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Early and Late Interstitial Pneumonia Following Human Bone Marrow Transplantation

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Abstract. Interstitial pneumonia is a major determinant of early and late morbidity and mortality following bone marrow transplantation. Among 952 patients receiving allogeneic marrow grafts in Seattle, 35% developed interstitial pneumonia within 100 days of transplant. Development of early cytomegalovirus (CMV) or idiopathic interstitial pneumonia was infrequent in patients with aplastic anemia prepared only with cyclophosphamide. Use of total body irradiation (TBI) in the transplant preparation, increasing patient age, pretransplant seropositivity for CMV antibody and post-transplant development of graft-versus-host disease (GVHD) all increased the risk of CMV pneumonia.

Late interstitial pneumonia was studied in patients with chronic GVHD. Among 198 patients with extensive chronic GVHD, 31 episodes of interstitial pneumonia (seven idiopathic, six CMV, six pneumocystis, five miscellaneous and four unknown causes, and three varicella-zoster) were observed 3-24 months after transplant. In untreated patients with chronic GVHD, 15% developed late interstitial pneumonia. Patients with chronic GVHD who received prednisone ± azathioprine as immunosuppressive therapy and trimethoprim sulfamethoxazole for infection prophylaxis had an 8% incidence of interstitial pneumonia. Patients with chronic GVHD given immunosuppressive treatment without trimethoprim sulfamethoxazole prophylaxis had a 28% incidence of interstitial pneumonia. Trimethoprim sulfamethoxazole significantly reduced the incidence of late interstitial pneumonia in patients with chronic GVHD ($p = 0.001$).

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Introduction

Shortly after the clinical introduction of bone marrow transplantation [reviewed in 1, 2], it became apparent that cytomegalovirus (CMV), pneumocystis and idiopathic interstitial pneumonia were major determinants of transplant-related mortality [3-5]. With the exception of effective prophylaxis of Pneumocystis carinii pneumonia with trimethoprim sulfamethoxazole [6, 7], initial attempts at prevention or treatment of interstitial pneumonia were largely unsuccessful [8]. Developments in the last several years, however, have aided in the diagnosis and prevention of interstitial pneumonia. This article will review the etiology, incidence, risk factors, prevention and treatment of interstitial pneumonias occurring early (before day 100) and late (after day 100) post-transplant.

Background

As with other herpes viruses, CMV infection may represent either primary infection or reactivation of latent virus. Reactivation occurs most commonly during periods of immunodeficiency. During the immunodeficiency associated with marrow transplantation, CMV represents the most frequent and lethal cause of interstitial pneumonia. Previous reports from Seattle have shown that the incidence of CMV pnemonia was higher among patients who were older, who developed severe graft-versus-host disease (GVHD) or who received total body irradiation (TBI) [9]. Cytomegalovirus pneumonia was not reported in 100 identical twin marrow transplants [10].

A study from the International Bone Marrow Transplant Registry suggested that interstitial pneumonia was associated with increased doses of TBI, dose rates greater than 5.7 cGy/min, administration of methotrexate as post-transplant immunosuppression and transplantation of marrow from female donors into male recipients [11]. Lung shielding to a maximum of 6.0 Gy after single-dose TBI, fractionation of TBI or avoidance of GVHD have been reported to improve survival and/or reduce the risk of interstitial pneumonia [12-15].

Laminar air flow protective isolation and microbial decontamination procedures have not lessened the incidence of early interstitial pneumonia [16]. Infectious agents such as mycoplasma, BK virus and Epstein-Barr virus have not been associated with idiopathic interstitial pneumonia. Chlamydia, mycobacteria, legionella and adenovirus infections have been rarely observed after marrow transplant [17-20].

Methods and Definitions

Details of the transplant procedure have been reported [1]. In general, patients with severe aplastic anemia were prepared only with cyclophosphamide, 50 mg/kg for each of four successive days. Patients with hematologic malignancies received cyclophosphamide, 60 mg/kg for each of two successive days, followed by 10 Gy single-dose or 12-15.75 Gy fractionated TBI. Selected leukemia patients received additional chemotherapy agents as pre-transplant preparation. Patients with hematologic malignancies in this study received TBI from opposing ^{60}Cobalt sources at dose rates of 5-8 R/min as measured in air at the midpoint [13].

