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Interstitial Pneumonitis Following Bone Marrow Transplantation: Pathogenesis and Therapeutic Considerations

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Abstract—*High-dose chemo-radiotherapy followed by allogeneic bone marrow transplantation has become standard treatment for a variety of hematological malignancies. Interstitial pneumonitis (IP) is a major complication after bone marrow transplantation, the incidence being approximately* 50% *(range* 20-65%*). Cytomegalovirus (CMV) is found in about half of these cases. If no infectious cause can be detected, the interstitial pneumonitis is labeled 'idiopathic'. The occurrence of CMV IP is related to the state of severe immunosuppression in combination with graft-vs-host disease (GvHD) in these patients. The most important factors contributing to idiopathic IP seem to be: chemotherapy, total-body irradiation, agents to prevent GvHD and GvHD itself. For preventing CMV IP hyperimmune globulin seems to be the most promising method at this moment. As long as the etiology of idiopathic IP remains unclear, no measures can be taken to prevent or treat this disease.*

INTRODUCTION

HIGH-DOSE chemo-radiotherapy followed by bone marrow transplantation (BMT) has become standard treatment for a variety of hematological malignancies in various centers. The standard treatment consists of cyclophosphamide given for 2 days (dose: 60 mg/kg/day) and total-body irradiation (TBI), with a total dose varying from 5 to 10 Gy and a dose rate ranging from 2 to 25 cGy/min [1]. This treatment suppresses the immune response of the host to prevent rejection of the bone marrow graft (from an HLA identical sibling) and at the same time destroys as many leukemic cells as possible. To date, BMT is also applied in the treatment of diseases such as severe combined immune deficiency (SCID), non-Hodgkin's lymphomas, aplastic anemia, osteopetrosis, thalassemia, solid tumors and inborn errors of metabolism. The percentage of long-term disease-free survivors is substantial. A growing number of patients can now be regarded as cured, while their prognosis was hopeless not very long ago.

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Results from prospective randomized clinical trials (Seattle) indicate that BMT in patients in first complete remission of acute non-lymphoblastic leukemia (ANL) is preferable to chemotherapy, especially as regards leukemia relapse [2]. Figure 1 shows the difference between BMT and chemotherapy for the actuarial 6-yr survival: about 50% of the ANL patients (<50 yr) are alive at 6 yr after BMT, as compared with 20% after chemotherapy [2, 3]. The final outcome of the treatment with BMT cannot yet be predicted because of a number of complications (Table 1). The most important are infections, especially interstitial pneumonitis (IP), graft-vs-host disease and leukemia relapse [1]. The incidence of IP is about 50% [4] in various centers. Cytomegalovirus (CMV) is found as an infectious agent in about 50% of the cases. In the other half of the cases no infectious cause can be detected, and this is designated as idiopathic interstitial pneumonitis (IIP). Herpes simplex and Herpes zoster viruses are found in a small number of cases. Infections with *Pneumocystis carinii* are greatly reduced because of the prophylactic treatment with trimethoprim-sulfametoxazol. Fifty percent of all IP cases are lethal. Thus the mortality due to IP as

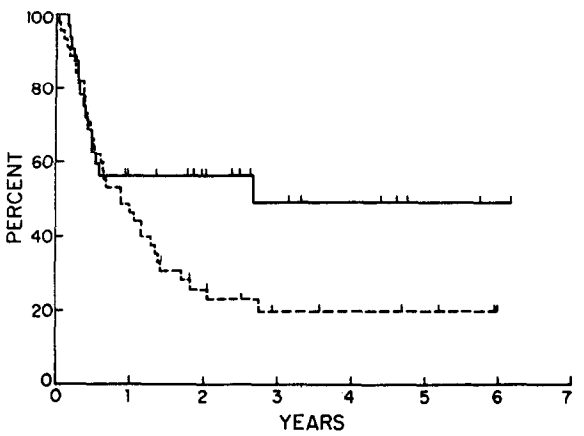

Fig. 1. Actuarial analysis of disease-free survival in patients treated with chemotherapy (dashed line) or with chemo-radiotherapy and bone marrow transplantation (solid line) [2].

a percentage of the total number of BMTs is 25% (Table 1). Leukemia relapse and graft-vs-host disease (GvHD) also result in an unacceptably high mortality rate after BMT. It is clear that if the incidence of IP could be decreased, the treatment of this group of patients with allogeneic BMT would be more rewarding.

