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Changed outlook in aplastic anaemia

Until very recently patients with chronic acquired aplastic anaemia have had a poor prognosis. Remissions and even eventual recovery may occur in some cases, but the median survival has been only 3-6 months.[1-3] The disease is particularly lethal when a neutrophil count of less than $0{\cdot}5 \times 10^9$ l is associated with a platelet count of less than 20×10^9 l and a reticulocyte count of less than 1%. Orthodox treatment with transfusions of blood components and antibiotics may help to control haemorrhage and infections, but it has little material influence on the outcome. Androgens have been used extensively in the past few years, but various trials have shown that they have limited value, and that only in the milder cases.

A change has come with the possibility that bone marrow transplantation may provide the prospect of recovery for some at least of these patients. The first report of marrow transplantation in aplastic anaemia was probably that from Dameshek's group, who described its use in five patients at a meeting of the American Blood Club in 1958.[4] This was followed by the dramatic report by Mathé and his co-workers,[5] who treated five victims of an irradiation accident. These were early floundering experiments, as were other attempts at marrow grafting carried out mainly on terminally ill patients during the next few years. But advances were being made in knowledge of histocompatibility typing, in the prevention and management of graft-versus-host disease, and in the management of infections and haemorrhagic complications of the immediate postgraft period. By 1970 new attempts were being made at treating aplastic anaemia with infusions of allogeneic marrow, and the first successful cases were reported in 1972 by the Seattle group. Since then there have been reports of promising results from several centres[7-9] and from a multicentre trial by the International Aplastic Anaemia Study Group.[10] In all, some 70 patients have been included in these studies, their course being compared with that of a control group of patients suffering from aplastic anaemia of similar severity and receiving more or less similar supportive measures with or without androgens. In the Seattle study[9] half the patients were alive with normal marrow function and continued evidence of successful grafting between three and five years later. In the other reported series there was a median survival of nine months with a 53% one-year survival—in contrast to a median survival of three months with only 20% prospect of survival beyond two years in non-grafted patients. Selection of patients and the quality of support facilities may have varied among different centres, and these factors may have influenced the results to some extent. Nevertheless, there can now be no doubt that bone marrow transplantation does decrease early mortality significantly and does improve the prospect for long-term recovery.

Bone marrow transplantation is a major undertaking, and the decision is not to be made lightly. Even so, it should not be delayed to the point that morbidity from infection and haemorrhage lessens the patient's chance of survival and sensitisation to blood products increases the risk of graft rejection. In patients found to have severe aplastic anaemia a transplant should be considered early in the course of the disease and not only when conventional treatments have failed. At present, however, the procedure has to be restricted to patients with a sibling donor compatible for the major histocompatibility complex. A patient with one sibling has a one in four chance of having such a compatible donor, and, in general, less than half of all these patients are likely to have a suitable sibling donor available. It is feasible to use an unrelated donor who is histocompatible with the patient, but finding a match in such a case usually needs a large panel of prospective donors gathered nationally or even internationally, and identification requires computer processing.

Even when the donor and recipient have been matched it is necessary (unless they are monozygous twins) to suppress the patient's immune defence mechanism to ensure that the allogeneic graft will be accepted. This can be achieved by total body irradiation or by giving cyclophosphamide for several days before grafting. When a patient has been presensitised to his donor as a result of previous blood transfusions antilymphocyte globulin may also need to be given. To avoid graft-versus-host disease after grafting an immunosuppressive agent such as methotrexate needs to be administered intermittently for about 100 days. During this period of depressed immunological defence there is a risk of infection, so that the patient should be maintained in a protected isolated environment and with intensive support by way of blood component transfusions, antibiotics, a sterile diet, and gut sterilisation when necessary. The protocol required for successful bone marrow grafting[6 9] demands formidable physical, financial, and personnel resources—beyond the means of all but a few centres. Nevertheless, the value of this form of treatment in aplastic anaemia is already proved, and its use will undoubtedly increase. Moreover, as histocompatibility testing and matching become more refined, and the use of immunosuppressive agents becomes more effective, the procedure may well become simplified and more broadly applicable.[11]

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Interferon options

The recent accident in which a research worker at Porton became infected with a strain of Marburg virus has focused attention upon the options available for emergency treatment in such cases. Laboratory investigators or hospital staff known or thought to have been in contact with an exotic virus, particularly a highly infectious one known to have a high mortality and no established means of prophylaxis, usually receive immediate treatment with homologous antiserum or separated immunoglobulin, if available. In addition human interferon may be given. In both cases intensive care is maintained under conditions of strict containment.[1]

