MEDICAL MANAGEMENT OF ACCIDENTALLY EXPOSED INDIVIDUALS

J.-C. NENOT
Institut de protection et de sûreté nucléaire,
Fontenay-aux-Roses,
France

Abstract

MEDICAL MANAGEMENT OF ACCIDENTALLY EXPOSED INDIVIDUALS.

Bone marrow aplasia is one of the main syndromes following a high dose accidental radiation exposure. Whilst transfusion and bone marrow transplantation have been used with some success starting with the first treatments of accident victims, other therapeutic strategies are needed. With the development of experimental and clinical haematology, promising new approaches to the treatment of aplasia have appeared. New trends for the treatment of haemopoietic injury based on bone marrow transplantation rely on new sources of compatible donor cells, such as cord blood, on the selection of immature haemopoietic cells and on new transplant regimens. Haemopoietic growth factors stimulate the proliferation and/or differentiation of haemopoietic progenitors and, possibly, stem cells. Furthermore, they act on the functions of mature cells. Currently, they have specific uses in haematology related to their role in the regulation of growth and in the differentiation of haemopoietic progenitor cells. Growth factors have already been used for the treatment of accidental radiation induced aplasia and lessons have been learned from their medical management and follow-up.

1. INTRODUCTION

Owing to fundamental differences in their management, a clear distinction must be drawn between two particular categories of radiological accidents:

(i) accidents which result in a few victims; the medical response will be comparable to that for any medical casualty and will adhere to the current rules of medical ethics where the participants in the medical management are limited to the victim and the responsible physician. Most of such accidents have been related to industrial and medical sources of radiation, each of them involving only one or a limited number of individuals.

(ii) Accidents which involve large groups of people, either workers or individuals of the general population. The management of such cases is performed according to the same principles as those which prevail in any major catastrophic event. This category requires medical triage, distinguishing overexposed individuals presenting other types of injuries from individuals likely to have received doses below the thresholds for deterministic effects. Events of this kind are exemplified by the Chernobyl and Goiânia accidents.

The radiation source at the root of the accident may have been external or internal, or both, in relation to the body. Accidental exposures involving internal contamination of medically significant importance are rare — the Goiânia accident is the most tragic example of this kind. When external and internal exposures are associated, the latter may complicate the bone marrow depression and compromise its recovery, as the internal exposure, even though it may have been received at relatively low dose rates, may be prolonged and result in continuous injury to haemopoietic tissues.

Since the discovery of penetrating ionizing radiation, namely X rays by Roentgen in 1895 and gamma rays by Becquerel in 1896, some accidents have occurred, a few of which resulted in whole body irradiation. A few tens of the victims died because of the acute radiation syndrome they developed: severe aplasia associated with its classical complications. The intercomparison of instances of severe whole body irradiation is often difficult, owing inter alia to (i) the lack or insufficiency of information (surrounding for instance historical accidents, especially in countries where political considerations prevented them from coming to light), (ii) the significant improvement in the medical management of prolonged aplasia and especially (iii) difficulties in assessing the homogeneity of bone marrow exposure.

2. THE CURRENT SITUATION

In the dose range where survival is possible with intensive medical care, the critical tissue on which prognosis first depends is the bone marrow. That notwithstanding, lethality after higher doses reflects the failure of particular organs which, in relation to the underlying cell kinetics, eventually fail within different time periods. Because of the rapid renewal of many important types of blood cells, bone marrow offers the best conditions for the study of radiation injury to the organs. Consequently, it is the focus of the greatest medical concern, at least during the first weeks of the acute manifestations of radiation induced illness. It can be concluded that radiation lethality is primarily and in principle a consequence of disturbed cellular kinetics in the renewal system which is critical for survival [1].

Consequently, the doses received by the bone marrow constitute a relevant index of severity, provided the exposure affects the whole body and is not significantly non-uniform. For accidental exposures, the physician will rely on the doses for planning purposes, as well as for a guidance concerning the need for supportive or aggressive treatment. It has been concluded that the $LD_{50/60}$ (lethal dose) for acute radiation is likely to be around 3 Gy to the marrow, if the patient receives no or little medical care [2, 3].