Defining IP

IP is a common name for a tissue reaction (infiltration, thickening) in the walls of the alveoli. It must be distinguished from a classical (infectious) pneumonia. In IP there is no consolidation of the inflammatory exudation filling alveolar spaces, in constrast with 'pneumonia' [5]. One finds in the literature an extensive nomenclature for this disease. This already indicates the state of confusion about IP [6]. According to Scadding [5], alveolitis would be a more appropriate name. 'Diffuse alveolar damage' is used for the more acute stages of IP [7]. A general summary of the etiology of IP is given in Table 2 [8].

Clinical picture

The symptoms are very non-specific. The clinical picture is characterized by a progressive dyspnea, tachypnea, fever, a non-productive cough and cyanosis. Chest X-rays show diffuse linear to patchy infiltrations and sometimes honeycombing (Fig. 2) [9]. Lung function studies indicate that the lung volume is decreased and the compliance is diminished. Blood gas analysis shows that there is hypoxemia and a normo- or hypocapnia because the diffusion capacity is restricted and the ventilation-perfusion ratios are disturbed.

IP FOLLOWING BMT

Infectious IP

IP most often occurs between 30 and 100 days after BMT. After day +100 IP is infrequently seen (Fig. 3). In about 50% of the cases of IP after BMT, CMV is cultured from open lung biopsies or autopsy material [4]. Herpes simplex and Herpes zoster viruses, as well as *Pneumocystis carinii*, are found in a small number of cases. The following factors are related to CMV IP [10]: (1) TBI increases the risk of CMV IP; (2) the age of the patient: older age is correlated with a higher incidence of IP; (3) patients with severe GvHD (grade II-IV) have a greater risk of developing CMV IP; (4) the use of anti-thymocyte globulin for the prevention of GvHD increases the risk of CMV IP.

Reactivation of endogenous CMV or exogenous CMV infections acquired through transfusions (granulocytes) or the graft itself [11] are important in the etiology of CMV IP. In general, immunosuppression plays an essential role in the development of CMV IP.

CMV infection after immunosuppression. CMV infections are not only frequently seen after BMT. Patients receiving kidney or heart trans-

Table 1. Lethal complications following allogeneic bone marrow transplantation (BMT) in first-remission of acute non-lymphoblastic leukemia

	% incidence (range)	% fatal	Mortality as % of total No. of BMT
1. Interstitial pneumonitis (50% CMV; 50% idiopathic)	50 (20-65)	50	25
2. Leukemia relapse	15 (5-45)	100	15
3. Graft-vs-host disease	30 (25-60)	30	10
4. Infections (septicemia)			
5. Veno-occlusive disease of the liver			
Total			50