Interstitial pneumonia was defined as a nonbacterial, nonfungal pneumonitis with histologic features of mononuclear cell infiltration of the pulmonary interstitium and relative sparing of the alveoli. Idiopathic interstitial pneumonia was diagnosed when lung material revealed interstitial inflammation and standard histologic and microbiologic methods demonstrated no infectious agents. Cytomegalovirus pneumonia was diagnosed by either growth of the virus from lung tissue or identification of characteristic intranuclear or cytoplasmic inclusion bodies in lung tissue. Titers of antibody to CMV were determined by microtiter complement fixation techniques. A titer of 1:8 was considered positive and a four-fold or greater increase in titer was considered significant seroconversion. However, seroconversion to CMV or recovery of CMV from sites other than lung were not considered diagnostic of CMV pneumonia. Pneumocystis carinii pneumonia was diagnosed when cysts were demonstrated in lung tissue by silver methenamine or toluidine blue 0 staining. Herpes simplex and adenovirus pneumonias were identified by recovery of the viruses from lung tissue. Varicella-zoster virus pneumonia was diagnosed when a patient with clinical varicella or disseminated herpes zoster developed diffuse interstitital infiltrates.

Patients who had either diffuse or localized pneumonia on chest radiograph but had no pathogens recovered from blood cultures or sputums and who did not undergo lung biopsy or autopsy were classified as having clinical pneumonia. The vast majority of patients reviewed here had a diagnosis of interstitial pneumonia established by open lung biopsy which was performed a median of two days after the onset of symptoms. In view of the requirement of tissue for histologic diagnosis, the incidence of CMV and other interstitial pneumonias may be underestimated and the mortality overestimated.

Selected factors were studied in relation to the time of onset of pneumonia by the statistical methods of Kaplan-Meier and Mantel-Cox. For both early and late interstitial pneumonias, only the first episode of pneumonia occurring either before or after day 100 was analyzed. Late interstitial pneumonia was analyzed

only among patients developing chronic GVHD [21]. Median time to diagnosis of chronic GVHD varied between three and nine months post-transplant.

Diagnosis of Interstitial Pneumonia

Manifestations of pneumonia included nonproductive cough, dyspnea, hypoxemia, fever and radiographic evidence of interstitial infiltrates. Pulmonary edema developing 7-21 days following TBI occasionally resembled interstitial pneumonia [22]. An aggressive course of diuresis usually distinguished these conditions. Because sputum was rarely available for diagnostic purposes, lung tissue was required for diagnosis.

In a prospective study comparing tissue diagnosis from transbronchial or open lung biopsy specimens, transbronchial biopsy specimens were often inadequate to provide etiologic diagnosis [23]. Infections from the chest tube site, poor wound healing and other postoperative complications of open lung biopsies were uncommon in these patients. This was similar to the surgical experience with abdominal operations in marrow graft recipients [24].

Touch imprints of lung specimens were studied for viral inclusions [25] and monoclonal antibody technology also aided in rapid diagnosis [26]. Infection with CMV was occasionally established by the technique of *in situ* hybridization with radiolabelled fragments of CMV DNA [27].

Incidence and Etiology of Early Interstitial Pneumonias

Between 1977 and 1982 the incidence of early interstitial pneumonia remained relatively constant at 25%-35% (Fig. 1).

Table I summarizes the incidence of interstitial pneumonia among 952 patients given allogeneic marrow transplants in Seattle between 1969 and 1982 for treatment of acute or chronic leukemia, lymphoma or aplastic anemia. Over the 13-year period, 35% of transplant recipients developed interstitial pneumonia, and CMV accounted for almost half of the cases. In the more recent experience, pneumocystis pneumonia occurred in fewer than 1% of patients.