From a medical point of view, especially when referring to therapy, it would be completely unrealistic to consider bone marrow depression as an isolated syndrome. Because of their widely differing specialized functions and cell renewal capacities, all other organs and tissues, such as gut and central nervous system, will produce complex but definable time and dose dependent overlapping patterns of clinical symptoms. Whole body irradiation will therefore include a sequence of combined interacting effects which will complicate medical management [4]. Depending upon the organs and tissues concerned, the time pattern for each clinical and/or biological manifestation will differ. Some of these manifestations may appear late after the exposure and may last for extended periods of time — they include effects on the lungs, liver, kidneys and endocrine systems, for example. All these effects may well be life-threatening. As for the more urgent medical management, it is possible to classify the early combined effects by taking into account the cell kinetics of the organ or tissue and their sensitivity to radiation, i.e. with reference to both overall exposure time and dose.

3. CONVENTIONAL MEDICAL MANAGEMENT

Assessment of severity

The quantitative evaluation of exposure and of its main parameters as outlined above rests mainly on physical and biological dosimetry. It should be stressed that most of the methods used for dose assessment need a minimum assay of time, depending upon the techniques. For instance, the full-size reconstruction of the accident requires many technical

and human resources and the time needed for chromosome aberration scoring cannot be reduced to below three days when using current methodology. This implies that, at the early stage, the dose will be assessed on clinical findings and simple blood cells counts. In fact, these delays in obtaining important data will not hinder the medical management of the victim, since the duration of the latent period allows some flexibility in decision making. Nonetheless, all necessary dosimetric explorations should be considered and initiated as soon as the severity of the exposure is suspected.

Physical dosimetry

Under ideal circumstances, the overexposed victim would have been wearing a dosimeter at the time of the accident. This is rarely the case in accidental situations, especially when members of the public are irradiated following the loss of a source, for instance. Either way, more information is needed than the measurement of a dose received at a particular point of the body. The reconstruction of the accident, whether carried out by experimentation or by calculation, enables a realistic evaluation of the dose distribution within the body. An experimental reconstruction at the accident site or simulated conditions of the accident can be carried out with the help of phantoms made of a tissue-equivalent material for the various types of radiation [5, 6]. When this is not possible, reconstruction by calculation can be performed, even though the results obtained by calculation are generally not as reliable as those obtained by a realistic reconstruction.

Biological dosimetry

Dose-response curves showing the change in concentration of various blood cells of healthy humans after whole body exposure are relatively easy to reproduce, especially with regard to lymphocytes. As the reduction in the number of lymphocytes is very rapid and significant after irradiation at high doses, this value represents the best early biological indicator of severity, if it is obtained as soon as possible after the exposure and repeated once or twice at intervals of approximately six hours. This simple test is the best quick guide, within the first two to three days, of the degree of severity with an acceptable degree of uncertainty. Many chromosomal aberrations may appear in irradiated lymphocytes. The aberrations currently taken as providing the most valuable information are the dicentrics, rings and fragments. Human blood may be used as an absolute dosimeter in the weeks following the exposure, since human T lymphocytes have a relatively long life and the reduction in the number of aberrations is not significant.

Changes in sperm counts are extremely significant indicators at relatively low doses, because the early differentiation forms of spermatogonia are extremely sensitive [2, 7, 8]. Assuming that the testes were exposed, the results of sperm counts and their variation with time can serve as a good indicator of the severity of exposure. Moreover, sperm counts will be helpful for the assessment of the degree of uniformity of the exposure when compared with other biological parameters such as blood counts and chromosome analysis.

Whole body overexposure rapidly results in functional modifications in the central nervous system. Early reactions are intra- and extracellular oedema, inflammatory infiltration and metabolic disturbances. After high doses around the $LD_{50/60}$, some structures such as the hippocampus are unable to maintain the basic rhythms. These abnormalities can be detected by electroencephalography with a threshold of around a few tenths of Gy.

Conventional treatment of bone marrow depression

A clear distinction is needed between medical actions which aim to prevent complications related to bone marrow injury and those which try to restore the bone marrow functions. The former belong to the conventional management of patients immunodepressed with other additional problems due to their global injury, whilst the latter imply specific haematological treatments.

Prevention and treatment of infection

Whatever the type of curative treatment chosen, the worst risk is the development of local or general superinfection, mainly as a result of immune deficiency. Patients with a severe degree of granulocytopenia lasting for prolonged periods are at great risk of bacteremia, especially gram-negative rod bacteremia. These patients require aggressive approaches to prevent infection. Medical management of such patients is well defined and specialized intensive care units nowadays have means to keep alive immunocompromised patients, such as those suffering from AIDS or other diseases.

