# Originalarbeit

# Total-Body Irradiation before Bone Marrow Transplantation for Acute Leukemia in First or Second Complete Remission

## Results and Prognostic Factors in 326 Consecutive Patients

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**Aim:** In order to assess the influence of total-body irradiation (TBI) on the outcome and incidence of complication after bone marrow transplantation (BMT), we retrospectively analyzed our patients treated for acute leukemia and conditioned with TBI prior to BMT.

**Patients and Methods:** Between 1980 and 1993, 326 patients referred to our department with acute non-lymphoblastic leukemia (ANLL, n = 182) and acute lymphoblastic leukemia (ALL, n = 144) in complete remission underwent TBI either in single dose (190 patients: 10 Gy administered to the midplane, and 8 Gy to the lungs [STBI]) or in 6 fractions (136 patients: 12 Gy on 3 consecutive days, and 9 Gy to the lungs [FTBI]) before BMT. The male-to-female ratio was 204/122 (1.67), and the median age was 30 years (mean: 30 ± 11, range: 3 to 63). The patients were analyzed according to 3 instantaneous dose rate groups: 118 patients in the LOW group (≤ 0.048 Gy/min), 188 in the MEDIUM group (> 0.048 and ≤ 0.09 Gy/min), and 20 in the HIGH group (> 0.09 cGy/min). Conditioning chemotherapy consisted of cyclophosphamide (CY) alone in 250 patients, CY and other drugs in 54, and 22 patients were conditioned using combinations without CY. Following TBI, allogeneic and autologous BMT were realized respectively in 118 and 208 patients. Median follow-up period was 68 months (mean: 67 ± 29, range: 24 to 130 months).

**Results:** Five-year survival, LFS, RI and TRM rates were 42%, 40%, 47%, and 24%, respectively. Five-year LFS was 36% in the STBI and 45% in the FTBI group (p = 0.17). It was 36% in the LOW group, 42% in the MEDIUM group, and 30% in the HIGH group (p > 0.05). Five-year RI was 50% in STBI, 43% in FTBI, 55% in LOW, 41% in MEDIUM, and 44% in HIGH groups (STBI vs. FTBI, p = 0.48; LOW vs. MEDIUM, p = 0.03; MEDIUM vs. HIGH, p = 0.68). TRM was not influenced significantly by the different TBI techniques. When analyzing separately the influence of fractionation and the instantaneous dose rate either in ANLL or ALL patients, no difference in terms of survival and LFS was observed. Fractionation did not influence the 5-year RI both in ANLL and ALL patients. However, among the patients with ANLL, 5-year RI was significantly higher (58%) in the LOW group than the MEDIUM group (31%, p = 0.001), whereas instantaneous dose rate did not significantly influence the RI in ALL patients. The 5-year TRM rate was significantly higher in allogeneic BMT group both in ANLL (37%) and ALL (37%) patients than those treated by autologous BMT (ANLL: 15%, ALL: 18%; p = 0.002 and 0.02, respectively). The 5-year estimated interstitial pneumonitis (IP) and cataract incidence rates were 22% and 19%, respectively, in all patients. IP incidence seemed to be higher in the HIGH group (46%) than the MEDIUM (19%, p = 0.05) or LOW (25%, p = 0.15) groups. Furthermore, cataract incidence was significantly influenced by fractionation (STBI vs. FTBI, 29% vs. 9%; p = 0.003) and instantaneous dose rate (LOW vs. MEDIUM vs. HIGH, 0% vs. 27% vs. 33%; p < 0.0001). Multivariate analyses revealed that the best factors influencing the survival were 1st CR (p = 0.0007), age ≤ 40 years (p = 0.003), and BMT after 1985 (p =

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0.008). The RI was influenced independently only by the remission status (p = 0.0002). On the other hand, the TRM rate was lower in patients who did not experience graft-vs.-host disease (GvHD, p < 0.0001), and in those treated after 1985 (p = 0.0005). GvHD was the only independent factor involved in the development of IP (p = 0.01). When considering the cataract incidence, the only independent factor was the instantaneous dose rate (p = 0.0008).

**Conclusion:** The outcome of BMT patients conditioned with TBI for acute leukemia was not significantly influenced by the TBI technique, and TRM seemed to be lower in patients treated after 1985. On the other hand, cataract incidence was significantly influenced by the instantaneous dose rate.

*Key Words: TBI · Dose rate · Fractionation · Acute leukemia · BMT*

**Ganzkörperbestrahlung vor Knochenmarktransplantation bei akuter Leukämie in erster oder zweiter Vollremission: Ergebnisse und prognostische Faktoren bei 326 untersuchten Patienten**

**Hintergrund:** Um den Einfluß der Ganzkörperbestrahlung (TBI) auf die Prognose und die Inzidenz von Komplikationen bei Knochenmarktransplantationen (BMT) zu evaluieren, haben wir retrospektiv unser Patientengut, das bei akuter Leukämie vor der BMT mit der TBI behandelt wurde, analysiert.

