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Lessons from bone marrow transplantation for a victim of a radiological accident with acute radiation syndrome

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Abstract. Unintentional acute exposure to whole body radiation has become a serious threat in recent years. Whole body irradiation leads to the acute radiation syndrome, with manifestations depending on the dose to which the patient was exposed. At high doses of radiation, a large number of cells die as a result of impairment of DNA replication owing to irreversible double-strand DNA damage. A whole body absorbed dose greater than 4–6 Gy causes severe gastrointestinal and bone marrow damage, and ultimately leads to death in most cases. Patients exposed to a total dose of ionising irradiation up to 12–14 Gy may be rescued with autologous or allogeneic stem cells, however the role of stem cell transplantation for patients exposed to higher doses of radiation is questionable and depends on the degree of damage to non-haematopoietic tissues. Here we report on a patient following an accidental exposure to whole body irradiation (estimated dose 10–20 Gy) from a γ-source in a commercial atomic reactor. The patient was treated with a haploidentically mismatched related stem cell allograft, featuring the problems associated in treating patients exposed to a supralethal but unknown dose of radiation.

Introduction

Unintentional acute exposure to whole body radiation has become a serious threat in recent years owing to exposure of personnel in atomic reactors following a disaster or improper commercial use of radiation facilities [1–5]. Use by terrorists of sources of radiation with the potential to cause human damage has also become a major potential threat [6, 7]. Whole body irradiation leads to the acute radiation syndrome (ARS), with manifestations depending on the dose to which the patient was exposed [8, 9]. At high doses of radiation, a large number of cells die as a result of impairment of DNA replication owing to irreversible double-strand DNA damage. Most sensitive to radiation are cells of those tissues that are rapidly dividing, for example cells of haematopoietic tissue. A whole body absorbed dose greater than 4–6 Gy causes severe gastrointestinal and bone marrow damage, and ultimately leads to death in most cases [9, 10]. Patients exposed to a total dose of ionising irradiation up to 12–14 Gy may be rescued with autologous or allogeneic stem cells. However, the role of stem cell transplantation (SCT) for patients exposed to higher doses of radiation is questionable and depends on the degree of damage to non-haematopoietic tissues. Here, we report on a patient treated following an accidental exposure to supralethal whole body irradiation with a fully haploidentically mismatched related stem cell allograft, featuring the problems associated in treating patients exposed to a supralethal but unknown dose of radiation.

Case report

A 32-year-old man was admitted to the department of Bone Marrow Transplantation at Hadassah University Hospital in Jerusalem, 8 h after exposure to an estimated whole body irradiation dose of a minimum of 10 Gy and maximum of 20 Gy from a γ-source in a commercial atomic reactor in Israel, in 1990. He had entered the reactor overcoming a locked door, in an attempt to fix a box stuck in a conveyer, and left the irradiation room because of a sensation of burning in the eyes. 5 min later he experienced nausea, one large emesis and some soft stool. He complained of subjective fever, severe abdominal pain and thirst.

Physical examination of the patient upon arrival at the hospital showed a somewhat confused individual but he was still in good general condition. His vital signs included: regular pulse rate 130 min^{-1}; respiration rate 16 min^{-1}; blood pressure 130/60 mmHg; and rectal temperature 40.7°C. He demonstrated isolated facial and palmar erythema, diffuse abdominal tenderness and slight corneal injection with mild swelling of the lower eyelids. The results of the physical examination were otherwise unremarkable. Laboratory tests results are shown in Table 1.

The initial blood count upon arrival was $22.0 \times 10^9\ l^{-1}$. Blood was drawn 4 h post exposure for routine tests, for human leukocyte antigen (HLA) typing of the patient and his siblings, and for cytogenetic evaluation using standard culture techniques. Prepared slides were screened and only nine metaphases or partial metaphases were observed. One ring was observed, but almost all the chromosomes were abnormal, with many translocations and fragments. The results were not sufficient for accurate dose estimation, although retrospective dosimetry considering estimated time of exposure, topography of the reactor and positioning of the worker who entered the reactor against all rules inferred that a very high radiation exposure had occurred. In view of the uncertainty in the exact dose of radiation exposure, it was decided to treat the patient as intensively as possible, assuming as a working hypothesis and thus providing the patient

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Table 1. Patient's laboratory results on admission

