

8/25/64
8/25

CONTRACT
AF 61(052)816

Report
Number

ADMINISTRATIVE REPORT
NUMBER 2

1 Aug 64 - 31 Dec 64

CONTROL OF SECONDARY SYNDROME FOLLOWING WHOLE BODY IRRADIATION
TREATMENT WITH BONE MARROW TRANSPLANTS

The research reported in this document has been sponsored by, or in part by, the United States Government. This report is intended only for the internal management uses of the contractor and the U.S. Government.

Professor G. MATHÉ
Director of the Center for
Cancerological and Radiopa-
thological Research of the
Claude-Bernard Association
Hôpital Paul-Brousse
VILLISJUIF - Seine - France

AR#2

a) Summary of the work accomplished during the period of the report.

During the period August '64 to Decembre '64 our research has been carried out on two main topics. First, the prevention of the secondary syndrome, by investigation of the effects of various methods of preparing the allogeneic haematopoietic cells that are used for the homografts. The second, is an examination of the effects of treatment of the secondary syndrome by various drugs, which are not anti-mitotic agents.

1) Reduction of the occurrence of secondary syndromes by the conservation of cells under various conditions.

A graft of allogeneic haematopoietic cells provides the animals, that has been given total body irradiation at a lethal dose, with myeloid cells, that ensure the restoration of the haematopoietic tissue. At the same time some of the donor cells are immunologically competent, which in becoming immunized against the host may provoke a lethal secondary syndrome.

These two types of cells may be dissociated by their sensitivities to certain types of treatment "in vitro". Incubation of the bone marrow during a 2 hour period at 37° in a protein-free solution (Tyrode's solution) has an effect of reducing the secondary syndromes induced without any apparent alteration of the myeloid restorative capacity of these homografts in the mouse. Quantitative studies show that less than 2 per cent of the cells, that are immunologically competent, remain active following this treatment "in vitro", whereas no reduction was observed in the haematopoietic potentials of the cells.

Maintaining the cells for 6 hours in the same solution at 16° (the permeability to eosin was the same after this treatment as those cells kept at 37° for 2 hours) had no effect on either the secondary syndrome or the myeloid restoration. The storage of haematopoietic cells at -70° in a solution containing dimethyl sulphoxide has an effect on the myeloid cells and on the immunologically competent cells, but the later appear to be ten times more liable to be destroyed by this type of cell preservation.

2) Examination of the effects of histamine, 5 hydroxytryptamine and protease inhibitors on the control of the graft versus host reaction (GVH).

The GVH reaction which follows the injection of allogeneic bone marrow into an animal after it has received total body irradiation, frequently induces a secondary syndrome that is often lethal. This syndrome starts earlier and is of a more acute form when the numbers of immunologically competent cells (ICC) ^{are} very high.

It is known that this reaction of GVH induces a lymphoid aplasia and loss of immunological memory in the host. This in turn, leads to a great susceptibility to bacterial, viral and mycotic infections: however, death in the acute secondary syndrome can occur during the phase of proliferation of allogeneic ICC that have been injected. Death in these circumstances is perhaps the outcome of a direct immunological reaction of the graft against the host. The role of the liberation of histamine, 5-hydroxytryptamine and of the proteolytic reactions in causing some of the various clinical signs in immunological reactions is well established. We have attempted to try to prevent the sequelae of a GVH reaction by the use of inhibitors of histamine, 5 hydroxy - tryptamine and proteases.

The results of these investigations showed that these agents could not prevent or attenuate either the acute GVH reaction induced by the injection of allogeneic lymphoid cells into an irradiated animal or the chronic GVH reaction that follows the injection of irradiated animals with allogeneic bone marrow cells.

A histamine inhibitor (mepyramine), a serotonin inhibitor (methysergide), and two different protease inhibitors (Kunitz's inhibitor and epsilon-amino-caproic acid) did not modify the lethality of the GVH reaction. The main reason for these failures can be due to either the fact that the liberation of histamine, serotonin and proteases does not play any part in the secondary syndrome. Alternatively, the inhibitors that were tested may have been ineffective. The doses of the drugs used were the maximal amounts that did not kill mice of the same genetic constitution when given the drug for the test period of 37 days.

b) The opening of the new research institute (I.C.I.) is going to permit our research groups to extend their work employing new techniques to study the problem of the control of the secondary syndrome.

c) In 1965 we intend, 1) to investigate the biochemical mechanisms which determine the particular sensitivity of ICC to certain types of preservation. 2) To investigate the effect of high doses of amino acids on the secondary syndrome, this treatment has been shown to inhibit certain immune reactions in the mouse, in particular against polio virus.

d) No inventions were made during this period.

e) During this period Prof. G. Mathe and his assistants Drs Aniel and Schwarzenberg organised a Meeting at the C.N.R.S. Headquarters in Paris on the subject of " the grafting of allogeneic haematopoietic cells " this meeting was attended by the principle research workers in this field from Europe and the U.S.A. and gave an opportunity for up to date survey and exchange of information about this problem.