Incidence and Etiology of Late Interstitial Pneumonias

Previous analyses have shown that late infections other than varicella-zoster were rare in long-term survivors free of chronic GVHD [28, 29]. Specifically, only five episodes of late interstitial pneumonia developed in 89 long-term survivors of transplant (66 of whom remained free of chronic GVHD). Therefore, we reviewed only patients with extensive chronic GVHD for the incidence and etiology of late interstitial pneumonia. One hundred ninety-eight patients with extensive chronic GVHD transplanted between 1972 and 1982 were studied. Seventy had

Table I. Incidence of early interstitial pneumonia among allogeneic marrow graft recipients

Etiology of pneumonia[a]	Number of episodes	
Cytomegalovirus	147	(42%)
Idiopathic	90	(26%)
Pneumocystis	39	(11%)
Other virus[b]	25	(7%)
Clincial diagnosis[c]	49	(14%)
Total pneumonia episodes	350	
Total pneumonia patients	332	(35%)
Total patients transplanted	952	

[a]Categories are not exclusive and patients may be listed under more than one type in mixed etiology pneumonias. Only first pneumonia episodes are shown. Numbers in parentheses represent the proportion of the total.
[b]Herpes simplex, varicella-zoster, adenovirus.
[c]No lung tissue obtained for diagnosis.

acute nonlymphocytic leukemia, 40 acute lymphocytic leukemia, 38 chronic myelogenous leukemia or other hematologic malignancies and 50 aplastic anemia. Patients were divided into three groups according to their therapy of chronic GVHD: 1) Twenty patients with no therapy, 2) 124 patients with immunosuppressive treatment (either corticosteroids alone or combined with azathioprine) and prophylactic trimethoprim sulfamethoxazole (1 DS p.o. b.i.d.) and 3) 54 patients with immunosuppressive therapy not receiving prophylactic trimethoprim sulfamethoxazole.

Table II summarizes late interstitial pneumonias developing in 28 of these 198 patients. Idiopathic interstitial pneumonia accounted for 23%, CMV for 19%, pneumocystis for 19% and varicella-zoster for 10% of late pneumonias. Fifteen of the 28 patients died of interstitial pneumonia. Figure 2 depicts Kaplan-Meier estimates of the probability of developing interstitial pneumonia after day 100. There were no first episodes of late pneumonia seen between the second and tenth years. Trimethoprim sulfamethoxazole significantly reduced the incidence of late interstitial pneumonia in patients with chronic GVHD ($p = 0.001$).

Risk Factor Analysis for Development of Early Interstitial Pneumonia

Patients with aplastic anemia who did not receive TBI developed less idio-

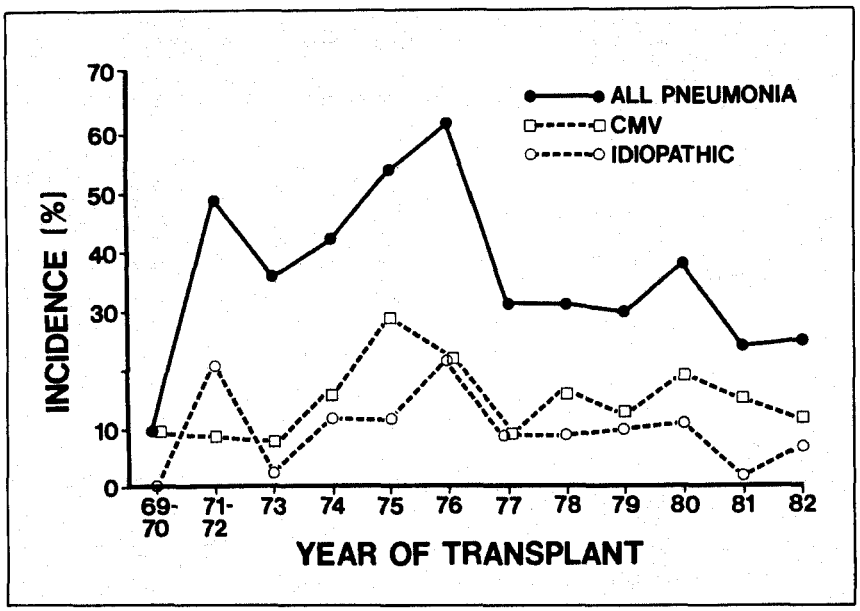

Fig. 1. Incidence of idiopathic, cytomegalovirus and all nonbacterial early interstitial pneumonias by year of marrow transplant. Reprinted from Recent Advances in Bone Marrow Transplantation, New York, Alan R. Liss, 1983, with permission (Reference 9).