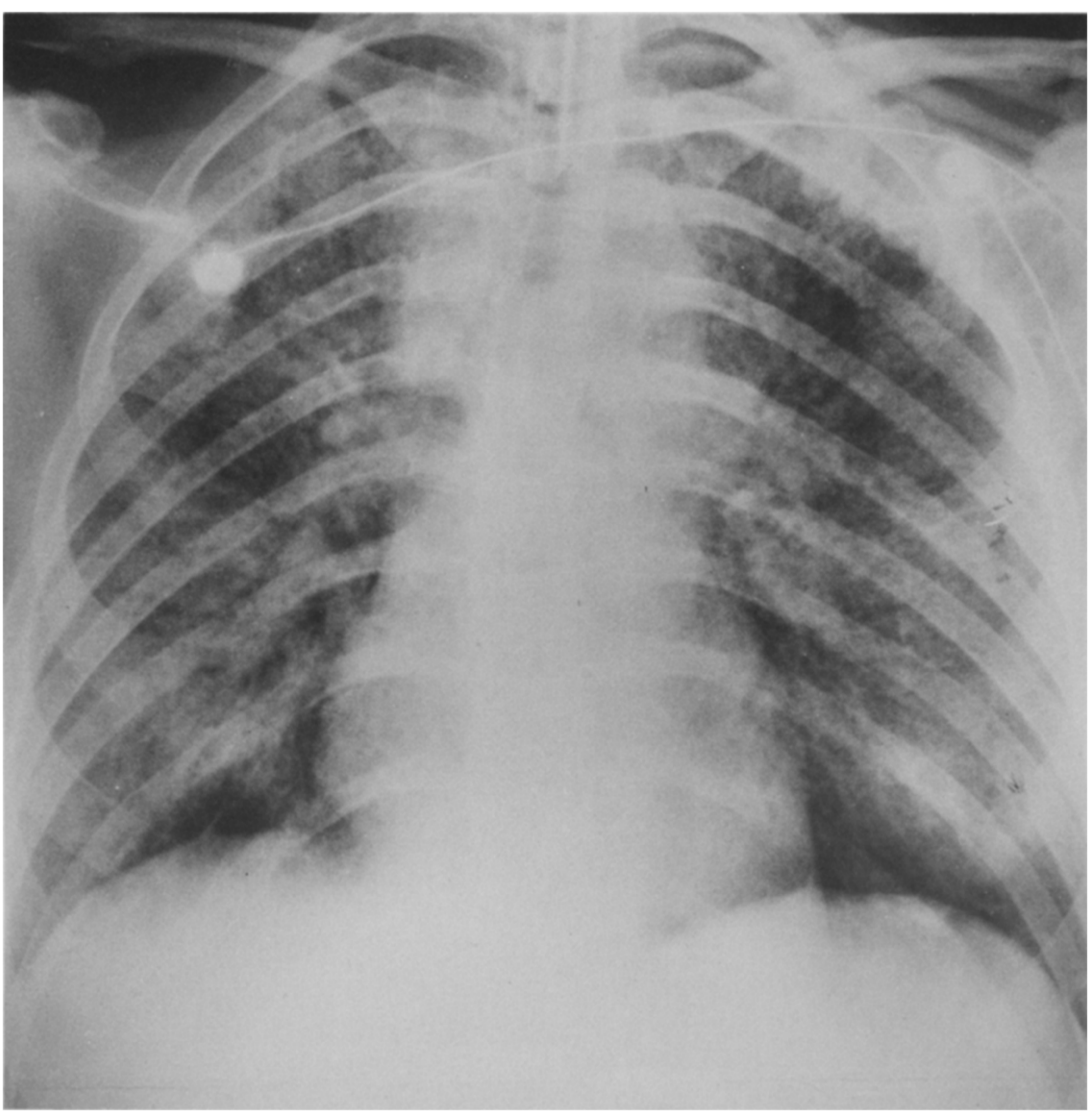

Fig. 2. Interstitial pneumonitis.

Table 2. Differential diagnosis of the etiology of interstitial pneumonitis

Bacteria	any Gram-negative or Gram-positive agent, including *Nocardia* and *Mycobacteria* spp.
Fungi	*Aspergillus* *Candida* *Zygomycetes* *Cryptococcus*
Parasites	*Pneumocystis carinii* *Toxoplasma gondii* *Strongyloides stercoralis*
Viruses	Herpes simplex Varicella zoster Cytomegalovirus Measles
Radiation	
Drug reactions	azathioprine, mercaptopurine, bleomycin, busulphan, cyclophosphamide, melphalan, nitrofurantoin, mitomycin C, etc.
Underlying disease	tumor sarcoidosis, etc.

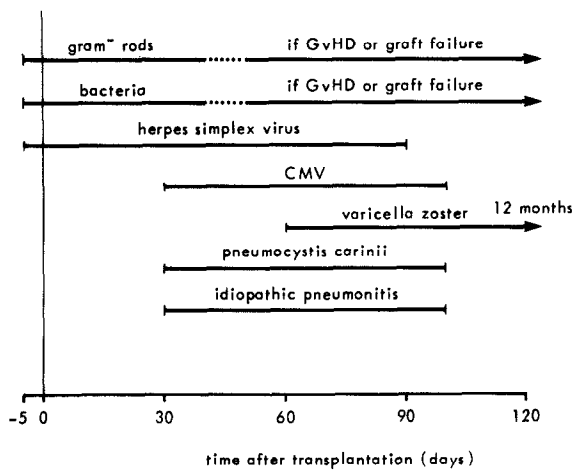

Fig. 3. Infections after bone marrow transplantation.

