Medical treatment of whole-body overexposed individuals

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1. Introduction

A severely irradiated casualty is a person who has received a radiation dose of a level such as to endanger his or her life. The whole-body dose which kills 50 % of victims within two months lies somewhere between 2.5 and 5 Gy [1, 2]. The differences in dose separating probable survival (mortality lower than 10 % for example) from more or less certain death (mortality of over 90 % for example) is small because the dose to the bone marrow has to increase from 2 to 5 Gy. The hematopoietic bone marrow is one of the most sensitive organs to radiation. After a latent period (the higher the dose, the shorter this phase), signs of medullary hypoplasia or aplasia appear ; their intensity is related to the mean absorbed dose to the bone marrow.

Irradiation is never uniform when an accident happens. The mean dose reflects an average level but areas which have been heavily exposed are critical points which can exacerbate the clinical pattern. The heterogeneity of irradiation is a very important factor, because it determines whether spontaneous medullary repair can take place or whether a bone marrow transplant is advisable. Even a few, small isolated patches of marrow which have received doses of less than 2 Gy will be enough for the repopulation of heavily irradiated areas. Repopulation will be possible only if the stroma and microenvironment have not been destroyed by excessively high doses. As with any damage to the bone marrow, priority when treating a severely irradiated casualty must go to preventing and curing the consequences of the insufficient production of the damaged blood cell lines. In addition to dealing with hematopoietic deficiency, the two main forms of treatment are therefore the prevention and treatment of infection and maintaining the nutritive and electrolyte balance.

The irradiation of the intestine with doses of more than 6 Gy results, within two weeks, in a serious digestive syndrome, the main complications of which are perforation, invagination and occlusion. The irradiation of the brain with doses higher than several tens of Gy can kill the patient in a few days. When doses are lower, the neurological symptoms are transitory and are mainly due to cerebral oedema.

The survival of a radiation victim therefore depends (1) on the absorbed dose to vital sensitive organs (human reproductive organs are extremely sensitive to radiation, but damage to them does not affect chances of survival), (2) on the distribution of irradiation in the body and (3) in time (for the same level of severity, the dose must be doubled or quadrupled if it is spread over two weeks or one month). Prognosis is based on clinical signs which reflect the extent to which to various sensitive systems are affected :

- brain : headache, obnubilation, or even coma and neurovegetative dysfunction, irregular electro-encephalogram ;
- intestine : nausea, stomach pains, diarrhoea, digestive complications ;
- blood :
  . platelet deficiency with the outward symptoms of hematomata, petechiae, ecchymoses and hemorrhaging,
  . anaemia with the external symptoms of pallor, dyspnea and tachycardia,
  . leukocyte deficiency with local or generalised superinfection or even septicaemia.

The level of the mean absorbed dose to the bone marrow is assessed from paraclinical tests such as working out the speed of decline of lymphocytes and platelets or the level of chromosomal abnormalities in lymphocytes in the circulating blood and estimating the level of exposure of various medullary areas from the results of marrow punctures in various carefully chosen areas and of cultures of stem cells, to mention only the main tests.

2. Treatment of hematopoietic damage

- The problems : anaemia and thrombopenia

Substitution therapy is the only treatment which can correct disorders connected with anaemia and thrombopenia [3, 4, 5]. Hemoglobin must be kept at a level which makes it possible to remedy disorders due to anoxia (limit approximately 7 to 8 g/100 ml. There is a distinct risk of hemorrhage once the level of platelets drops below 50,000/µl. It is a major risk below 10,000/µl. Platelet transfusions are carried out if these values are reached and in the event of a hemorrhagic syndrome, which may be revealed by hemorrhagic blisters, hemorrhages at the back of the eye, hemorrhaging in the skin or mucous membranes or visceral hemorrhages.

- Transfusions

A complete check must be made before the transfusion 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. The transfusion products consist of phenotyped packed red cells with a low leukocyte content and with compatible HLA platelets from a single donor. One red cell pack must contain at least 45 g of hemoglobin. In an adult, the transfusion of 200 to 250 ml of packed red cells gives a 2 to 2.5 % rise in the hematocrit. Platelets increase by approximately 10,000 per transfused unit and per m^2 of body surface. The frequency of transfusions varies with the daily readings of blood counts, the purpose being to maintain a level above that at which anaemia or hemorrhages could occur. Tests must be carried out for antibodies in the various systems one week after transfusion. No product may be taken from a person who might be a donor of a bone-marrow transplant, because a transfusion can lead to the formation of antibodies against the donor's private antigens.