**Patienten und Methode:** Von 1980 bis 1993 wurden 326 Patienten mit akuter nichtlymphatischer Leukämie (ANLL, n = 182) und akuter lymphatischer Leukämie (ALL, n = 144) in Vollremission in unserer Abteilung mit einer TBI vor einer BMT behandelt. Die TBI wurde entweder mit einer Einzeldosis (STBI; n = 190: 10 Gy L4, 8 Gy Lungen) oder in sechs Fraktionen (FTBI; n = 136: an drei aufeinanderfolgenden Tagen 12 Gy L4, 9 Gy Lungen) appliziert. Die Männer/Frauen-Ratio betrug 204/122 (1,67), und das mediane Alter betrug 30 Jahre (± 11, 3–63). Außerdem wurden die Patienten in Relation zu drei momentanen Dosisraten analysiert: 118 Patienten waren in der Gruppe mit niedriger Dosisrate (LDR; ≤ 0,048 Gy/min), 188 wurden mit mittlerer Dosisrate (MDR; > 0,048 und ≤ 0,09 Gy/min) und 20 mit einer hohen Dosisrate (HDR; > 0,09 Gy/min) bestrahlt. Die konditionierende Chemotherapie bestand aus Cyclophosphamid (CY) alleine bei 250 Patienten, CY und anderen Medikamenten bei 54 Patienten, und 22 Patienten wurden mit Kombinationen ohne CY behandelt. Nach der TBI wurden allogene und autologe BMT bei respektive 118 und 208 Patienten durchgeführt. Das mediane Follow-up betrug 68 Monate (67 ± 29, 24 bis 130 Monate).

**Ergebnisse:** Das Fünf-Jahres-Überleben, das leukämiefreie Überleben (LFS), die Fünf-Jahres-Rezidivinzidenz (RI) und die therapiebedingte Mortalität (TRM) betrugen jeweils 42%, 40%, 47% und 24%. Das LFS betrug 36% in der STBI- und 45% in der FTBI-Gruppe (p = 0,17). Es betrug 36% in der LDR-, 42% in der MDR- und 30% in der HDR-Gruppe (p > 0,05). Die RI betrug 50% in der STBI-, 43% in der FTBI-, 55% in der LDR-, 41% in der MDR- und 44% in der HDR-Gruppe (STBI vs. FTBI, p = 0,48 ; LDR vs. MDR, p = 0,03 ; MDR vs. HDR, p = 0,68). Die TRM wurde durch die unterschiedlichen Bestrahlungstechniken nicht signifikant beeinflußt. Bei der getrennten Analyse des Einflusses der Fraktionierung und der momentanen Dosisrate bei ANLL- oder ALL-Patienten wurde kein Unterschied für das Überleben oder das LFS beobachtet. Die Fraktionierung beeinflußte die RI weder bei den ANLL- noch bei den ALL-Patienten. Jedoch war bei den ANLL-Patienten die RI signifikant höher (58%) in der LDR- als in der MDR-Gruppe (31%, p = 0,001), die momentane Dosisrate zeigte aber keinen signifikanten Einfluß auf die RI bei ALL-Patienten. Die Fünf-Jahres-TRM-Rate war in der allogenen BMT-Gruppe bei den ANLL- (37%) und ALL-Patienten (37%) signifikant höher als bei der autologen BMT-Gruppe (ANLL 15%, ALL 18%; respektive p = 0,002 und 0,02). Die Fünf-Jahres-Inzidenzraten für die interstitielle Pneumonitis (IP) und Katarakt betrugen 22% respektive 19% bei allen Patienten. Die IP-Inzidenz schien höher zu sein in der HDR- (46%) als in der MDR- (19%, p = 0,05) und LDR-Gruppe (25%, p = 0,15). Außerdem wurde die Kataraktinzidenz signifikant durch die Fraktionierung (STBI vs. FTBI, 29% vs. 9%, p = 0,003) und die momentane Dosisrate (LDR vs. MDR vs. HDR, 0% vs. 27% vs. 33%, p < 0,0001) beeinflußt. Multivarianzanalysen zeigten folgende Hauptfaktoren, die die Überlebensraten beeinflußten: erste Vollremission (p = 0,0007), Alter < 40 Jahre (p = 0,003) und BMT nach 1985 (p = 0,008). Die RI wurde unabhängig nur durch den Remissionsstatus beeinflußt. Außerdem war die TRM-Rate niedriger bei Patienten, die keine Graft-vs.-Host-Reaktion (GvHD, p < 0,0001) hatten, und bei den Patienten, die nach 1985 behandelt wurden. GvHD war der einzige unabhängige Faktor in der Entwicklung der IP (p = 0,01). Für die Kataraktinzidenz fand sich als einziger unabhängiger Faktor die momentane Dosisrate (p = 0,0008).

**Schlußfolgerungen:** Die Prognose der BMT-Patienten, die mit einer TBI bei akuter Leukämie behandelt wurden, wurde nicht durch die TBI-Technik signifikant beeinflußt, und die TRM schien bei den Patienten, die nach 1985 behandelt wurden, niedriger auszufallen. Außerdem wurde die Kataraktinzidenz durch die momentane Dosisrate signifikant beeinflußt.

*Schlüsselwörter: TBI · Dosisrate · Fraktionierung · Akute Leukämie · BMT*

## Introduction

Total-body irradiation (TBI) combined to intensive chemotherapy plays an important role in the conditioning regimen before bone marrow transplantation (BMT) in the treatment of patients with acute leukemia and many other hematological malignancies [1, 3, 24, 26, 30, 41, 54–56]. Apart from acute toxicity, TBI may lead to late toxic effects, including pneumonitis, cataracts, renal complications, endocrinologic disturbances, secondary malignancies, and in children, growth retardation [4, 5, 9, 17, 18, 33, 40, 42, 43, 53, 65]. Despite this intensive chemo- and radiotherapeutic treatment, relapse is one of the major causes of death in patients undergoing BMT.