The first step is the prevention of exogenous infection. Whatever the degree to which prophylactic therapy should be pursued, isolation of the patient is mandatory. It should be underlined that using efficient and refined means of isolation is useless if the personnel are not correctly trained and aware of all the procedures used to control potential infection pathways. The use of laminar air flow rooms in which all air presented to the patient is previously filtered and maintained at a positive air pressure in relation to the remainder of the building is a current means for keeping patients correctly isolated. Regular bacteriological surveillance of the patient (at least skin and faeces) is mandatory. In addition, all monitoring, life support systems and consumable supplies should be sterile. The use of a suite with a separate work and changing room is of great help for the medical personnel. These facilities should periodically be disinfected. In addition, when normal feeding is possible, all oral foods and fluids should be sterile. As these patients require frequent sampling and administration of parenteral drugs and fluids, the prior placement of a double or triple lumen central venous access line will greatly simplify the medical care and reduce the risks of infection. This intravenous access line will be inserted with great care, since it may be one of the major iatrogenic factors increasing risks of infection, resulting in tunnel infection often due to *Staphylococcus aureus*.

The risk of endogenous contamination must be assessed as soon as the patient is admitted. It is standard practice to carry out antibacterial and antiviral therapy associated with digestive decontamination (antibacterial, antifungal) [9, 10]. Some authors recommend the use of associated antibiotics in order to obtain a broad-spectrum coverage and adequate serum bactericidal activity for both gram-negative and gram-positive pathogens. As viral infections, such as herpetic infection, may cause a severe problem by their dissemination in other organs, prophylactic antiviral treatment should be carried out as soon as a radiation exposure at high dose is suspected.

It seems that there are more advantages than risks to instituting prophylactic oral anti-biotherapy in order to eliminate pathogens usually present in the gut. Doing so prevents subsequent systemic bacterial invasion, which may have disastrous effects on highly immunodepressed patients. In addition, maintenance of gastric acidity may prevent bacteria from colonizing and invading the gastric mucosa and therefore, reduce the probability of the development of nosocomial pneumonia. Antifungal therapy should be started very early,

especially as damage to flora from antibiotic therapy encourages the settlement of yeasts which colonize the upper respiratory tract, and from there become disseminated.

With the onset of fever and the increase in the erythrocyte sedimentation rate, the source of infection must be sought as a matter of urgency. The immediate administration of several broad spectrum antibiotics is required, and then adapted in accordance with the disc sensitivity test.

Nutrition and fluid balance

Whole body irradiation in the mid-lethal range may lead to a syndrome of serious malnutrition. The nutritional and caloric equilibrium must therefore be maintained without waiting until the syndrome develops. Oral feeding is preferable to parenteral feeding, especially as it is psychologically reassuring. For patients in bad conditions, total parenteral nutrition may be necessary through the central venous line, in particular in the presence of severe mucositis of the oropharynx. Basal fluid intakes should be administered in accordance with the losses from diarrhoea, stomal output, naso-gastric suction and possible drainage. When intravenous fluid replacement is absent, electrolyte imbalance can be life threatening as a result of fluid loss due to severe vomiting (with or without diarrhoea) or sweating from exertion.

Blood products

The use of blood products requires careful evaluation so that these materials are not administered indiscriminately. Specific indications are warranted for red blood cells and platelets. The frequency of transfusions varies with the daily reading of blood counts, the purpose being to maintain a level above that at which anaemia and haemorrhages can occur. All blood products should be irradiated at about 50 Gy to inactivate the viable immunocompetent lymphocytes present in the products and consequently prevent GVHD (graft versus host disease). This irradiation does not adversely affect the red blood cells or the platelets, but may minimize the risk of viral diseases, such as cytomegalovirus. If a bone marrow transplantation is envisaged for the future, the use of products from related donors should be avoided. A complete check-up should be made prior to the transfusions in order to reduce the risk of immunological complications; this includes determining or confirming ABO groups, the Rhesus factor together with the complete phenotype in other blood group systems and tests for irregular agglutinins and the HLA complex.

Erythrocytes should be provided in order to correct tissue anoxaemia by maintaining haemoglobin at a sufficient level. Healthy individuals may tolerate rather low haematocrits, provided that their activities are circumscribed and appropriate care is given to other injuries. As for erythrocytes, the requirement for platelet support depends on the patient's condition. In the absence of other medical problems, the platelets should be maintained at least at $20 \times 10^9\ l^{-1}$, although many victims have sustained lower counts without bleeding.