plantations under immunosuppression with azathioprine, prednisone, cyclophosphamide or ATG have a 90% chance of developing an active CMV infection [11, 12]. The pathogenicity of CMV is mainly regulated by host factors. Cell-mediated immunity is more important than humoral antibody production, as the presence of antibody against CMV does not give protection against reactivation of latent CMV [13]. In immunosuppressed patients the cellular immunity in particular is disturbed [13]. CMV infection itself also has a negative influence on the defense mechanisms of the host and this might create conditions for other opportunistic infections. Studies with murine CMV have shown a suppression of the humoral response and the lymphocyte response to B and T cell mitogens [14-16]. GvHD after BMT gives rise to an even more serious immunosuppression. ATG suppresses specific antiviral host defense systems such as cytotoxic T lymphocytes. Finally, damage to lung tissue by irradiation and chemotherapy increases the possibility of opportunistic infections. Studies from Seattle (100 syngeneic transplantations [17]) have shown that CMV IP does not occur after syngeneic transplantation, in contrast to a 16% incidence after allogeneic transplantations. There was no significant difference in the incidence of idiopathic IP in the allogeneic or syngeneic situation. The underlying mechanism for this observation is unknown. There might be a relation with GvHD and additional immunosuppression induced by methotrexate, cyclosporin A or ATG after allogeneic BMT. Patients receiving syngeneic transplantation are probably in a better condition immunologically than are allogeneic transplantation patients.

There remains the possibility of an unknown infectious agent. Isolation of CMV and IP might be independent factors related to each other by a third factor, e.g. immunosuppression.

Idiopathic IP (IIP)

In about 50% of the cases of IP no infectious cause can be demonstrated by means of invasive diagnostic methods. This is designated as idiopathic IP [18, 19]. The following factors are supposed to be related to IIP after BMT [20-22] (Fig. 4): (1) previous remission-induction chemotherapy; (2) high-dose cyclophosphamide in the pretransplant conditioning regimen; (3) TBI, total dose and dose rate; (4) transfusions; (5) methotrexate or cyclosporin A as prophylaxis for GvHD; (6) GvHD; and (7) unknown endogenous