To assess the influence of TBI regimen on the outcome, we retrospectively evaluated our clinical data concerning 326 consecutive patients with acute leukemia in first or second complete remission (CR), conditioned with high-dose chemotherapy and single-dose or fractionated TBI, and who underwent allogeneic or autologous BMT.

## Patients and Methods

### Patients

A total of 326 patients with acute non-lymphoblastic leukemia (ANLL, n = 182) and acute lymphoblastic leukemia (ALL, n = 144) referred to the Department of Radiation Oncology of the Hôpital Tenon, Paris, France, between 1980 and 1993 underwent TBI either in single dose (STBI, n = 190) or in 6 fractions (FTBI, n = 136) before BMT.

There were 204 male and 122 female patients, and the male-to-female ratio was 1.67. Their ages ranged from 3 to 63 years (mean: 30 ± 11; median: 30). The patients were analyzed according to 3 instantaneous dose rate groups: 118 patients in the LOW group ($\leq$ 0.048 Gy/min), 188 in the MEDIUM group (> 0.048 and $\leq$ 0.09 Gy/min), and 20 in the HIGH group (> 0.09 Gy/min). All patients were in CR: 239 in their first CR (73%) and 87 in second CR (27%). Following TBI, allogeneic or autologous BMT was performed in 118 and 208 patients, respectively. There was no difference in terms of age distribution either between the STBI (mean: 31 ± 11 years) and the FTBI (mean: 29 ± 12 years) groups, or between the LOW (mean: 29 ± 12 years), MEDIUM (mean: 31 ± 11 years), and HIGH (mean: 29 ± 11 years) groups. However, ALL patients (mean: 27 ± 12 years) were younger than ANLL patients (mean: 32 ± 10 years; p < 0.001). The patients were homogeneously distributed in terms of type of BMT, type of leukemia, and remission status in the 3 dose rate groups (Table 1).

The follow-up period ranged from 24 to 130 months (median: 68; mean: 67 ± 29 months). The mean follow-up period was 70 ± 33 months in the STBI group, and 63 ± 22 months in the FTBI group (p = 0.15). When considering the instantaneous dose rate groups, in the LOW group the mean follow-up period (55 ± 28 months) was lower than in the MEDIUM (74 ± 28 months; p < 0.001) and in the HIGH (77 ± 14 months; p = 0.07) groups.

### Graft-vs.-Host Disease (GvHD) Prophylaxis

In the allogeneic BMT patient group (n = 118), the GvHD prophylaxis consisted of methotrexate in 31 pa-

| | Single-dose TBI (n = 190) | | | | | | Fractionated TBI (n = 136) | | | | | | |
| | LOW (n = 37) | | MEDIUM (n = 135) | | HIGH (n = 18) | | LOW (n = 81) | | MEDIUM (n = 53) | | HIGH (n = 2) | | |
| | Allo | Auto | Allo | Auto | Allo | Auto | Allo | Auto | Allo | Auto | Allo | Auto | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANLL | | | | | | | | | | | | | |
| 1st CR | 6 | 13 | 10 | 53 | 3 | 10 | 14 | 10 | 7 | 12 | 0 | 0 | 138 |
| 2nd CR | 3 | 6 | 7 | 10 | 2 | 0 | 5 | 5 | 1 | 4 | 1 | 0 | 44 |
| ALL | | | | | | | | | | | | | |
| 1st CR | 6 | 2 | 18 | 23 | 2 | 1 | 12 | 17 | 3 | 16 | 1 | 0 | 101 |
| 2nd CR | 0 | 1 | 5 | 9 | 0 | 0 | 7 | 11 | 5 | 5 | 0 | 0 | 43 |
| Total | 15 | 22 | 40 | 95 | 7 | 11 | 38 | 43 | 16 | 37 | 2 | 0 | 326 |

TBI: total-body irradiation; LOW instantaneous dose rate: $\leq$ 0.048 Gy/min; MEDIUM instantaneous dose rate: > 0.048 and $\leq$ 0.09 Gy/min; HIGH instantaneous dose rate: > 0.09 Gy/min; Allo: allogeneic bone-marrow transplantation; Auto: autologous bone-marrow transplantation; ANLL: acute non-lymphoblastic leukemia; All: acute lymphoblastic leukemia; CR: complete remission.

Table 1. Distribution of irradiation modalities according to type of disease, remission status, and bone-marrow transplantation type.

Tabelle 1. Übersicht der Strahlentechniken in Abhängigkeit vom Krankheitstyp, Remissionsstatus und Knochenmarktransplantationstyp.

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tients, and cyclosporine combined with methotrexate in 87 patients. When considering the year of BMT, among the patients transplanted during or before 1985, GvHD prophylaxis was done either by methotrexate in 25 patients, or by cyclosporine combined with methotrexate in 11 patients, whereas after 1985, only 6 patients received methotrexate, and 76 received cyclosporine and methotrexate (p < 0.0001).

### Conditioning Chemotherapy

Conditioning chemotherapy consisted of intravenous cyclophosphamide (CY) alone (60 mg/kg body weight on each of 2 successive days) in 250 patients (77%), CY in combination with other chemotherapeutic agents in 54 patients (16%). Twenty-two patients (7%) received combinations of drugs without CY. When considering the TBI technique, in the STBI, FTBI, LOW, MEDIUM, and HIGH groups 148, 102, 90, 148, and 12 patients received CY alone, 35, 19, 18, 31, and 5 patients CY in combination with other drugs, and 7, 15, 10, 9, and 3 patients other combinations without CY, respectively. No difference was observed in terms of conditioning chemotherapy either between the STBI and FTBI groups, or between the LOW, MEDIUM, and HIGH groups (STBI vs. FTBI, p = 0.63; LOW vs. MEDIUM vs. HIGH, p = 0.17).