Granulocyte transfusions should be reserved for patients presenting deep granulopenia, persistent signs of infection (especially gram-negative bacterial infection) and after antibiotic therapy has proved to be inefficient. However, their explicit clinical efficiency is still questionable and moreover, they contain HLA antigens which limit their usefulness. If such a drastic treatment is initiated, it should be continued for a few days, in accordance with the short lifespan of these cells.

4. NEW TRENDS FOR THE TREATMENT OF HAEMOPOIETIC INJURY

In the 1970s and 1980s, bone marrow transplantation (BMT) had become enshrined in the literature as a proposed final successful therapy for acute radiation syndrome [9, 11, 12]. There were at least two primary reasons behind this medical attitude: bone marrow appeared to be the most sensitive tissue to whole body exposure and clinicians had gathered experience with several thousand procedures of this kind, including preconditioning therapy for transplantation. After the Chernobyl accident, which was the first time a large number of heavily irradiated victims had to be treated and several BMTs were performed, it was concluded that the benefits of this intervention were limited [13, 14]. In the opinion of the physicians in charge of the victims, this therapy resulted in worsening the conditions of their patients and they advised against its use. It is recognized that a BMT must be regarded as an exceptional and potentially hazardous measure [15]. Although BMT may not be completely contraindicated, the particular conditions prevailing in accidental overexposure explain the need for exploring other therapeutic approaches.

Bone marrow transplantation

Indications for transplanting bone marrow to a radiation casualty rest on high doses received by all areas; doses which are incompatible with spontaneous recovery and result in the absence of any relatively protected areas that might provide a basis for autorepopulation. It may be concluded that the bone marrow transplants will be useful only in a small proportion of victims, probably those who have received doses exceeding 8 Gy [16]. At these levels, digestive and possibly neurological syndromes are likely to cause grave concern and may require more urgent treatment than the haemopoietic syndrome. The main limitations of transplants are (i) the presence of residual endogenous haemopoiesis inducing rejection, (ii) difficulties in setting up the transplant, including difficult tissue typing after irradiation and insufficient availability of a graft and (iii) the deleterious effect of the transplant (immunosuppressive treatment and/or GVHD). Apart from consuming enormous technical and professional resources, the complications which may follow allogeneic BMT may pose major threats to the survival of the patient. These include (i) engraftment failure, (ii) GVHD, (iii) infections and (iv) other complications of minor importance owing to their lower frequency or a lesser degree of potential severity [9]. In addition to these complications, other radiation induced effects may occur and raise important medical problems. They include: radiation pneumonitis, hepatic veno-occlusive disease, gastrointestinal manifestations and deterministic effects in any organ or tissue with thresholds lower than the dose received by the patient.

In such a fast-changing field, directions of research of specific interest for radiation induced aplasia include (i) the source of HLA compatible donor cells, (ii) transplantation with selected haemopoietic stem and progenitor cells, and (iii) new transplant regimens.

(i) Source of HLA compatible donor cells

The availability of a graft is often a problem for bone marrow transplantation. As the size of the modern family tends to diminish, the probability of finding a matched related donor falls. Although the size of the bone marrow registry for unrelated donors is increasing, there are still patients with no matching donors. Furthermore, the delays caused by the donor search and for planning the transplant may impair its results.

New sources of haemopoietic stem cells for transplantation are needed. Cord blood may offer useful prospects. A cord blood bank has recently been established in order to study the feasibility of unrelated transplants. Cord blood samples are collected upon delivery, and

become readily available once frozen and typed [17]. Cord blood cell transplants are well established in matched related situations for children. Whereas GVHD has seldom been observed in cord blood transplants, a delay in platelet recovery has frequently been noted. These transplants have never been used for adult recipients although the number of stem cells present in a sample may theoretically be sufficient [18]. The possible success of such transplants in the future will condition their usefulness for the treatment of radiation induced aplasia.