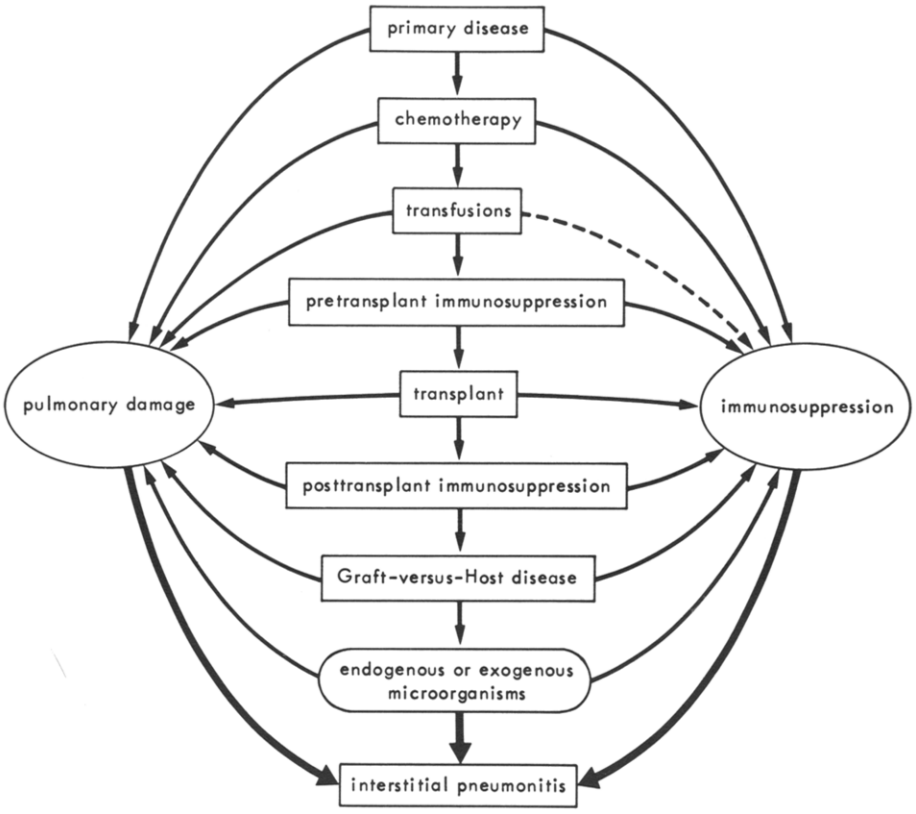

Fig. 4. Pathogenesis of interstitial pneumonitis.

or exogenous microorganisms. Almost all of these factors are known to cause immunosuppression, as well as direct damage to lung tissue.

Previous chemotherapy in leukemia patients, mostly a combination of daunomycin, vincristine and cytosine arabinoside, causes immunosuppression and lung damage [23]. Lung function studies in BMT patients indicate that there is already a significant disturbance prior to BMT. Furthermore, it is known that various cytostatic drugs such as cyclophosphamide are toxic to the lungs in experimental animals as well as in man [24]. The pathological changes in these are characteristic for IP [24-26]. High-dose cytosine arabinoside (ara-C) may cause the 'capillary leakage syndrome' [27].

TBI causes immunosuppression. The total dose used in various treatment centers varies from 8 to 10 Gy, while the total lung dose generally does not exceed 8 Gy if the lungs are shielded. The usual dose rate varies from 2 to 25 cGy/min. IP caused by irradiation of the lungs only occurs if the total dose used is higher than 8 Gy (Fig. 5). The patients represented in this figure received half-body irradiation for a variety of (metastatic) malignancies. It appears that there is a steep actuarial dose-response curve for radiation pneumonitis [28, 29]. At doses lower than 8 Gy no radiation pneumonitis occurs. However, these data cannot be directly compared with those of

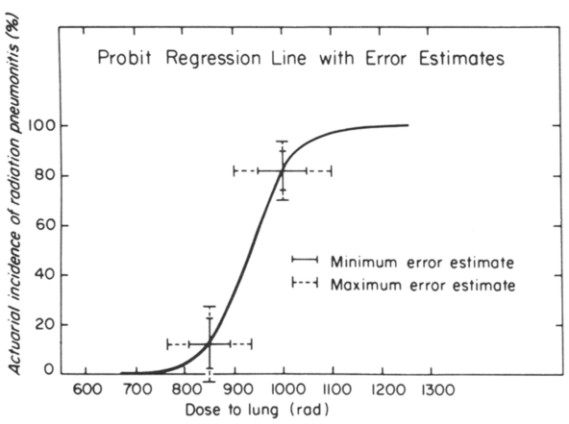

Fig. 5. Actuarial incidence of radiation pneumonitis [29].

patients who receive TBI prior to BMT because the dose rate used (2-25 cGy/min) is substantially lower than in the dose-response curve presented by van Dijk (Fig. 5; 40-500 cGy/min) [29]. The effect of fractionated TBI as opposed to single-dose TBI is being studied in Seattle in a randomized controlled trial. There is a tendency — although not significant so far [30] — that fractionated irradiation results in a decrease in the incidence of IP.

Transfusions, particularly granulocyte transfusions, are well-known transmitters of CMV and may give rise to immunosuppression in an indirect way.

Methotrexate used as GvHD prophylaxis is known to give rise to lung problems [24, 26]. Methotrexate also reduces the immune defense systems of the host. Cyclosporin A [31], another form of immunosuppressive treatment, is presently used more often as anti-GvHD therapy. So far no toxic effects to the lungs have been described after cyclosporin A treatment. However, it remains possible that GvHD induces subclinical damage to the lungs. The skin, liver and intestines are clearly the predilection sites. GvHD disturbs the immune system considerably. Recent studies reported by Powles *et al.* [32] show that leukemia patients transplanted with bone marrow from a non-HLA identical donor (haplo-identical BMT) are more liable to suffer from GVHD. Twelve of 35 of these patients died with a 'capillary leakage syndrome'. Edema of the lungs and increased permeability of the capillaries are the main features of this disease. Both GvHD and drugs might play a role in this new disease entity. Finally, there is still the possibility that an unknown infectious agent (endo- or exogenous) causes IIP. For example, chlamydia trachomatis can be detected in a small number of IP cases [33]. More advanced detection methods might reveal other infectious agents.