Parameter	Value	Parameter	Value
White blood cells	22.0×10^9 l^{-1}	Prothrombin time	67%
Lymphocytes		Partial thromboplastin time	29 s
at 17 h	1%	Thrombin time	11 s
at 60 h	0%	Fibrinogen	206 mg l^{-1}
Platelets	205×10^9 l^{-1}	Serum lactate dehydrogenase (LDH)	236 IU l^{-1}
Haemoglobin	13.8 g dl^{-1}	Creatine phosphokinase	
Haematocrit	43.2	at 17 h	167 IU l^{-1}
Glucose	6.3 mmol l^{-1}	at 25 h	348 IU l^{-1}
Sodium	144 mEq l^{-1}	Urinalysis	Normal
Potassium	3.4 mEq l^{-1}	Chest radiograph	Normal
Urea	8.8 mmol l^{-1}	Blood cultures (repeated)	Negative
Uric acid	516 mmol l^{-1}		
Creatinine	159 mcmol l^{-1}		

the benefit of doubt, that radiation damage may be reversible.

Treatment with recombinant human granulocyte–macrophage colony-stimulating factor (GM-CSF) 250 μg day^{-1}, acyclovir, cefazolin and fluid support was initiated. Because of constant nausea and repeated vomiting, total parenteral nutrition was introduced from day 3 after exposure. On day 4, the white blood cell count dropped to 8.5×10^9 l^{-1}, with no lymphocytes visible in the peripheral blood smear. The same day, the decision to perform bone marrow transplantation from a haploidentical, mixed leukocyte reaction positive brother was made since it appeared after the estimated dosimetry was calculated that complete marrow aplasia was incipient. HLA typing indicate that the donor was mismatched in three loci; the patient's blood group was B+ and his brother's blood group was AB+. Cytomegalovirus (CMV), herpes simplex virus and varicella zoster virus studies revealed that both the patient and his donor were immunoglobulin G (IgG) seropositive. The patient was seronegative for Epstein-Barr virus, while his brother was seropositive (IgG).

Transplantation of stem cells was done on day 4 after the accident with T-cell depleted bone marrow stem cells. T-cell depletion was done with monoclonal rat anti-human CD52 IgM (Campath-1M) (kindly provided by Dr G Hale and Dr H Waldmann, Cambridge University, Cambridge, UK) with donor serum serving as complement, as described previously [11]. A total number of 2.36×10^8 kg^{-1} viable cells was infused, including 0.08% residual T-cells (analysed at the time by E-rosettes formation). Cyclosporin was administered as additional prophylaxis against graft-versus-host disease (GVHD). Facilitation of haematopoietic reconstitution was attempted by continuous treatment with GM-CSF in combination with recombinant human interleukin-3 (IL-3) (kindly provided by Dr HP Kraemer, Behringwerke, Hamburg, Germany) at a dose of 130 μg day^{-1} [12].

During the first week post transplantation, the patient's condition did not improve. Pancytopenia was accompanied by severe grade III mucositis. His body temperature rose to 40°C despite maintenance on broad spectrum antibiotic treatment. The patient continued to vomit once or twice daily and had watery stools (up to 1 l day^{-1}), with some days without any bowel movement. He gradually developed renal insufficiency, with blood urea level rising to 15.2 mmol l^{-1} and creatinine rising to 165 mmol l^{-1}. Liver function started to deteriorate, with rising total bilirubin (51 mmol l^{-1}), sensitive palpable liver and rising γ-glutamyl transpeptidase (γGTP) (145 IU l^{-1}), all consistent with veno-occlusive disease of the liver. The creatine phosphokinase (CPK) level declined to 46 IU l^{-1} and the amylase level to 16 IU l^{-1}. On day 9 post SCT, engraftment was documented with $>0.5 \times 10^9$ l^{-1} neutrophils. On day 11, neutrophils rose to 3.2×10^9 l^{-1}. On day 14, the growth factors were discontinued. Assays for chimerism disclosed >10:1 donor:recipient ratio, confirming rapid marrow engraftment. Bone marrow biopsy revealed regenerating marrow with all lineages presented. Despite rapid engraftment, the patient's condition remained poor, with aggravated gastrointestinal symptoms. The patient developed some facial swelling and oedema of both hands, with no obvious signs of cutaneous GVHD. The patient was receiving steroids, starting with dexamethasone 24 mg day^{-1} from day 6, which was substituted with methylprednisolone 100 mg day^{-1} from day 18 post transplant. Liver and kidney function tests deteriorated: the bilirubin level rose to 120 mmol l^{-1}, alkaline phosphatase to 226 IU l^{-1}, aspartate aminotransferase (AST) was 88 IU l^{-1}, γGTP was 192 IU l^{-1}, prothrombin (blood clotting factor II) time was 45% (normal 70–80%) and partial thromboplastin time was 67 s (normal 25–37 s). The blood level of urea increased to 27 mmol l^{-1} and creatinine to 213 mmol l^{-1}. The findings were suggestive of veno-occlusive disease of the liver. Blood cultures were negative. The colour of his skin on the face and extremities became darker, with marked swelling and bullous changes noted in the skin, similar to burn injuries.