pathic and less CMV pneumonia than patients with hematologic malignancies given irradiation. However, when selected patients with aplastic anemia were prepared with 10 Gy TBI, the probability of developing interstitial pneumonia rose from 19% to 62%. When other chemotherapy agents were added to the standard cyclophosphamide and TBI regimen given to patients with leukemia, the risk of CMV pneumonia increased. The development of grade II-IV acute GVHD also increased the incidence of CMV pneumonia (22% compared to 10%), but had no influence on the development of idiopathic interstitial pneumonia. Among 614 patients with leukemia, idiopathic interstitial pneumonia developed in 40/299 (13%) of patients given single-dose TBI compared to 6/315 (5%) of patients given fractionated TBI (univariate analysis, $p < 0.001$). Since patients in the early 1970s were much sicker with heavily treated, end-stage leukemia and only single-exposure TBI was used in these early years, the analysis over the 13-year period could also be influenced by patient selection or prior treatment.

Table III presents a multivariate analysis of several factors influencing the development of early interstitial pneumonia. Cytomegalovirus pneumonia was more common in patients who were older, who were given TBI for malignancies

Table II. Incidence of late interstitial pneumonia among patients with extensive chronic graft-versus-host disease (C-GVHD)

Etiology of pneumonia[a]	Number of episodes in patients with		
	no therapy for C-GVHD	immunosuppressive therapy with TMP-SMX[b]	without TMP-SMX
Cytomegalovirus	1	2	3
Idiopathic	1	2	4
Pneumocystis	0	0	6
Miscellaneous[c]	0	5	3
Clinical diagnosis[d]	1	2	1
Total pneumonia episodes	3	11	17
Total pneumonic patients	3 (15%)	10 (8%)	15 (28%)
Total patients with C-GVHD	20	124	54

[a]All pneumonias developed after day 100 post-transplant. Categories are not exclusive and patients may be listed under more than one type in mixed etiology pneumonias. Only first late pneumonia episodes are shown. Numbers in parentheses represent the proportion of the total.
[b]TMP-SMX = trimethoprim sulfamethoxazole
[c]Varicella-zoster (3), respiratory syncytial (1) or measles virus (1), lymphocytic bronchitis (2) or Legionnaire's disease (1).
[d]No lung tissue obtained for diagnosis.

and who were CMV antibody-positive before transplant. Figure 3 shows the influence of age on the incidence of interstitial pneumonia. There was no apparent difference in interstitial pneumonia incidence in fractionated TBI recipients given either methotrexate or cyclosporine after transplant. This is in contrast to the International Bone Marrow Transplant Registry report which showed a decreased incidence of interstitial pneumonia with cyclosporine [11]. However, the Registry report could not differentiate the influence of cyclosporine from low-dose rate TBI in a multicenter study.

Treatment and Outcome

The mortality of CMV pneumonia was 88% in this series. Mortality was unchanged by treatment [30-32], nor was survival substantially altered by seroconversion to CMV following transplant. Median survival was 19 days after the diag-