The Porton worker received human interferon and later homologous immune serum within 48 hours of a rise in his temperature on the fifth day after infection.[2] The human interferon was given twice daily for 14 days in doses of 3 million units—a total dose of over 80 million units. There was a dramatic fall of viraemia from 10^4 infective units/ml to about 10 units/ml during the first 24 hours of treatment.[3] Thereafter the illness abated: nausea and vomiting declined on the 12th day and there was no bleeding from mucosal surfaces. Whether the interferon (supplied by Professor K Cantell[4] and produced in peripheral blood leucocytes stimulated in vitro with Sendai virus) contributed in any way to this favourable outcome is impossible to say.

Interferon was discovered by Isaacs and Lindenmann[5] in 1956 as a result of the treatment of fragments of chick chorioallantoic membranes with influenza virus inactivated at 56°C for 1 hour. After incubation for a day at 37°C the cell-free supernatant fluid contained a substance that inhibited the growth of influenza virus in fresh membrane fragments. The virus-interfering substance, in this case chick-interferon, is a complex of interferons that differ in charge and molecular weight. The heterogeneous interferons[6 7] induced by viruses in mouse, chick, or human cells have molecular weights of 18 000-25 000 in the monomeric form and up to 40 000 or more in dimeric or heavier forms. Generally the interferons are antigenic proteins with essential disulphide bonds, stable at 56°C for 1 hour and at pH 2 for 24 hours at 4°C, trypsin sensitive, and nuclease resistant. They are members of the larger group of effector molecules (lymphokines[8]) which are released from specialised cells after stimulation by foreign antigens. These effector molecules subsequently act in vivo in the regulation of cellular processes and as a component of host defence against foreign antigens. There is, then, an intimate (but at present obscure) relationship between the activities of interferon and the immune response, a factor that should not be overlooked in emergency treatments with massive doses.

Unlike neutralising antibody, which acts directly on virus in the absence of cells, interferon acts to block virus replication in the cell.[6] The action is specific to the host and not to the stimulating antigen: so that a particular interferon may be stimulated by and active against a wide range of viruses, rickettsiae, protozoa, and bacteria. This non-specific interference is the basis of its possible role as a therapeutic agent, and of the usual assay method, expressed in terms of the sample dilution that will inhibit by half the in vitro infectivity of a standardised test virus.

The stage in virus replication that determines the formation of interferon, at least for RNA viruses, appears to be the synthesis of a double-stranded replicative form of RNA. This then reacts with the host cell genome to derepress the gene that controls interferon synthesis. Double-stranded polynucleotides of fungal or synthetic origin[9 10] may be effective inducers of interferon, as also may be non-infective viruses if they initiate limited RNA synthesis through retained activity of their RNA-directed RNA-polymerases. The mechanism of induction of interferon by DNA viruses is less well understood.

The direct local application of a significant dose of interferon within a day of infection or first clinical signs may control conditions such as virus conjunctivitis, herpetic lesions of the lips, or rhinovirus infection[11] of the nasal epithelium. Human leucocyte interferon depresses the level of virus antigens in the serum of patients with chronic active hepatitis so long as the treatment is maintained.[12] Such observations in man and animals[13 14] suggest that interferon acts at accessible sites to block an initial infection or reduce the infecting dose but is much less effective in controlling the outcome of an infection once this is established or generalised.[15] In emergencies, therefore, interferon should be applied very early and, if possible, at the site of infection: if application is delayed then even massive doses may fail to control the proliferation of virus at inaccessible sites. Clearly a strategy[15] is needed for using the very limited and expensive supplies of purified human interferon, which can be given either as single massive early doses or as many delayed and smaller doses. For infections by immunomodifying viruses, an advantage of the earliest application of interferon may be that if virus replication can be blocked before immune stimulation occurs then the worst immunopathological consequences of long-term virus excretion and the failure to clear virus-antibody complexes may be avoided.

Interferon inducers[7 9] offer a possible future option to the use of interferon itself. These have been administered as an alternative to interferon in several virus-animal systems,[10 12] and the results have tended to confirm the limitations of time of treatment and inaccessibility of site. Unfortunately the toxicity of synthetic interferon inducers may be closely associated with their antivirus activity. A further future option may be the use of an established live-attenuated virus vaccine as an interferon inducer. Such active non-specific interference by a sufficiently rapidly replicating vaccine may provide high interferon activities at the right place and at the right time.

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