of the patients and suggesting some reversibility to the problem. For patients with other autoimmune sequelae, immune modifiers are also helpful in a number of cases; however, the risk of immunosuppressants in this population makes these modalities more problematic.

Hence patients with CGD are in need of curative options. In the last decade advances in both autologous transplantation using genetically modified cells as well as allogeneic transplantation suggest that many of these patients can look forward to a possible cure. However, questions regarding whom, when, and how to transplant need to be further studied.

## Newer therapies

### Gene therapy

The idea of gene therapy has long been a goal for hematopoietic-based monogenetic disorders such as CGD, particularly as levels of only 5–10% of corrected cells may be sufficient for full phenotypic correction of the disease. A number of small animal studies including xenogeneic and disease-specific models confirmed the ability of vectors containing either the p47 or the gp91 gene to correct the mutation[20–23]. Current methods of gene transduction involve the use of non-replicative viruses encoding the gene of interest to be inserted into a target population of cells by culturing them together ex vivo. Advances in the design of vectors including their envelopes, the use of various cytokines and supplements such as fibronectin in the culturing, and the ability to collect large numbers of target cells using peripheral blood stem cell mobilization and apheresis, have made the reality of gene therapy for CGD more likely. In fact, in large animal models, using these methods

genetic correction of up to 10% of circulating cells can be obtained when the animals are also conditioned with myeloablative radiation [20, 21].

Moreover, in 1999 the first successful gene therapy trial was reported and in fact was developed for patients with an immunodeficiency. Using a retroviral vector, autologous bone marrow was collected from patients with X-linked severe combined immunodeficiency (XSCID) and transduced with a vector encoding the common gamma chain. The corrected cells were infused into patients without any prior conditioning given their immunoincompetent state. The proliferative advantage conferred upon the newly corrected cells allowed outgrowth of the genetically modified cells and correction of the underlying immunodeficiency in initially 10 out of 11, and subsequently 13 out of 14 patients [22]. Unfortunately, this outgrowth of T cells combined with the propensity of retroviral vectors to insert into active genes has led to the development of leukemia in five patients treated with gene therapy. This adverse outcome appears to be somewhat specific to XSCID in that the proliferative advantage that contributed to the success of the treatment was probably also responsible for the propensity to develop leukemia. However, the relation of the vector to its insertion site is still problematic as all five patients have been found to have activation of the human oncogene LMO2. Other oncogenes were also found to be upregulated in three of the five patients [23] (and personal communication). It is unclear how this relates to other gene therapy trials for other disease, but issues of safety have naturally become paramount for all ongoing and future studies.

The first gene therapy trial for CGD was performed at the NIH and the results initially reported in 1997 [24]. Malech et al. [25] treated patients with either p47 or gp91 phox deficient CGD. Patients were given multiple infusions of genetically modified cells and marking was detectable out to 6 months beyond the last infusion but only at very low levels. Notably, the infusions were performed without any conditioning, similar to the XSCID trial; however, the correction for the CGD mutation, unlike XSCID, does not lead to a proliferative outgrowth and therefore explains the lack of clinical benefit seen.

More recently, in 2006 Ott et al. [26] reported and subsequently published the results regarding two patients with CGD using gene therapy, but this time combined the infusion with a transplant conditioning regimen consisting of busulfan at 8 mg/kg. They also used a retroviral vector known as the spleen focus forming virus (SFFV) which has myeloid-specific enhancers.

Initially the patients were thought to be cured as the marking levels in the two patients reached over 20% and as high as 60% in one patient; however, this was primarily due to the outgrowth of a few specific clones with insertion into myeloid promoting genes, specifically EVI1-MDS1 and PRDM16 as well as SetBP1. Both patients eventually developed a myelodysplastic syndrome of monosomy 7 along with apparent silencing of the transgene and the first patient died due to overwhelming sepsis. The second patient has undergone allogeneic transplantation from an unrelated donor and is apparently doing well (personal communication, M. Ott). Insertions into MDS-EVI1 have been seen in large animal studies using retroviral vectors and therefore MDS-EVI1 appears to be a hotspot for insertion; however, the development of oligoclonality and ultimately myelodysplasia may also be related to the specific vector backbone used in this study [27].

In our own gene therapy trial initiated in 2006 at the NIH, we have enrolled patients with a progressive or ongoing infection not curable by standard treatment. We have used an MFGS-based retroviral vector encoding the gp91 phox gene and conditioned the recipients with a total of 10 mg/kg of busulfan. To date we have treated two patients. Although our marking levels have not been as high as seen in the Ott study, the level of correction on a per cell basis is almost that of normal as the MFGS vector is able to produce large amounts

of the protein but without myeloid-specific enhancers. In contrast, the prior study by the Frankfurt group appeared to have superoxide production levels of only 30% or less of normal on a per cell basis.