(ii) Positive selection of immature haemopoietic cells

New techniques for the preservation and storage of haemopoietic stem cells have been developed recently. It has been shown that it is possible, by reproduction, to prepare highly enriched samples of haemopoietic stem and progenitor cells. These cells can be obtained from bone marrow, cord blood or peripheral blood by immunological recognition of a specific marker (CD 34). They are isolated from mature cells by reversible binding to a specific device (antibody bound to magnetic beads, biotin-avidin interaction, plastic binding). CD 34+ enriched samples are small in size, and a few millilitres may contain the same quantity of progenitors and stem cells as a whole litre of bone marrow. These cells have been used clinically in autologous haemopoietic cell transplantation trials with some success [19]. The development of this technique may be interesting for the creation of haemopoietic sample banks taken from potentially exposed workers (workers with a significant probability of receiving high doses, as were the intervening firemen at the Chernobyl accident).

(iii) New transplant regimens

New strategies are under development to limit the risk of GVHD or prevent graft failure when transplanting cells with a poor HLA compatibility.

The use of a T cell-depleted haploidentical graft has had little success because of the high risk of graft failure. It has been recently shown that it is possible to realize, in leukaemia patients, a successful transplantation with three HLA mismatches with a low GVHD incidence by transplanting a large number of T cell-depleted bone marrow and peripheral blood stem cells from the donor at the same time [20]. The average concentration of myeloid precursors in the final inoculum was seven- to tenfold greater than that found in the bone marrow sample alone. In addition, an increased conditioning regimen (when compared with standard practice) was applied to provide both immunosuppression and myeloablation. One patient rejected the graft, sixteen had early and sustained full donor type engraftment. One patient who received a high quantity of lymphocytes died from acute grade IV GVHD, nine patients died from transplant related toxicity, and six patients are alive and event-free. This approach may be of interest for treatment of radiation victims when a bone marrow transplantation is needed but only a haploidentical HLA marrow donor can be found.

Most T cell depletions are negative selection processes; CD 34+ selection is a positive selection process ending with a sample, theoretically almost totally depleted from cells involved in the acute GVHD reaction. In order to limit the risks associated with this disease, it has been suggested to use CD 34+ cells in allogenic bone marrow transplantation. The preliminary results have shown the feasibility of the transplant using G-CSF (granulocyte colony-stimulating factor) mobilized CD 34+ peripheral blood immature cells in combination with unmanipulated bone marrow. None of the six patients treated developed more than a grade II GVHD. It was suggested that the use of CD 34+ selected allogenic cells may circumvent the need for potentially toxic immunotherapy to minimize GVHD [21].

Haemopoietic growth factors

Haemopoiesis is under the control of growth and differentiation factors (cytokines) which allow the tissue to adapt itself to new situations by continuously modulating its response. Some of these factors are well known, others are only hypothetical. Recent advances in the study and large scale production of these haemopoietic growth factors have allowed their use for therapeutic purposes. The factors most studied are the granulocyte-macrophage colony-stimulating factor (GM-CSF) and the granulocyte colony-stimulating factor (G-CSF). These factors stimulate the proliferation and/or differentiation of haemopoietic progenitors. Furthermore, they act on the functions of mature cells. Other factors with broader effects, such as interleukin 1 (IL-1), interleukin 3 (IL-3), interleukin 6 (IL-6), interleukin 11 (IL-11) or stem cell factor (SCF) are only entering preclinical or clinical trials now. Although numerous in vitro or in vivo experiments suggest a benefit from their effects, their possible uses in therapy are still questionable. The same conclusion applies for other factors under development, such as PIXY 321, erythropoietin (EPO), macrophage colony-stimulating factor (M-CSF) and thrombopoietin (TPO). Some growth factors have already been used for the treatment of accidental radiation induced aplasias and lessons have been learned from their medical management and follow-up.