### Total-Body Irradiation

The details concerning our TBI technique are described elsewhere [36]. Single-dose TBI was done using a 6-MV linear accelerator (Neptune; GE-CGR, Buc, France) with horizontal beams (patient lying on his side, and irradiated anteriorly and posteriorly). The total dose administered to the midplane at the level of L4 was 10 Gy in 1 day, and the lung dose was limited to 8 Gy by partial shielding. Fractionated TBI was done in 6 fractions over 3 consecutive days, with a teletherapy unit (Alcyon; GE-CGR, Buc, France) using vertical beams (anterior and posterior ports, patient lying in prone and supine positions). A total dose of 12 Gy was delivered to the midplane (level of L4), and the lung dose was limited to 9 Gy by partial shielding.

Irradiations were performed using 3 main instantaneous dose rate groups, i. e., using 0.03, 0.06 or 0.15 Gy/min. In the LOW group, the instantaneous dose rate at the midplane (level of L4) for an average 20-cm-thick patient was less than or equal to 0.048 Gy/min (mean: 0.037 ± 0.0058 Gy/min; range: 0.029 to 0.0476 Gy/min). It was more than 0.048 Gy/min, but

less than or equal to 0.09 Gy/min (mean: 0.057 ± 0.005 Gy/min; range: 0.0486 to 0.084) in the MEDIUM group, and more than 0.09 Gy/min in the HIGH group (mean: 0.154 ± 0.014 Gy/min; range: 0.122 to 0.178 Gy/min).

During each TBI session, the dose was monitored by in vivo dosimetry, using semiconductor diodes placed in pairs directly on the front and back of the patient at 5 main areas (head, lungs, mediastinum, level of umbilicus [L4], and calves). The semiconductor diodes were calibrated by an ionization chamber the day before each treatment.

### Veno-Occlusive Disease (VOD) Prophylaxis

VOD prevention was registered in 258 cases, and was usually started 4 or 5 days before BMT and continued until 14 to 30 days following BMT. In 116 (45%) patients, it consisted of heparin (1 mg/kg/day by 24-h continuous infusion), or dinoprostone (0.5 mg total daily dose by 24-h continuous infusion) and pentoxifylline (400 mg × 2/day, PO) in 142 patients (55%). The diagnosis of VOD based on clinical criteria, i. e., icterus, hepatalgia or hepatomegaly, excessive weight gain, and ascites [31].

### Statistical Analysis

Means were compared by Student's t-test. Proportions were compared using the $\chi^2$ test for values greater than 5, and Fisher's exact test for those less than or equal to 5. Kaplan-Meier [25] product-limit estimates were used to evaluate the survival, leukemia-free survival (LFS), relapse incidence (RI), treatment-related mortality (TRM), and the complication rates such as interstitial pneumonitis (IP) and cataract incidence rates. The events were death (all causes of death included) for overall survival, relapse for RI, and relapse and/or death for LFS. When computing the TRM, the event was considered by all causes of death except relapses (patients who relapsed were censored at time of death), and for the IP and cataract incidence rates, patients who died without having developed IP or cataract were censored at time of death. The analysis of the data was realized in July 1994. Differences between groups were assessed using the logrank test [38]. Confidence intervals (CI) were calculated from standard errors. Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor thought to be influencing the different analyzed events [16].

## Results

### Relapses

In a median period of 6 months (range: 1 to 99 months), 125 (38%) of the 326 patients had had a relapse. When considering the TBI technique, there were 75 (39%) relapses in the STBI group, 50 (37%) in the FTBI group, 54 (46%) in the LOW group, 61 (32%) in the MEDI-UM group, 10 (50%) in the HIGH group (STBI vs. FTBI, p = 0.70; LOW vs. MEDIUM vs. HIGH, p = 0.04).

The estimated 5-year RI was 47.1% (95% CI, 41 to 53%) in all patients (Figure 1). It was 50.1% in the STBI group, 43.4% in the FTBI group, 54.6% in the LOW group, 41% in the MEDIUM group, and 44% in the HIGH group (Table 2). When analyzing separately the influence of fractionation and instantaneous dose rate either in ANLL or ALL patients, among the patients with ANLL, the 5-year RI was significantly higher in the LOW group (58.3%) than the MEDI-UM group (31.3%, p = 0.001), whereas the instantaneous dose rate did not significantly influence the RI in ALL patients. The 5-year RI rates in different groups are shown in Table 2.

### Survival

The 5-year survival rate was 42.3% (95% CI, 37% to 48%) in all patients (Figure 1). It was 39% in the STBI group, 46.9% in the FTBI group, 42% in the LOW group, 43.7% in the MEDIUM group, and 30% in the

HIGH group (Table 2). Among the patients with ANLL, neither the fractionation nor the instantaneous dose rate seemed to influence the survival, whereas in the ALL group, patients receiving FTBI did better (45.1%) than those receiving STBI (27.2%, p = 0.02). The 5-year survival rates in different groups are shown in Table 2, and the causes of death in Table 3.