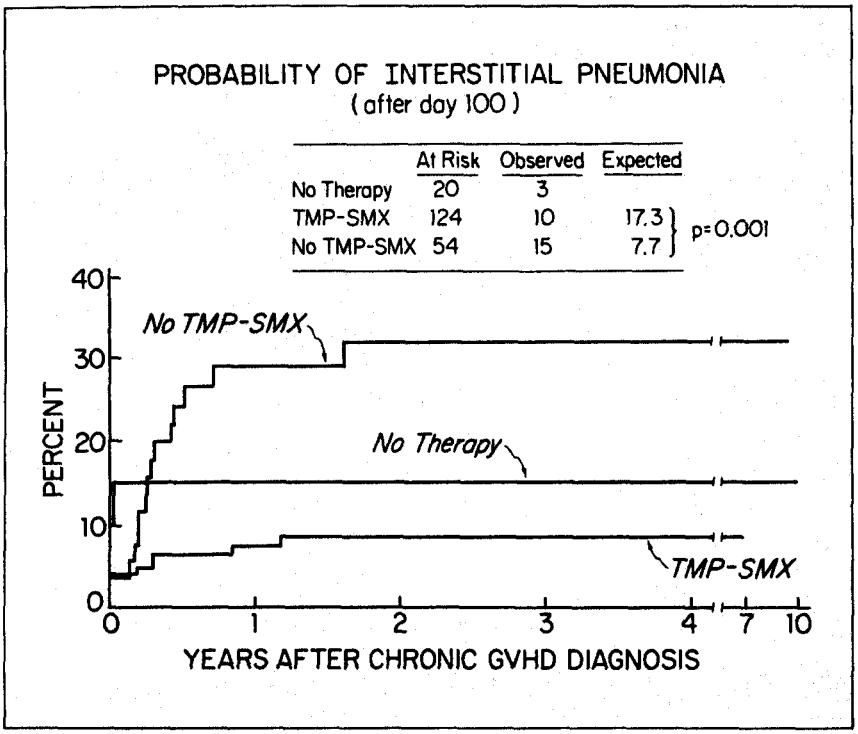

Fig. 2. Probability of late interstitial pneumonia developing in patients with extensive chronic graft-versus-host disease. TMP-SMX = trimethoprim sulfamethoxazole. See text for description of treatment groups.

nosis of pneumonia and was not altered with a variety of antiviral therapies (Fig. 4).

The fatality rate of idiopathic interstitial pneumonia was 64%. Although occasional patients appeared to improve following treatment with high-dose corticosteroids, no controlled trials of therapy have been performed.

Prevention of Interstitial Pneumonia

Marrow transplant recipients require numerous blood component transfusions [33]. Although prophylactic granulocyte transfusions may prevent septicemia, survival was not improved [34]. Moreover, granulocytes from CMV seropositive donors given to seronegative recipients appeared to increase the acquisition of CMV infection [35, 36]. Table IV summarizes 540 patients in whom donor and

Table III. Proportional hazards regression analysis of risk factors for early interstitial pneumonia

Risk factor	Cytomegalovirus pneumonia		Idiopathic pneumonia	
	Relative risk	p[a]	Relative risk	p[a]
Age (in decades)	1.2	0.02	1.2	NS
Diagnosis (aplastic anemia)[b]	0.4	0.003	0.4	0.02
CMV seropositivity	1.9	0.001	0.8	NS
Added chemotherapy[c,d]	2.2	0.02	1.8	NS
Fractionated TBI + MTX[c,e]	0.8	NS	0.5[g]	0.02
Fractionated TBI + CSP[c,f]	0.8	NS	0.3[g]	NS
Grade II-IV acute GVHD	2.5	0.0001	1.3	NS
ATG therapy for GVHD	1.6	0.06	1.8	NS

[a]Two-sided p values
[b]Aplastic anemia (no TBI) versus hematologic malignancies (TBI)
[c]Hematologic malignancy (TBI) patients only
[d]Other cytoreductive drugs added to cyclophosphamide
[e]Fractionated versus single-dose TBI (all methotrexate)
[f]Fractionated versus single-dose TBI (all cyclosporine)
[g]Relative risk = 0.4 when both groups combined (p = 0.002)

Table IV. Percent of patients excreting cytomegalovirus following marrow transplantation

CMV titer of donor	Recipient pretransplant CMV titer	
	Negative	Positive
Negative	21%	62%
Positive	38%	62%

patient CMV antibody titers were measured before transplant. If patients were CMV seropositive before transplant, 62% excreted CMV following transplant regardless of donor CMV status. If patients were CMV seronegative before transplant, 38% excreted CMV following transplant if the donor were CMV seropositive compared to only 21% excretion if the donor were seronegative. It is presumed that CMV infection in seronegative patients with seronegative donors was due to virus transmitted in red cell or platelet transfusions.