The first patient from our trial continues to have marking at 1% now almost 2 years beyond the infusion with no evidence of oligoclonal outgrowth or myelodysplasia. He appears to have had a reduction in the number of infections he experiences, but of course continues on his prophylactic antibiotics with which he is only partially compliant. The second patient appeared to have immune mediated clearance of the marked cells after initially achieving levels of 5% genetically corrected cells in the peripheral blood. He eventually succumbed to his infection before being able to proceed to an unrelated donor transplant. Hence to date, with the current vectors and despite the use of conditioning, there has not yet been a patient with CGD cured by gene therapy. However, the development of lentiviral vectors and the use of an RD114-based envelope may be sufficient to attain adequate transduction levels with improved safety, and our next trial will include at least one of these modifications [28, 29].

## Allogeneic transplantation

Unlike gene therapy, allogeneic transplantation has been shown to be curative for patients with CGD and there has been increasing use of bone marrow or peripheral blood stem cell transplantation with either a human leukocyte antigen [HLA]-matched sibling or HLA-matched unrelated donor [MUD] to treat CGD, using either non-myeloablative [30] or more conventional myeloablative approaches [31]. However, the variable severity of CGD and the episodic nature of the infections have made pediatricians and immunologists reluctant to refer patients to transplant at an early age. Further, advances in medical management, particularly with the newer and less toxic antifungals, would suggest to some that close medical management is sufficient for this group of patients. Transplantation for CGD is further complicated by the fact that often the only HLA-matched sibling is a carrier female, who may have less than 50% oxidase normal neutrophils due to X-chromosome inactivation and lack of any selective survival advantage to the normal versus CGD phenotype lineages. Paradoxically though, outcomes from transplant would most likely be improved if patients were referred at younger ages and more importantly, prior to multiple bouts of infection. Additionally, unlike standard of care, transplantation may be able to prevent and even reverse the complications of the associated autoimmune phenomena seen in many of these patients.

To date, approximately 37 patients have been reported to the CIBMTR as having undergone transplant within the US and 55 in non-US centers. The overall survival at 1 year is 87% and at 3 years 83% for this group. Seventy-seven percent of these patients were transplanted at less than age 10 with 37% percent of the recipients less than 2 years of age. The majority of these transplants have occurred from 2000 on and have a median follow-up of 25 months.(personal communication) An additional 50 patients outside of the US and Canada are reported in various publications including single case reports and a survey of the European experience [31–44] with an overall survival rate of 94% and a success rate of 43 out of the 50 achieving stable donor engraftment. The longest reported follow up to date from the Europeans is 5 years in a patient transplanted using a HLA-matched sibling and a Busulfan/Cytoxan-based conditioning regimen. Similar to the US data, the majority of these patients are less than 10 years of age with only seven of the entire cohort being of age 18 or greater at the time of transplant.

The largest single reported group within the US was transplanted at our own institution, the NIH, where a non-myeloablative regimen was used to treat 14 patients, including a number of adults. Two patients died due to graft versus host disease, three patients had failure to engraft with one death as a result, and three had late graft rejection but are still alive to date [30]. Two patients have stable mixed chimerism, one of whom has only 43% lymphoid engraftment and 15% myeloid engraftment more than 6 years beyond his transplant but continues to be infection free. We have also performed a second transplant in a young male who, despite a conditioning regimen consisting of Campath 1-H, Melphalan, and Fludarabine and four donor lymphocyte infusions, failed to maintain myeloid engraftment after a transplant using his HLA-matched sister as the donor. Using the same donor, the patient was treated with busulfan at 10 mg/kg, achieved 100% myeloid engraftment, and is now 3 years post-transplant doing well (manuscript in preparation).

While observation of these patients appears to confirm that replacement of their hematopoietic system reduces or eliminates their CGD-related infections and improves or prevents their CGD-related inflammatory events, statistical proof is lacking that transplantation actually achieves these goals given the small numbers, scattered reports, limited follow up, and lack of previous efforts to compare transplanted patients to an appropriately age/genotype/phenotype-matched untransplanted control group in a statistically meaningful way. Further, patients with CGD, as with many congenital disorders, have even more difficulty in finding appropriate related donors although the use of unrelated HLA-matched donors has been slowly increasing, primarily due to the improved techniques for performing typing at the molecular level. The use of cord blood too allows for more discrepancy between HLA types and the advent of double cord transplants has made cell dose less of a restriction for older patients. With the long awaited institution of an agreement between the NIH and the National marrow donor program (NMDP), we have initiated a new transplant protocol for patients with immunodeficiencies, in particular, patients with CGD, using either a related or unrelated HLA-matched donor. The conditioning regimen consists of Busulfan, Campath, and Rapamycin with radiation added for those using an unrelated donor. To date we have transplanted a 32-year-old male patient with CGD who achieved 100% engraftment by donor cells without evidence of any acute Graft versus host disease, but who ultimately died due to renal failure. The trial is ongoing and although it appears promising, it is too soon yet to determine if this regimen is effective enough for engraftment while minimizing graft versus host disease.