### Leukemia-Free Survival

In all patients, the 5-year LFS was 39.5% (95% CI, 34% to 45%) (Figure 1). It was 35.8% in the STBI group, 44.7% in the FTBI group, 36.4% in the LOW group, 42.3% in the MEDIUM group, and 30% in the HIGH group (Table 2). The 5-year LFS rates in different groups are presented in Table 2.

### Graft-vs.-Host Disease

In patients treated with allogeneic BMT (n = 118), acute GvHD was observed in 35 (56%) of 62 STBI patients: 11 (73%) of 15 in the LOW, 18 (45%) of 40 in the MEDIUM, and 6 (86%) of 7 patients in the HIGH group. This reaction occurred in 36 (64%) of 56 FTBI patients: in 61% (23 of 38) in the LOW, 75% (12 of 16) in the MEDIUM, and 50% (1 of 2) in the HIGH groups. TBI technique did not seem to be an influencing factor in the occurrence of GvHD (STBI vs. FTBI, p = 0.50; LOW vs. MEDIUM vs. HIGH, p = 0.28).
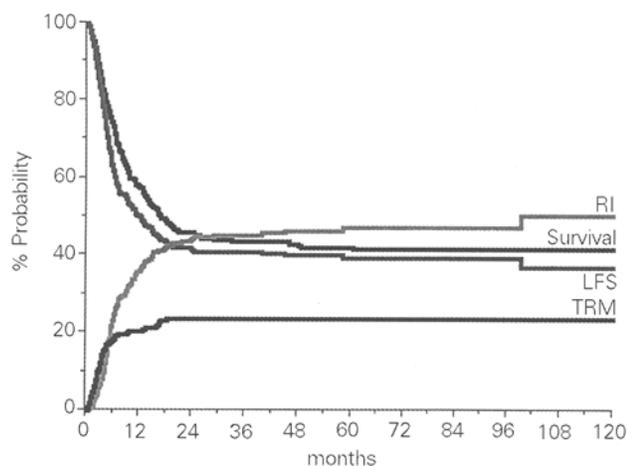


Figure 1. Ten-year projected probabilities of survival, leukemia-free survival (LFS), relapse incidence (RI), and treatment-related mortality (TRM) in 326 patients.

Abbildung 1. Die wahrscheinliche Zehn-Jahres-Überlebenszeit, die leukämiefreie Überlebenszeit, die Rezidivinzidenz, die therapiebedingte Mortalität von 326 Patienten.

|  | No. of patients / total (%) |
|---|---|
| Total as of July 1994 | 186 / 326 (57) |
| Relapse | 115 I 186 (62) |
| Complications | 71 / 186 (38) |
| IP | 22 |
| VOD | 14 |
| Sepsis | 11 |
| GvHD | 10 |
| Graft rejection | 4 |
| ARDS | 3 |
| MOF | 2 |
| Pulmonary embolism | 1 |
| Drug toxicity | 1 |
| Virus-related hemato-phagocytosis syndrome | 1 |
| Tuberculosis | 1 |
| Duodenal ulcer | 1 |

IP: interstitial pneumonitis; VOD: veno-occlusive disease of the liver; GvHD: graft-vs.-host disease; ARDS: acute respiratory distress syndrome; MOF: multiple organ failure.

Table 3. Causes of death.

Tabelle 3. Die Todesursachen.