THERAPEUTIC CONSIDERATIONS

CMV IP

The source of a CMV infection after transplantation may be endogenous or exogenous, i.e. transfusions of blood products, the donor bone marrow or the environment. It is probable that CMV is present in a latent form in the leukocytes of blood donors and becomes activated (active CMV) after transplantation. To prevent contamination with CMV, blood products obtained from non-infected, i.e. anti-CMV IgG-negative, donors should be used if the recipient has a low or absent serum antibody titer against CMV [34]. Theoretically, it is possible to give less immunosuppression to the host, but the 'take' of the infused bone marrow should not be jeopardized. Other preventive and therapeutic possibilities [35] are: (1) hyperimmune globulin (passive immunization); (2) antiviral agents; (3) interferon; and (4) CMV vaccine (active immunization).

Prospective randomized trials [36–38] have shown that passive immunization with hyperimmune plasma or globulin (human γ-globulin) has a protective effect against CMV disease in BMT patients (Table 3). There is a difference between CMV infection (asymptomatic) and CMV disease (symptomatic). CMV immune plasma prophylaxis does not prevent CMV infections after BMT but it does prevent CMV disease, particularly IP [39]. The effect is more pronounced if no leukocyte transfusions are used. So far antiviral agents have not been successful against CMV infections. High-dose acyclovir is not effective in the treatment of CMV IP [40]. Prophylactic treatment with acyclovir shows no positive results [41]. Other agents such as adenine arabinoside and trifluorothymidine are also ineffective [42].

Human leukocyte interferon alone or in combination with acyclovir was tested in clinical trials. In kidney transplantation leukocyte interferon delayed the start of CMV excretion and decreased the uremia [43]. Interferon was not effective against CMV IP after BMT; however, it might be useful in prophylaxis because the amount of virus at the start of the infection is still limited [44].

Whether CMV vaccine (active immunization) may prevent a future CMV infection [45] remains debatable. Plotkin *et al.* developed a live attenuated CMV vaccine of the Towne strain [46]. Healthy vaccinated adults developed antibodies against CMV and a specific cell-mediated immune response [47]. Cautious use of CMV

Table 3. Incidence of CMV infection and CMV interstitial pneumonitis in bone marrow transplantation patients after passive immunization with anti-CMV immunoglobulin

	UCLA*		SKMCR†		FHCRC‡	
	-CMVIG	+CMVIG	-CMVIG	+CMVIG	-CMVIG	+CMVIG
Total No. of patients	18	17	20	17	19	17
CMV infection§	9	7	10	0	8	2
CMV interstitial pneumonitis	6	0	4	0	1	0

Serum anti-CMV antibody titer (complement fixation): *1:128 (University of California; [37]); †1:2048 (Memorial Sloan Kettering Cancer Center; [38]); ‡1:256 (Fred Hutchinson Cancer Research Center; [36]); §as characterized by positive cultures from the throat or the urine and/or the appearance of anti-CMV IgM antibodies in the serum.

vaccine is necessary because reactivation of attenuated live virus is possible after immunosuppression and because of the oncogeneic potential of the virus [47, 48].

Other infectious causes of IP

The effective prohylactic treatment of *Pneumocystis carinii* infections has already been mentioned. Acyclovir is helpful in the treatment of Herpes simplex and Herpes zoster infections [41].

Idiopathic IP

It is clear that, without intensive investigations of this pathological condition, no prevention or therapy is feasible. It is necessary to return to preclinical studies to collect more information. In an animal model the contribution of the various etiologic factors in IP alone or in combination are presently being analyzed in our institute.

In summary, it may be assumed that damage to lung tissue in combination with a disturbed or suppressed immune system causes IIP and these might set the stage for the activities of endogenous or exogenous microorganisms (opportunistic infections, particularly CMV) which will eventually lead to infectious (CMV) IP.

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