Although questions have been raised about the real clinical efficiency of growth factors [22], the results of the clinical trials, in vivo and in vitro radiobiology experiments and lessons learned from the management of accidents all suggest that growth factor therapy could be of use after an accidental overexposure to stimulate the remaining haemopoietic stem cells so as to shorten the duration of aplasia. While G-CSF has already demonstrated a proven efficacy against granulocytopenia in numerous clinical and experimental settings, so far, it has been used only once for the treatment of a radiation injured patient [23]. The broader action of GM-CSF and IL-3 and especially their possible role in thrombopoiesis stimulation, added to their proven action on granulopoiesis in vivo, seems to be beneficial for the patients. However, neither the clinical trials nor the management of accidental irradiations allow the definition of a precise schedule for the treatment of thrombocytopenia by growth factors. In situations where a bone marrow transplantation is indicated and can be performed, these growth factors might be used after the transplantation in order to promote haemopoietic recovery and to limit the risk of infection for the patient, without effects on GVHD. It has been suggested after the Goiânia accident (where a victim experienced a late hypoplasia) that, when internal exposure is involved, the use of growth factors would stimulate haemopoiesis induced progenitors or stem cells to progress in the cell cycle, while the cells are still being irradiated. The combination of haemopoietic growth factors inducing mitosis and simultaneous prolonged radiation exposure might result in the depletion of the stem cell pool. This has not been confirmed by observations. However, this hypothesis could be important in situations where internal exposure persists during treatment. Interleukin 6, Interleukin 11 and SCF are promising haemopoietic growth factors entering clinical trials for the treatment of aplasia. Furthermore, clinical trials have been set up for the combination of growth factors. Other growth factors are entering preclinical trials, such as thrombopoietin and leukaemia inhibiting factor (LIF), which is known to increase IL-3-dependent proliferation of early human haemopoietic progenitors and to stimulate thrombopoiesis. However, the doses and the schedules of administration are not yet established, their side-effects are not well identified and their long term effects are mostly unknown; these elements may be of particular importance for factors which are known to stimulate the growth of some leukaemia cell lines. Advances in growth factor research suggest that it is possible to design new, more efficient therapies for radiation injured patients.

Ex vivo expansion of haemopoietic precursor stem cells and differentiated cells is a new approach in growth factor therapy [24, 25]. These studies aim to expand the pool of progenitors and stem cells for transplantation (or to expand differentiated cells for transfusion). This is made possible due to the development of techniques allowing the selection of a population of haemopoietic progenitors and stem cells from the blood (with stimulation by growth factors prior to stem cell harvesting) or bone marrow using CD 34+ cell positive selection. The next step, consisting in their culture with combinations of growth factors or additional stroma cells, is also under development. The use of continuous perfusion cultures may help to solve some of the technical problems arising from the size of the samples and reproducibility of the experiments. This approach is interesting for the treatment of patients with radiation induced aplasia, either because the cells necessary for ex vivo expansion have been stored in a cell bank before the radiation accident or if such cells can be found in the blood or marrow and harvested in sufficient quantity after the accidental irradiation and it is possible to collect them. Such cells might be available in the blood after various types of irradiation, as suggested by results obtained from haemopoietic progenitors in the peripheral blood after therapeutic irradiation [26]. Some of the growth factors, although their effects on haemopoiesis might be useful, have restricted use in vivo due to their toxic side-effects. Ex vivo experiments might allow their use without adverse reaction. Important research is necessary to adapt the ex vivo expansion of haemopoietic precursor and stem cells for transplantation or of differentiated cells for transfusion in the treatment of radiation induced aplasia, as in vitro cultures are different for both purposes. To be of therapeutic use, the cells produced must retain their normal function and regulation properties. In this respect, potential mitotic ageing during expansion may prove counter-productive.

Several growth factors (such as GM-CSF) inhibit programmed cell death in vitro and in animal models [27]. This property might be of great interest for the treatment of radiation induced aplasia, as it may help to lengthen the lifetime of the irradiated cells, thus reducing the severity and duration of aplasia. Research on the effects in vivo of growth factors on apoptosis must therefore be designed bearing in mind the role of irradiation.

5. LATE EFFECTS RELATED TO TREATMENT

Chronic GVHD occurs later than acute GVHD, i.e. later than three months after bone marrow transplantation. It is manifested by cholestatic serum chemistry, dermatologic changes similar to scleroderma or dermatomyositis, dry stomatitis, and keratoconjunctivitis [9]. In severe cases, a variety of other organ-specific inflammatory processes may occur. Continued infections via the lungs and digestive tract may require specific treatment. Careful and rapid attention should be directed to the earliest and most minimal indications of infection. The overall risk of chronic GVHD one year after unrelated donor transplantation is 55 per cent [28].

Whether G-CSF or GM-CSF are potentially carcinogenic or indeed whether stimulation with growth factors may result in bone marrow exhaustion or stem cell failure are open questions. It has been reported that, at a high dose, GM-CSF trials for myelodysplastic syndrome patients initiated rather than prevented the onset of acute myeloid leukaemia. Adverse reactions with stimulation of leukaemia blast cells under GM-CSF administration have been reported in some sporadic acute myeloid leukaemia cases [29].