4 weeks after SCT, despite successful engraftment and intensive treatment, the patient developed respiratory failure manifested by tachypnoea, severe hypoxia, metabolic acidosis, and massive bilateral interstitial infiltrates of the lungs on chest radiography.

36 days after the accident, the patient died with a clinical feature of irreversible multi-organ failure.

Post-mortem examination

Post-mortem investigation showed adequate bone marrow engraftment and haematological differentiation. There was lymhoplasmocytoid infiltration, which could be in part the result of mild GVHD and/or reaction to massive CMV infection, as was indeed the case.

Detailed evaluation of histopathological findings compatible with GVHD was not possible owing to overlapping histopathological findings resulting from radiation injuries to all tissues. Morphology compatible with acute though not severe GVHD in addition to radiation injury documented in the skin could not be ruled out. A typical cell necrosis at the dermoepidermal junction was seen, with very mild inflammatory reaction.

Marked depletion of the lymphatic tissue was noted in all lymph nodes examined and also in the white pulp of the spleen. Complete disappearance of all lymphoid elements was noted along the entire gastrointestinal tract.

The gastrointestinal system was severely affected, including severe erosive oesophagitis and erosive gastritis all along the mucosa. In addition to marked lymphoid depletion, the most striking finding was complete disappearance of the normal crypt anatomy, with complete denudation of the epithelial layer along the small intestine.

Massive secondary infection with CMV was recognised by observation of abundant typical inclusion bodies mostly in the gut and lungs as well as in other tissues, indicating severe systemic CMV disease. Formation of pseudomembranes in the lumen of the colon was also noted.

The architecture of the liver was preserved, but marked oedema due to hepatic congestion was noted. Acidophilic bodies representing necrosis of hepatocytes were also noted, with occasional extravasation of red blood cells. The findings were suggestive of radiation-induced veno-occlusive liver disease with centrilobular necrosis.

Severe radiation-induced pneumonitis was noted, with complete obliteration of the alveolar spaces in large areas of both lungs and in addition, inclusion bodies typical of CMV infection.

In summary, the autopsy disclosed severe generalised radiation injuries affecting mostly the gastrointestinal tract and both lungs plus systemic CMV disease. Some of the findings were also compatible with mild acute GVHD, but the specific role and severity of the GVHD could not be fully assessed because of the overlapping severe multi-systemic injuries that were attributed to radiation.

Discussion

The case presented features the clinical dilemma of the clinician facing a patient with acute radiation exposure of unknown intensity, where evaluation of the dose of radiation has to rely on minor signs and symptoms before the full picture of major radiation injury is apparent. For practical purposes, it seemed reasonable at that stage to treat the patient as one would do for a transplant recipient exposed to intentional myeloablative chemoradiotherapy, since it was clear that acute radiation syndrome will follow an estimated exposure to radiation dose exceeding 10 Gy. Indeed, the case presented subsequently demonstrated all the classical developments of the haematological and gastrointestinal phases of radiation injury, with subsequent development of fulminant multi-organ failure despite intensive medical care and successful reconstitution of the bone marrow compartment. The clinical experience following accidental acute whole body exposure is limited, and all treatment approaches are rather restricted and in general not successful for patients exposed to radiation doses that exceed the threshold of multi-organ toxicity. Patients exposed to sublethal doses of radiation may be successfully treated with haematopoietic growth factors such as GM-CSF or granulocyte colony-stimulating factor (G-CSF) that can facilitate engraftment [13, 14].

In treating cases like the one described, three major directions had to be considered. The first goal was directed towards prevention of infections and bleeding, using appropriate antimicrobial agents, isolation techniques, supportive fluid and electrolyte balance, and parenteral nutrition. These measures can prolong a patient's life but do not provide a chance of survival following lethal exposure to radiation.