## Discussion

Although there has been much progress made in the newer antibiotics and particularly antifungals, there are still the same infection rates and the continued morbidity related to these recurrent infections as well as from the other sequelae of CGD such as inflammatory bowel disease. These continued problems, not surprisingly then, have a significant negative impact on the overall quality of life of these patients. While the risks of transplantation including graft rejection and graft versus host disease still exist, outcomes are improving and will continue to improve particularly if patients are referred at earlier ages. In fact, patients with X-linked CGD and an HLA-matched sibling donor should be offered transplant prior to developing multiple infections, given the success with related donor transplant even in its current state. Moreover, as more and more investigators develop disease-specific transplant regimens, with development of tolerance inducing regimens such as the ones we at the NIH are working to develop, versus using the standard malignancy directed

regimens, the risks of transplantation should diminish significantly. As such, transplantation may be recommended for all patients, including those with only an unrelated donor available. Finally, continued advances in gene therapy may obviate the need for allogeneic transplant altogether, assuming that the presence of oxidase-positive cells in sufficient numbers is adequate for treatment and prevention of all the complications of CGD. Although in its current iteration, gene therapy has not been proven curative, with the development of lentiviral vectors and other modifications we may see the first truly successful gene therapy for patients with CGD by the year 2010 or even sooner.

## References


1. Ahlin A, et al. Prevalence, genetics and clinical presentation of chronic granulomatous disease in Sweden. Acta Paediatr. 1995;84(12):1386–94.
2. Winkelstein JA, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79(3):155–69.
3. Roos D. The genetic basis of chronic granulomatous disease. Immunol Rev. 1994;138:121–57.
4. Segal BH, et al. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore). 2000;79(3):170–200.
5. De Ravin SS, et al. Sarcoidosis in chronic granulomatous disease. Pediatrics. 2006;117(3):e590–5.
6. Strate M, Brandrup F, Wang P. Discoid lupus erythematosus-like skin lesions in a patient with autosomal recessive chronic granulomatous disease. Clin Genet. 1986;30(3):184–90.
7. Manzi S, et al. Systemic lupus erythematosus in a boy with chronic granulomatous disease: case report and review of the literature. Arthritis Rheum. 1991;34(1):101–5.
8. Lee BW, Yap HK. Polyarthritis resembling juvenile rheumatoid arthritis in a girl with chronic granulomatous disease. Arthritis Rheum. 1994;37(5):773–6.
9. Ortiz-Romero PL, et al. Lupus like lesions in a patient with X-linked chronic granulomatous disease and recombinant X chromosome. Dermatology. 1997;195(3):280–3.
10. Bendhack ML, et al. Chronic granulomatous disease masquerading as a bladder tumor: a potential source of diagnostic error. Eur Urol. 1997;32(3):380–4.
11. al-Tawil YS, et al. Steroid-responsive esophageal obstruction in a child with chronic granulomatous disease (CGD). J Pediatr Gastroenterol Nutr. 1996;23(2):182–5.
12. Lindahl JA, Williams FH, Newman SL. Small bowel obstruction in chronic granulomatous disease. J Pediatr Gastroenterol Nutr. 1984;3(4):637–40.
13. Johnson FE, et al. Gastric outlet obstruction due to X-linked chronic granulomatous disease. Surgery. 1975;78(2):217–23.
14. Gallin JI, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med. 2003;348(24):2416–22.
15. Weening RS, Leitz GJ, Seger RA. Recombinant human interferon-gamma in patients with chronic granulomatous disease—European follow up study. Eur J Pediatr. 1995;154(4):295–8.
16. Marciano BE, et al. Long-term interferon-gamma therapy for patients with chronic granulomatous disease. Clin Infect Dis. 2004;39(5):692–9.
17. Ohga S, et al. Interferon-gamma therapy for infection control in chronic granulomatous disease. Acta Paediatr Jpn. 1995;37(3):315–20.
18. Woodman RC, et al. Prolonged recombinant interferon-gamma therapy in chronic granulomatous disease: evidence against enhanced neutrophil oxidase activity. Blood. 1992;79(6):1558–62.
19. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N Engl J Med. 1991;324(8):509–16.
20. Tisdale JF, et al. Ex vivo expansion of genetically marked rhesus peripheral blood progenitor cells results in diminished long-term repopulating ability. Blood. 1998;92(4):1131–41.
21. Kiem HP, et al. Improved gene transfer into baboon marrow repopulating cells using recombinant human fibronectin fragment CH-296 in combination with interleukin-6, stem cell factor, FLT-3 ligand, and megakaryocyte growth and development factor. Blood. 1998;92(6):1878–86.
22. Cavazzana-Calvo M, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease [see comments]. Science. 2000;288(5466):669–72.
23. Hacein-Bey-Abina S, et al. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med. 2003;348(3):255–6.