6. CONCLUSIONS

Only a few hundred radiation accidents with health consequences have occurred in the elapsed half century. These accidents resulted in close to 1000 casualties including some 100 deaths, among which bone marrow injury played a prevailing role. The casualty list shows that about half of the severe injuries derive from the unsafe handling of industrial and medical sealed sources, while the other half can be traced to the civilian and military nuclear industry (most of them arising from the Chernobyl accident in 1986, with 28 deaths directly related to radiation exposure) [30]. Without wishing in any way to minimize the problem, this figure is trivial when set against the total number of safe operations involving radiation sources (such as industrial radiography devices, industrial irradiation facilities, radiotherapeutic devices, etc.).

Nevertheless, this paucity of cases explains the limited interest generated by radiation accidents in both the medical and political spheres— unless an accident occurs which affects a large number of people. As this current attitude seems difficult to accept, the only way to ensure that the best medical management will be available to overexposed victims in the future is to provide for coherent, permanent and comprehensive radiation accident preparedness. This includes planning, education and preparation. These three tasks are crucial to an effective response in medical emergencies and should be accorded the highest consideration in preparing for accidents involving ionizing radiation. The medical response should rest on the experience and lessons learned in serious nuclear and radiological emergencies, which thus deserve to be reviewed in this light. These reviews should also consider the time scale in relation to the availability of data which are essential for a precise diagnosis and appropriate prognosis. Practitioners should be ready to face situations where decisions will need to be taken in the absence of reliable dosimetric results, which may be unavailable.

REFERENCES

[1] BOND, V.P., SUGAHARA, T., Comparative Cellular and Species Radiosensitivity, Williams and Wilkins, Baltimore, MD 1969.

[2] UNITED NATIONS, "Early effects in man of high doses of radiation", Annex G, Sources, Effects and Risks of Ionizing Radiation (1988 Report to the General Assembly, with annexes), Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), UN, New York (1988) 545–612.

[3] UNITED STATES NUCLEAR REGULATORY COMMISSION, Health effects models for nuclear power plant accident consequence analysis, Low LET radiation, Part I, prepared by Evans J.S., Harvard University, NUREG/CR-4214, SAND85-7185, Rev. I, Part I, Washington, DC (1990).

[4] DIXON, B., The biological and clinical effects of acute whole or partial body irradiation, J. Soc. Radiol. Prot. **5** 3 (1985) 121–128.

[5] PARMENTIER, N., BOULENGER, R., PORTAL, G., Problèmes de dosimétrie lors de l'accident de criticité survenu au réacteur Venus à Mol, en date du 30 Décembre 1965 (Proc. First international congress of radiation protection, Rome, 1966), Pergamon Press, Oxford (1968) 1231–1248.

[6] PARMENTIER, N., NENOT, J.C., JAMMET, H.J., "A Dosimetric Study of the Belgium (1965) and Italian (1977) Accidents", The Medical Basis for Radiation Accident Preparedness (HUBNER, K.F., FRY, S.A., Eds), Elsevier/North Holland, New York (1980) 105–112.