Second, because the haematopoietic tissue is one of the most sensitive tissues to radiation-associated cytotoxicity, bone marrow transplantation had to be attempted, despite lack of a matched sibling, using a haploidentically mismatched donor from the family; this was successfully accomplished in this case. This approach in previously treated cases achieved only occasional success [15]. A similar approach was first used for the treatment of radiation victims in 1958 after an atomic reactor accident in Vinca, Yugoslavia; however, in those days the clinical experience using tissue typing and evaluating chimerism was not yet available [16].

Our experience as well as published data show that in cases of acute radiation syndrome, SCT *per se* may be successfully accomplished even across major histocompatibility barriers. A detailed review by Chiba et al [16] of cases transplanted between 1958 and 1999 shows that bone marrow recovery was documented in most cases, whilst 9 of 29 patients became long-term survivors (13–19 years). Those patients who received a dose of more than 10 Gy died within 2–79 days following transplantation. In another atomic reactor disaster in Chernobyl, although transient donor engraftment was confirmed in only two of the patients alive, there is indirect experimental evidence that suggests that even transient engraftment can improve survival in mice exposed to lethal total body irradiation, which may be the case in humans as well [15, 18]. Nevertheless, a survival rate of approximately one-third of patients justifies intensive treatment and early consideration of SCT, at least for those victims of radiation accidents who receive a dose of 4–10 Gy. Whenever in doubt, which in reality may be the case before physicists can estimate the dosimetry and which in many cases like the one described cannot be exactly reconstructed, patients with clinical signs of myeloablative radiation exposure should get the benefit of the doubt and receive haematopoietic support.

Third, since 1980 when the first haematopoietic growth factors became available, their use in cases of high dose exposure, and certainly following exposure to low or intermediate doses of total body irradiation, should be considered to avoid possible untoward effects of a SCT procedure, especially GVHD, which may not be indicated for underexposed patients. Data show that cytokine combination, such as we used for our patient, can be more effective than each growth factor used as a single agent [12, 19–21]. In the future, as far as the risk of GVHD is concerned, this complication can be totally avoided while avoiding the use of post-transplant GVHD prophylaxis, by using transplantation of purified stem

cells, either positively selected by CD34 or AC 133 immunomagnetic beads [22–24], using negatively selected stem cells, or using Campath-1H in the bag or *in vivo* [11, 25, 26]. Data regarding the role of GVHD in our case are doubtful, because even after a detailed post-mortem examination as reported here, possible features of GVHD could not be clearly separated from irradiation-induced multi-organ damage.

Finally, a growing number of recent publications suggest other possible future considerations related to adult tissue-derived stem cell plasticity [27–30]. Recent evidence suggests that bone marrow-derived stem cells and mesenchymal cells can be coaxed to develop into various tissues by environmental influence [31, 32]. As has been shown in a few other reports, bone marrow-derived cells as well as purified haematopoietic stem cells may give rise to non-haematopoietic tissues including brain, muscle, heart, liver, intestine and lung [33–36]. Some published data also show that stem cells given locally or systemically can induce neovascularisation and myocardial rehabilitation in animals in which myocardial infarction was induced [37]. Stem cell engraftment was found to be higher in damaged tissues than in normal tissues [38]. At present, it is still unclear whether the plasticity phenomenon is a result of transdifferentiation or rather fusion with host cells [39–41]. Furthermore, the possible role of stem cell plasticity for correction of radiation injuries remains to be assessed.

Autologous cell grafting by mature or stem lineage cells expanded *in vitro* appears to be a promising strategy for repair of multi-organ damage [42]; the role of such strategies involving either autologous or allogeneic stem cells already demonstrated as efficacious in experimental animal models needs to be confirmed in clinical practice [43–45]. Promising results were recently published by Strauer et al [46], who grafted bone marrow cells in 10 recent post-myocardial infarction patients. Their results indicate that bone marrow engraftment was safe, without any remarkable side effects, and significantly decreased the non-viable regions on the thallium scan. Recent observations in our own laboratory as well as clinical practice suggest that bone marrow stem cells may be used for reconstruction of the haematopoietic microenvironment as well as for correction of damage in bones and cartilage [47].

In conclusion, although the treatment of radiation accidents represents a major problem to the treating physician faced with uncertainty of the severity of the injury, we believe that intensive treatment may be justified, whilst novel approaches based on cumulative knowledge of stem cell biology and stem cell plasticity may be applied and should be considered in similar cases of unfortunate exposures to a high dose of radiation. However, like in many situations in medicine, prevention rather than treatment remains the optimal approach, since most radiation accidents, such as the one described, can be prevented by following instructions and common sense. People at risk should thus be better informed.

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