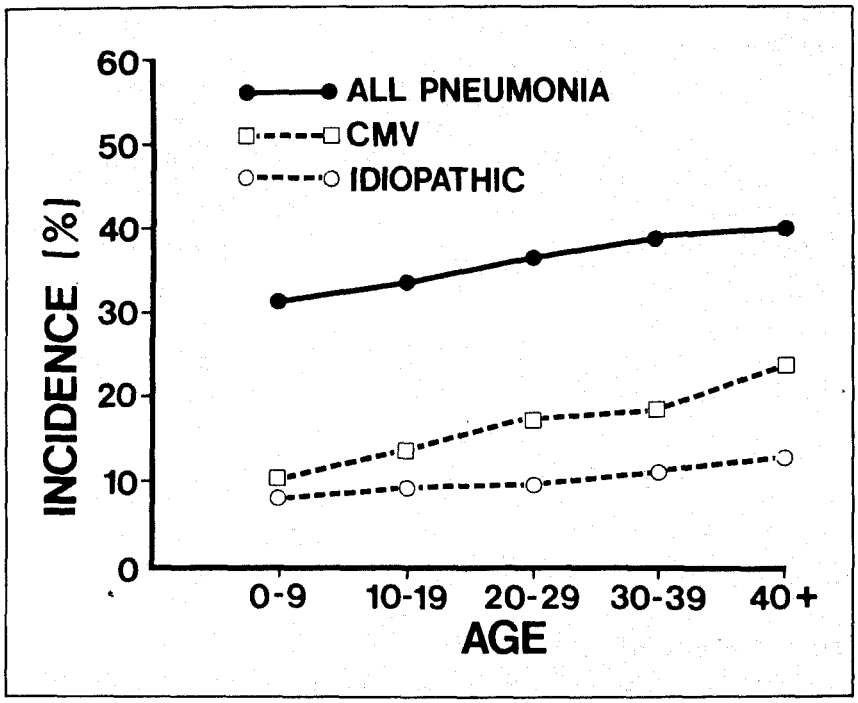

Fig. 3. Incidence of idiopathic, cytomegalovirus and all nonbacterial early interstitial pneumonias by patient age in decades. Reprinted with permission (Reference 9).

The use of globulin and plasma with high antibody titer to CMV has been studied for the prevention of CMV infection and interstitial pneumonia. In a study using high-titer plasma, CMV infection was not altered but CMV disease was lowered [37]. In a report of globulin prophylaxis both CMV infection and disease were lessened [38]. In a study of marrow graft patients not receiving granulocyte transfusions, immune globulin prevented CMV infection among seronegative patients when compared to controls (12% versus 42% CMV infection) [39].

Future Directions

Effective therapy of established CMV pneumonia remains a crucial but elusive goal. New antiviral drugs including trifluorothymidine and derivatives of Acyclovir are being introduced into clinical trials.

At present, reduction in the mortality of CMV and idiopathic interstitial pneumonia will require more effective means of prevention. Advances in preparative and immunosuppressive transplant regimens are potential avenues of exploration.