[7] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Non stochastic effects of ionizing radiation, Publication 41 **14**, Pergamon Press, Oxford, New York (1984).
[8] LADNER, H.A., "Reproductive organs", Radiopathology of organs and tissues (SHERER, E., STREFFER, C., TROTT, K.R., Eds) Springer-Verlag, Berlin (1991) 433–459,
[9] DRUM, D.E., RAPPEPORT, J.M., "Treatment of whole body radiation accident victims", Medical management of radiation accidents (METTLER, F.A., KELSEY, C.A., RICKS, R.C., Eds), CRC Press, Boca Raton, FL (1990) 89–108.
[10] OLIVEIRA, A.B., "Treatment of Infectious Complications of the Hematopoietic Syndrome", Treatment of Radiation Injuries (BROWN, D., WEISS, J.F., MACVITTIE, T.J., PILLAI, M.V., Eds), Plenum Press, New York (1990) 95–100.
[11] WALD, N., Diagnosis and Therapy of Radiation Injuries, Bull. N.Y. Acad. Med., Second Series **59** 10 (1983) 1129–1138.
[12] SAENGER, E.L., Radiation Accidents, Ann. Emerg. Med. **15** (1986) 1061–1066.
[13] GALE, R.P., Immediate Medical Consequences of Nuclear Accidents. Lessons from Chernobyl, J. Am. Med. Assoc. **258** 5 (1987) 625–628.
[14] GUSKOVA, A.K., et al., "Acute Effects of Radiation Exposure Following the Chernobyl Accident. Immediate Results of Radiation Sickness and Outcome of Treatment", Treatment of Radiation Injuries (BROWN, D., WEISS, J.F., MACVITTIE, T.J., PILLAI, M.V., Eds), Plenum Press, New York (1990) 195–209.
[15] GALE, R.P., "Dose injury assessment and medical effects at Chernobyl", Workshop on Short-Term Health Effects of Reactor Accidents: Chernobyl (BOND, V.P., CONKRITE, E.P., Eds), Brookhaven National Laboratory, BNL 52030/UC 48 (Biology and Medicine-TIC - 4500) Upton, NY (1986) 12–13.
[16] GALE, R.P., Perspective – Medical Response to Radiation And Nuclear Accidents: Lessons for the Future. J. Natl. Cancer Inst. **80** (1988) 995–997.
[17] SNYDER, E.L., ANDERSON, K., SILBERSTEIN, L., ADAMSON, J., "Transfusion Medicine", Haematology 1994, Education Program (BENZ, E.J., McARTHUR, J.R., Eds), Am. Soc. Haematol., Nashville, TE (1994) 96–106.
[18] THIERRY, D., et al., Hemopoietic Cell Progenitors in Cord Blood, Bone Marrow Transplant. **9** 1 (1992) 101–104.
[19] BERENSON, R.J., et al., Engraftment after Infusion of CD 34+ Marrow Cells in Patients with Breast Cancer or Neuroblastoma, Blood **77** (1991) 1717–1722.
[20] AVERSA, F., et al., Successful Engraftment of T-Cell-Depleted Haploidentical "Three-Loci" Incompatible Transplants in Leukaemia Patients by Addition of Recombinant Human Granulocyte Colony-Stimulating Factor-Mobilized Peripheral Blood Progenitor Cells to Bone Marrow Inoculum, Blood **84** (1994) 3948–3955.
[21] DIPERSIO, J., MARTIN, B., ABBOUD, C., RYAN, D., BERENSON, R., Allogenic BMT Using Bone Marrow and CD 34 Selected Mobilized PBSC, Comparison to BM Alone and Mobilized PBSC Alone, Blood **10** 1 (1994) Abstract 351, 91a.
[22] QUESENBERRY, P.J., Growth Factor Frenzy, Exp. Hematol. **21** (1993) 831–836.
[23] THIERRY, D., GOURMELON, P., NENOT, J.C., Le sang désert des irradiés, La Recherche **299** (1997) 31–33.
[24] WILLIAMS, D.A., Ex Vivo Expansion of Hematopoietic Stem and Progenitor Cells — Robbing Peter to pay Paul?, Blood **81** (1993) 3169–3172.
[25] HAYLOCK, D.N., TO, L.B., DOWSE, T.L., JUTTNER, C.A., SIMMONS, P.J., Ex Vivo Expansion and Maturation of Peripheral Blood CD 34+ Cells into the Myeloid Lineage, Blood **80** (1992)1405–1412.

[26] THIERRY, D., et al., Human Blood Granulocyte Macrophage Progenitors (GM-CFU) During Extended Field Radiation Therapy, Acta Radiol., Oncol. **24** (1985) 521–526.
[27] BRACH, M.A., DEVOS, S., GRUSS, H.J., HERRMANN, F., Prolongation of Survival of Human Polymorphonuclear Neutrophils by Granulocyte-Macrophage Colony-Stimulating Factor is Caused by Inhibition of Programmed Cell Death, Blood **80** (1992) 2920–2924.
[28] McGLAVE, P., VOGELSANG G., PETERSDORF E., ANTIN J., "Graft-versus-host disease: Clinical Course and Underlying Mechanisms", Haematology 1994, Education Program (BENZ, E.J., McARTHUR, J.R., Eds), Am. Soc. Haematol., Nashville, TE (1994) 118–123.
[29] THIERRY, D., GOURMELON, P., PARMENTIER, C., NENOT, J.C., Hematopoietic growth factor in the treatment of therapeutic and accidental irradiation-induced bone marrow aplasia, Int. J. Radiat. Biol. **67** 2 (1995) 103–117.
[30] NENOT, J.C., Overview of the Radiological Accidents in the World, updated December 1989, Int. J. Radiat. Biol. **57** 6 (1990) 1073–1085.