| | No. of patients | 5-year RI | | | 5-year survival | | | 5-year LFS | | | 5-year TRM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % | 95% CI | p-value | % | 95% CI | p-value | % | 95% CI | p-value | % | 95% CI | p-value |
| **Gender** | | | | | | | | | | | | | |
| Male | 204 | 45.1 | 33–57 | 0.63 | 44.6 | 38–52 | 0.13 | 42.5 | 36–49 | 0.13 | 21.3 | 15–27 | 0.10 |
| Female | 122 | 50.4 | 40–61 | | 38.5 | 30–47 | | 34.7 | 26–43 | | 27.8 | 19–36 | |
| **Age (year)** | | | | | | | | | | | | | |
| ≤ 20 | 69 | 59.8 | 46–73 | 0.06 | 33.5 | 22–45 | 0.06 | 29.6 | 19–41 | 0.04 | 24.7 | 14–35 | 0.32 |
| > 20 and ≤ 40 | 189 | 42.1 | 34–50 | | 49.1 | 42–56 | 0.006 | 45.7 | 39–53 | 0.02 | 19.4 | 13–25 | 0.01 |
| < 40 | 68 | 48.5 | 35–62 | 0.29 | 32.4 | 21–44 | | 32.4 | 21–44 | | 35.1 | 22–48 | |
| **Type of disease** | | | | | | | | | | | | | |
| ANLL | 182 | 43.4 | 35–52 | 0.21 | 46.8 | 39–54 | 0.20 | 43.3 | 36–51 | 0.12 | 22.1 | 16–29 | 0.48 |
| ALL | 144 | 52.0 | 43–61 | | 36.5 | 28–45 | | 34.5 | 27–42 | | 25.6 | 18–33 | |
| **Remission status** | | | | | | | | | | | | | |
| 1st CR | 239 | 39.8 | 33–47 | 0.0002 | 48.0 | 42–54 | 0.002 | 45.3 | 39–52 | 0.003 | 23.2 | 18–29 | 0.91 |
| 2nd CR | 87 | 67.2 | 56–77 | | 26.3 | 17–36 | | 23.6 | 15–33 | | 25.7 | 15–36 | |
| **Influence of GvHD in allogenetic BMT** | | | | | | | | | | | | | |
| GvHD+ | 71 | 43.3 | 28–59 | 0.22 | 31.7 | 20–43 | 0.59 | 30.4 | 20–41 | 0.80 | 43.6 | 31–56 | 0.18 |
| GvHD- | 47 | 55.3 | 39–72 | | 35.9 | 22–50 | | 31.5 | 18–45 | | 28.3 | 14–42 | |
| **Conditioning chemotherapy** | | | | | | | | | | | | | |
| CY alone | 250 | 44.7 | 35–54 | 0.34 | 46.3 | 40–53 | 0.02 | 42.9 | 37–49 | 0.05 | 20.8 | 15–26 | 0.04 |
| Other drugs ± CY | 76 | 55.7 | 42–69 | | 29.8 | 19–40 | | 28.7 | 18–39 | | 33.0 | 22–44 | |
| **Year of BMT** | | | | | | | | | | | | | |
| ≤ 1985 | 79 | 51.5 | 38–65 | 0.80 | 30.4 | 20–41 | 0.007 | 29.1 | 19–39 | 0.04 | 38.2 | 27–50 | 0.002 |
| > 1985 | 247 | 45.6 | 39–52 | | 46.3 | 40–53 | | 43.2 | 37–49 | | 19.0 | 14–24 | |
| **Fractionation in all patients** | | | | | | | | | | | | | |
| STBI | 190 | 50.1 | 42–58 | 0.48 | 39.0 | 32–46 | 0.16 | 35.8 | 29–42 | 0.17 | 26.8 | 20–34 | 0.14 |
| FTBI | 136 | 43.4 | 34–53 | | 46.9 | 38–55 | | 44.7 | 36–53 | | 19.2 | 12–26 | |
| *in ANLL* | | | | | | | | | | | | | |
| STBI | 123 | 46.0 | 36–56 | 0.51 | 45.5 | 37–54 | 0.78 | 41.3 | 32–50 | 0.59 | 22.2 | 14–30 | 0.98 |
| FTBI | 59 | 38.6 | 25–52 | | 49.2 | 36–62 | | 47.5 | 35–60 | | 22.0 | 11–33 | |
| *in ALL* | | | | | | | | | | | | | |
| STBI | 67 | 59.5 | 45–74 | 0.41 | 27.2 | 16–39 | 0.02 | 25.3 | 15–36 | 0.05 | 35.3 | 23–47 | 0.02 |
| FTBI | 77 | 47.0 | 35–59 | | 45.1 | 34–57 | | 42.6 | 31–54 | | 17.0 | 8–26 | |
| **Instantaneous dose rate /cGy/min) in all patients** | | | | | | | | | | | | | |
| ≤ 4.80 | 118 | 54.6 | 44–65 | 0.03 | 42.0 | 33–51 | 0.99 | 36.4 | 27–45 | 0.45 | 18.3 | 11–26 | 0.11 |
| > 4.80 and ≤ 9.00 | 188 | 41.0 | 33–49 | | 43.7 | 37–51 | | 42.3 | 35–49 | | 26.8 | 20–33 | |
| < 9.00 | 20 | 44.0 | 21–67 | 0.68 | 30.0 | 10–50 | 0.47 | 30.0 | 10–50 | 0.38 | 26.7 | 3–50 | 0.59 |
| *in ANLL* | | | | | | | | | | | | | |
| ≤ 4.80 | 62 | 58.3 | 45–72 | 0.001 | 43.0 | 30–56 | 0.67 | 35.9 | 23–48 | 0.20 | 12.5 | 4–21 | 0.03 |
| < 4.80 and ≤ 9.00 | 104 | 31.3 | 21–42 | | 51.0 | 41–61 | | 49.5 | 40–59 | | 27.5 | 19–36 | |
| > 9.00 | 16 | 43.1 | 17–69 | 0.84 | 31.2 | 8–54 | 0.36 | 31.2 | 8–54 | 0.21 | 25.0 | 0–52 | 0.54 |
| *in ALL* | | | | | | | | | | | | | |
| ≤ 4.80 | 56 | 50.1 | 35–65 | 0.86 | 41.0 | 28–54 | 0.60 | 36.8 | 24–50 | 0.73 | 24.3 | 13–36 | 0.87 |
| < 4.80 and ≤ 9.00 | 84 | 53.2 | 41–65 | | 34.6 | 24–54 | | 33.2 | 23–43 | | 26.0 | 16–36 | |
| > 9.00 | 4* | | | | | | | | | | | | |

RI: relapse incidence; LFS: leukemia-free survival; TRM: treatment-related mortality; CI: confidence interval; ANLL: acute non-lymphoblastic leukemia; ALL: acute lymphoblastic leukemia; CR: complete remission; BMT: bone-marrow transplantation; GvHD: graft-vs.-host disease; CY: cyclopsphamide; STBI: single-dose total-body irradiation; FTBI fractionated (6 fractions) total-body irradiation. * not evaluated for statistical analyses.

Table 2. Influence of prognostic factors and total-body irradiation regimen on relapse incidence, survival, leukemia-free survival, and treatment-related mortality (univariate analyses).