- Bone-marrow transplantation

Bone-marrow transplantation has become enshrined in the literature as a proposed final successful therapy for the Acute Radiation Syndrome. In the **Chernobyl** accident, bone-marrow transplantation was attempted in 13 patients with one survival. None of the transplants have taken definitively. In the opinion of USSR physicians, this therapy resulted in worsening of the conditions of their patients and they advice against its use [6, 7, 8]. The overall marow transplantation results suggest that it will be of benefit to few exposed individuals in similar types of radiation accident [9, 10]. However, it is impossible to say for certain whether the transplants carried out in Moscow were warranted, as many cases among the most heavily irradiated developped complications chiefly due to the associated burns. It must be borne in mind that a bone-marrow transplant must still be regarded as an *exceptional measure* and that it is *dangerous* [6, 11, 12]. The decision as to whether it is indicated must be taken as soon as possible, for any delay prejudices the chances of the transplant taking (blood transfusions, infections, etc...).

The indication for transplanting bone-marrow to a radiation casualty rests on [10, 11, 13, 14] : (1) high doses received by all medullary areas and which are incompatible with spontaneous recovery ; (2) the absence of any relatively protected areas (less than 4 Gy) which could provide a basis for hematological recovery ; (3) the results of the immunological examination ; (4) a very poor general state, reflecting a very low tolerance of aplasia. If doses at these levels have been received, it must not be forgotten that the neurological and digestive syndromes are likely to cause grave concern and to require more urgent treatment than the hematopoietic syndrome.

The possibility of conducting a transplant must first be discussed bearing in mind the biological criteria of serious medullary aplasia combined with : (1) reticulocytosis of less than 20,000/µl ; (2) neutropenia below 500/ µl ; (3) thrombopenia below 10,000/µl ; especially if these values are continuing to fall. A transplant is indicated only if marrow punctures at different places which are assumed to be the least damages (following the establishment of a dose-rate contour map based on the reconstruction of the accident) show a barren marrow after an interval of several days. Moreover, these examinations must be backed up by medullary biopsies, stem cell cultures and blood cell cultures which show whether or not any repair is in progress. As the results of these examinations are not known for one to two weeks, they must be carried out as soon as possible. All the criteria for selecting the donor have now been established and the same rules must be followed as with bone-marrow transplants based on more traditional indications.

3. Preventing and treating infections

- *Prevention*

The risk of infection is probably the most therapeutic challenge initially confronting the patient. The patient must be kept in a protected environment. No matter what techniques are used (from taking ad hoc isolation measures to laminar flow beds or sterile rooms), the situation is critical and necessitates measures against exogenous and endogenous infections.

Exogenous contamination can come from the immediate environment or from food. As far as the first source is concerned, strict isolation must be coupled with the observance of extremely strict rules and the daily disinfection of any traps in drains. As regards the second source, it is illusory to hope that sterile food or even food with a low germ content can be obtained by using the hospital's catering system. The preparation of sterile food should therefore be arranged. It must be varied as these patients rapidly become anorexic.

The risk of endogenous contamination must be assessed as soon as the patient is admitted. It is standard practice to carry out digestive decontamination which must be closely supervised and adapted during aplasia. The treatment must be both anti-bacterial and anti-fungal. The former is selected in the light of the results of the coproculture. The latter is especially important because damage to flora from antibiotic treatment encourages the settlement of yeasts which colonise the upper respiratory tract. From here, they will regularly reinvade the alimentary canal. The oral cavity must be alkalinised and the yeasts must also be eliminated before the bacterial vacuum is created by removing enterobacteria. A residue-free diet helps to reduce secretions. Nothing must be prescribed to slow the speed of passage in the event of diarrhoea.

- *Treatment of infection*

Close supervision (at least every two days) based on coproculture and samples taken from the pharynx makes it possible to detect the emergence of a potentially pathogenic strain of bacteria. If there is fever, the source of the infection must be sought as a matter of urgency, especially if there is severe granulocytopenia. The treatment is traditional : a massive dose of antibiotics is always given at the site of the infection in accordance with the disc sensitivity test. Granulocyte transfusions are reserved for patients suffering from severe granulocytopenia, if the signs of infection continue after one or two days of intensive antibiotic therapy which has been especially worked out for that patient's needs or if the patient's life is threatened by an acute infection.

4. Maintaining the nutritive and electrolyte equilibrium

Whole-body irradiation with a lethal dose leads to a syndrome of serious undernutrition. The nutritive and caloric equilibrium must therefore be maintained without waiting until undernutrition sets in [5, 6, 13]. Normal feeding through the mouth is preferable to parenteral feeding whenever possible : it is physiologically natural and is psychologically reassuring. During the critical phase, it is often impossible to avoid artificial feeding. The sound is introduced deeply into a vein in absolutely aseptic conditions. An adult needs approximately two litres of liquid per day : the caloric intake is gradual and is maintained at 2,000 to 3,000 calories per day, made up of 50 % carbohydrates, 30 % of lipids and 20 % of proteins. Regular metabolic supervision is necessary and must form part of the daily examination so that any losses can be offset by adding the appropriate substance [5, 13]. Hydroelectrolytic supervision comprises a daily electrolytogram of the patient's blood and urine and the determination of the blood plasma effective osmotic pressure.

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