24. Malech HL, et al. Extended production of oxidase normal neutrophils in X-linked chronic granulomatous disease (CGD) following gene therapy with $gp^{91phos}$ transduced CD34+ cells. Blood. 1998;92(10(Suppl)):690a.
25. Malech HL, et al. Prolonged production of NADPH oxidase-corrected granulocytes after gene therapy of chronic granulomatous disease. Proc Natl Acad Sci USA. 1997;94(22):12133–8.
26. Ott MG, et al. Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med. 2006;12(4):401–9.
27. Calmels B, et al. Recurrent retroviral vector integration at the MDS1-EVI1 locus in non-human primate hematopoietic cells. Blood. 2005;106(7):2530–3.
28. Roesler J, et al. Third-generation, self-inactivating gp91(phox) lentivector corrects the oxidase defect in NOD/SCID mouse-repopulating peripheral blood-mobilized CD34+ cells from patients with X-linked chronic granulomatous disease. Blood. 2002;100(13):4381–90.
29. Brenner S, et al. Concentrated RD114-pseudotyped MFGS-gp91phox vector achieves high levels of functional correction of the chronic granulomatous disease oxidase defect in NOD/SCID/{beta}2-microglobulin−/− repopulating mobilized human peripheral blood CD34+ cells. Blood. 2003;102(8):2789–97.
30. Horwitz ME, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. N Engl J Med. 2001;344(12):881–8.
31. Seger RA, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985–2000. Blood. 2002;100(13):4344–50.
32. Bhattacharya A, et al. Successful umbilical cord blood stem cell transplantation for chronic granulomatous disease. Bone Marrow Transplant. 2003;31(5):403–5.
33. Watanabe C, et al. Successful unrelated bone marrow transplantation for a patient with chronic granulomatous disease and associated resistant pneumonitis and *Aspergillus osteomyelitis*. Bone Marrow Transplant. 2001;28(1):83–7.
34. Ozsahin H, et al. Successful treatment of invasive aspergillosis in chronic granulomatous disease by bone marrow transplantation, granulocyte colony-stimulating factor-mobilized granulocytes, and liposomal amphotericin-B. Blood. 1998;92(8):2719–24.
35. Kobayashi S, et al. Clinical features and prognoses of 23 patients with chronic granulomatous disease followed for 21 years by a single hospital in Japan. Eur J Pediatr. 2008.
36. Kansoy S, et al. Successful bone marrow transplantation in an 8-month-old patient with chronic granulomatous disease. Turk J Pediatr. 2006;48(3):253–5.
37. Schuetz C, et al. Successful unrelated bone marrow transplantation in a child with chronic granulomatous disease complicated by pulmonary and cerebral granuloma formation. Eur J Pediatr. 2007;166(8):785–8.
38. Sastry J, et al. Allogeneic bone marrow transplantation with reduced intensity conditioning for chronic granulomatous disease complicated by invasive Aspergillus infection. Pediatr Blood Cancer. 2006;47(3):327–9.
39. Gungor T, et al. Successful low toxicity hematopoietic stem cell transplantation for high-risk adult chronic granulomatous disease patients. Transplantation. 2005;79(11):1596–606.
40. Leung T, et al. Bone marrow transplantation for chronic granulomatous disease: long-term follow-up and review of literature. Bone Marrow Transplant. 1999;24(5):567–70.
41. Ho CM, et al. Successful bone marrow transplantation in a child with X-linked chronic granulomatous disease. Bone Marrow Transplant. 1996;18(1):213–15.
42. Hasegawa D, et al. Successful treatment of chronic granulomatous disease with fludarabine-based reduced-intensity conditioning and unrelated bone marrow transplantation. Int J Hematol. 2008;87(1):88–90.
43. Parikh SH, et al. Correction of chronic granulomatous disease after second unrelated-donor umbilical cord blood transplantation. Pediatr Blood Cancer. 2007;49(7):982–4.
44. Suzuki N, et al. Treatment of McLeod phenotype chronic granulomatous disease with reduced-intensity conditioning and unrelated-donor umbilical cord blood transplantation. Int J Hematol. 2007;85(1):70–2.