Tabelle 2. Einfluß der Prognosefaktoren und der TBI-Techniken auf die Rezidivinzidenz, die Überlebenszeit, die leukämiefreie Überlebenszeit und die therapiebedingte Mortalität (Einzelvarianzanalysen).
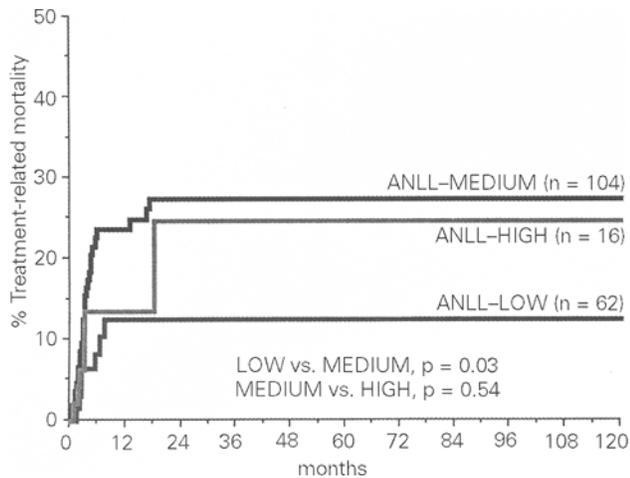
Figure 2. Ten-year treatment-related mortality (TRM) probability in acute non-lymphoblastic leukemia (ANLL) patients according to 3 instantaneous dose rate groups: LOW ($\leq 0.048$ Gy/min); MEDIUM ($> 0.048$ and $\leq 0.09$ Gy/min); and HIGH ($> 0.09$ Gy/min).

Abbildung 2. Die wahrscheinliche Zehn-Jahres-therapiebedingte Mortalität in der Gruppe der akuten nichtlymphatischen Leukämiepatienten in Abhängigkeit von den Dosisratengruppen: niedrige Dosisrate ($\leq$ 0,048 Gy/min), mittlere Dosisrate ($>$ 0,04 und $\leq$ 0,09 Gy/min), Hochdosisrate ($>$ 0.09 Gy/min).
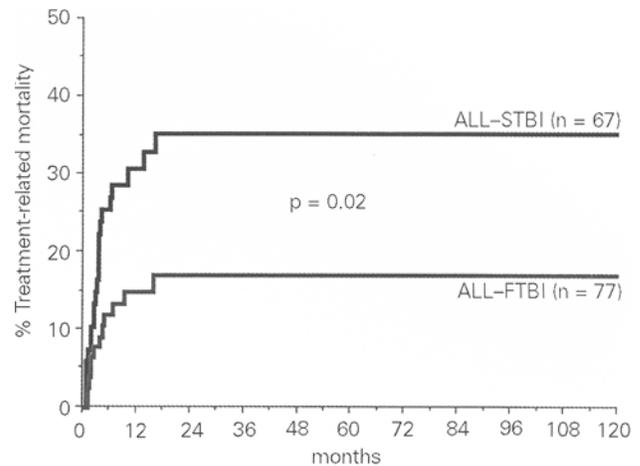


Figure 3. Ten-year treatment-related mortality (TRM) probability in acute lymphoblastic leukemia (ALL) patients according to fractionation technique: single-dose (STBI; 10 Gy in 1 day, 8 Gy to the lungs) and fractionated (FTBI; 12 Gy in 6 fractions over 3 consecutive days, 9 Gy to the lungs) total-body irradiation.

Abbildung 3. Die wahrscheinliche Zehn-Jahres-therapiebedingte Mortalität in der Gruppe akuter lymphatischer Leukämiepatienten in Abhängigkeit von der Fraktionierungstechnik: Einzeldosis (STBI: 10 Gy – 1 Tag mit 8 Gy Lungendosis), Fraktionierung (FTBI: 12 Gy in sechs Fraktionen an drei Tagen mit 9 Gy Lungendosis).

## Treatment-Related Mortality

The 5-year TRM was 23.7% (95% CI, 19% to 29%) for all patients (Figure 1). When considering all patients together, no statistically significant difference was observed between the different TBI regimens (Table 2). However, in the ANLL group of patients, it was lower in the LOW group (12.5%) than in the MEDIUM (27.5%, p = 0.03) or HIGH (25%, p = 0.49) groups (Figure 2). In the ALL patients, patients irradiated with FTBI (17%) had lower TRM rate than those irradiated with STBI (35.3%, p = 0.02) (Figure 3). When considering the type of BMT, patients treated with autologous BMT did better than those treated with allogeneic BMT, both in the ANLL and ALL group of patients (Table 2) (Figure 4). The 5-year TRM rates in different groups of patients are shown in Table 2.

## Influence of TBI Regimen and Prognostic Factors on Outcome

Besides the TBI technique (fractionation and instantaneous dose rate), various prognostic factors, including gender, age, type of leukemia, type of conditioning chemotherapy (CY alone vs. other drugs ± CY), remission status (1st CR vs. 2nd CR), presence or not of GvHD in allogeneic BMT patients, time from diagnosis to transplantation (6 months or less vs. more