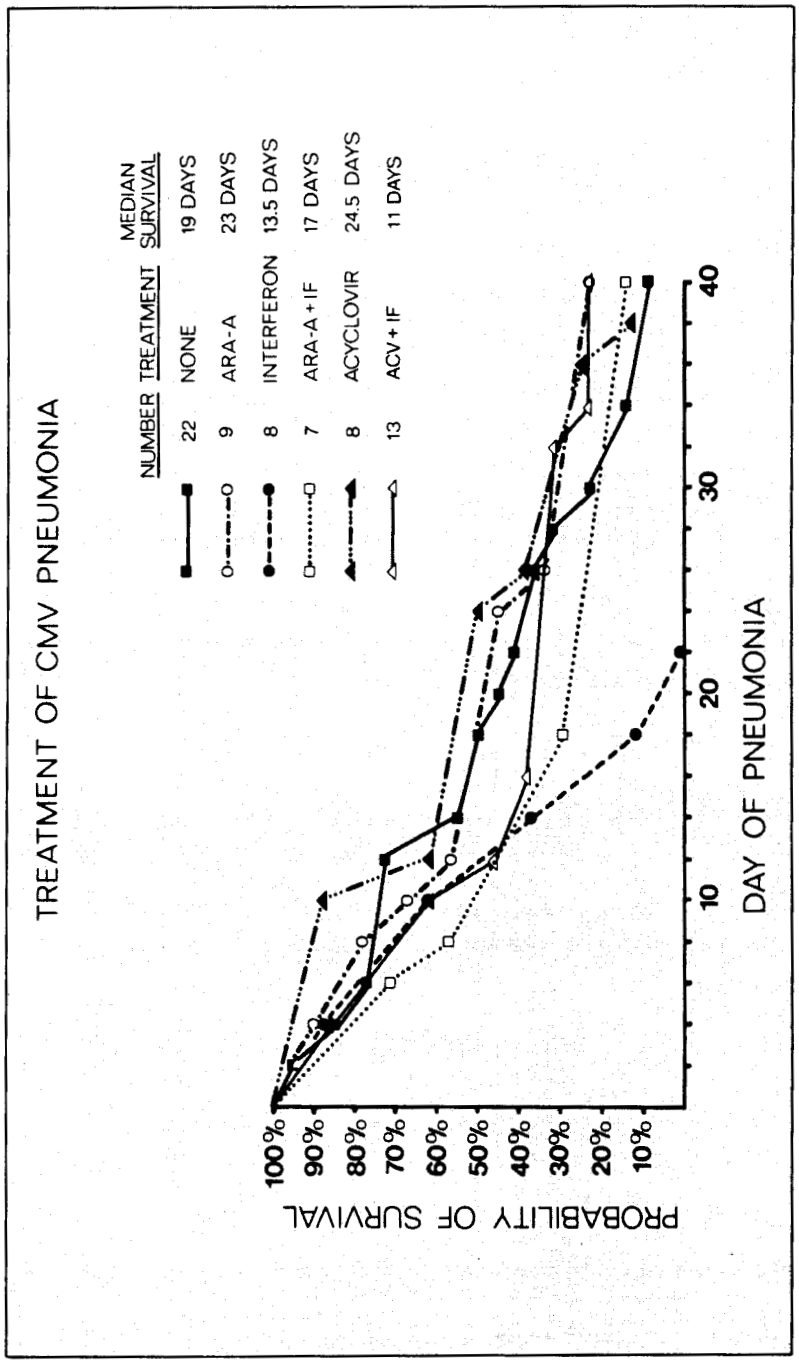

Fig. 4. Probability of survival among patients with biopsy-proven cytomegalovirus pneumonia. Treatment regimen, number of patients treated and median survival are indicated in the figure. Ara-A = vidarabine; IF = interferon. Reprinted with permission (Reference 9).

Total dose of TBI, dose rates and dose fractions are all being studied. However, not all interstitial pneumonias appear TBI-related, as evidenced by both aplastic anemia and hematologic malignancy patients transplanted without total body irradiation [40].

It has been shown that generation of HLA-restricted cytotoxic T cell responses correlate with recovery from CMV infection after marrow transplant [41]. Methods to enhance cytotoxic T cell production could be explored. To date attempts at accelerating immune reconstitution following transplantation have been unsuccessful [42]. However, methods of preventing acute and chronic GVHD could accelerate the tempo of immune reconstitution and decrease early and late interstitial pneumonias [43, 44]. Possible beneficial effects of protective (laminar air flow) environment or cyclosporine immunosuppression in prevention of acute GVHD are being studied [45, 46]. With prevention of acute and subsequent chronic GVHD other factors may be affected which contribute to the development of late interstitial pneumonia. For example, prevention of chronic GVHD might restore the low to absent levels of salivary immunoglobulin A which have been reported in patients with chronic GVHD [47].

Both obstructive and restrictive pulmonary abnormalities have been observed late after marrow transplantation [48, 49]. Whether these disorders are the result of late effects of chemoradiotherapy, direct effects of graft-versus-host reaction in the lung or secondary abnormalities from chronic GVHD involving the oral cavity or esophagus are not known [50-52].

Finally, newer methods may be of benefit in prevention of interstitial pneumonia of viral etiology. Antiviral agents such as the Acyclovir derivatives might be of prophylactic value. Interferon has been reported to reduce CMV reactivation following renal transplantation [53]. Results of clinical trials of interferon prophylaxis in marrow graft recipients are currently being analyzed.

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