than 6 months), and year of BMT (before or during 1985 vs. after 1985), were first analyzed in univariate analyses (Table 2) to determine their influence on RI, survival, LFS, and TRM, then stepwise multivariate analyses (Cox regression model) were realized using the same parameters (Table 4). Both fractionation and instantaneous dose rate had no significant influence on the outcome after adjustment for other prognostic factors. When considering all patients together, the only independent factor influencing the RI was the remission status (p = 0.0002). Survival was influenced independently by the remission status (p = 0.0007), age (p = 0.003), and year of BMT (p = 0.008). The factors influencing independently the LFS were remission status (p = 0.003), and age (p = 0.01). On the other hand, TRM was significantly lower in patients who did not experience GvHD (p < 0.0001), and in those treated after 1985 (p = 0.0005). When analyzing separately the patients with ANLL or ALL, remission status was the only independent factor influencing the RI (respectively, p = 0.03 and 0.003), survival (respectively, p = 0.004 and 0.01), or LFS (respectively, p = 0.01 and 0.02) in both groups. Both in ANLL and ALL patients, TRM was influenced independently by 2 prognostic factors: year of BMT (p = 0.006 for ANLL, and p = 0.03 for ALL patients) and the presence of GvHD (p = 0.01 for ANLL, and p = 0.001 for ALL patients).
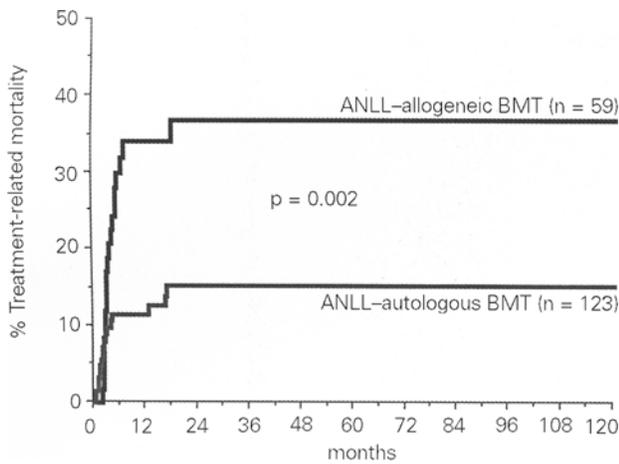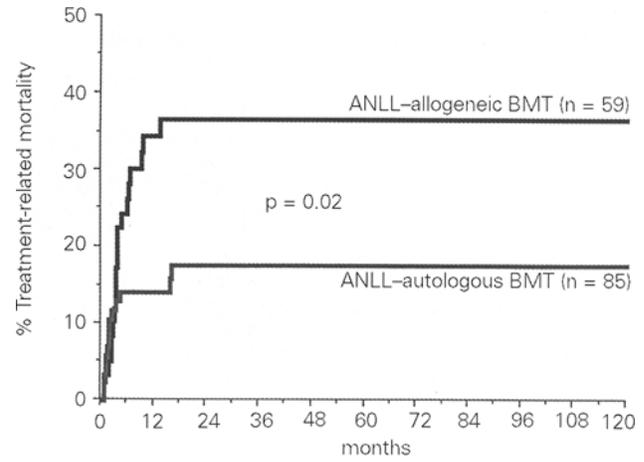
Figure 4a – Abbildung 4a



Figure 4b – Abbildung 4b

Figures 4a and 4b. Ten-year treatment-related mortality (TRM) probability a) in acute non-lymphoblastic leukemia (ANLL) and b) in acute lymphoblastic leukemia (ALL) patients according to allogeneic or autologous bone-marrow transplantation.

Abbildungen 4a und 4b. Die wahrscheinliche Zehn-Jahres-therapiebedingte Mortalität: a) bei akuter nichtlymphatischer Leukämie; b) bei akuter lymphatischer Leukämie in Abhängigkeit vom Transplantationstyp, allogen oder autolog.

## Interstitial Pneumonitis

In 62 (19%) of 326 patients, IP developed with an estimated incidence of 22.4% (95% CI, 17% to 28%) at 5 years. IP was of idiopathic or unknown origin in 22 (6.7%) patients. For the other 40 patients, IP was caused by cytomegaloviral (n = 15), fungal (n = 10) or bacterial (n = 5) infections, or GvHD (n = 10). In the allogeneic BMT patients (n = 118), 27 (23%) had IP. Of 27 IPs, 6 (22%) occurred in patients not experiencing GvHD (n = 47), whereas the other 21 (30%) oc-

curred in those (n = 71) with GvHD (p = 0.05). The IP incidence was 17% (32 of 190) in the STBI group, 22% (30 of 136) in the FTBI group, 20% (24 of 118) in the LOW group, 16% (31 of 188) in the MEDIUM group, and 35% (7 of 20) in the HIGH group (STBI vs. FTBI, p = 0.29; LOW vs. MEDIUM vs. HIGH, p = 0.12).

The 5-year estimated IP incidence rates were 20.5% in the STBI group, 24.7% in the FTBI group, 24.5% in the LOW group, 19.2% in the MEDIUM group, and 46% in the HIGH group (STBI vs. FTBI, p = 0.29; LOW vs.

Table 4. Prognostic factors influencing relapse, survival, leukemia-free survival and treatment-related mortality (multivariate analysis – Cox model).

Tabelle 4. Die beeinflussenden Prognosefaktoren hinsichtlich der Rezidivinzidenz, der Überlebenszeit, der leukämiefreien Überlebenszeit und der therapiebedingten Mortalität (Multivarianzanalyse, Cox-Modell).

| Covariables | All patients (n = 326) | | AML patients (n = 182) | | ALL patients (n = 144) | |
|---|---|---|---|---|---|---|
| | RR | p-value | RR | p-value | RR | p-value |
| *Relapse incidence* | | | | | | |
| Remission status* | 1.98 | 0.0002 | 1.77 | 0.03 | 2.17 | 0.003 |
| *Overall survival* | | | | | | |
| Remission status | 1.70 | 0.0007 | 1.86 | 0.004 | 1.69 | 0.01 |
| Age** | 1.69 | 0.003 | | | | |
| Year of BMT | 0.66 | 0.008 | | | | |
| *Leukemia-free survival* | | | | | | |
| Remission status | 1.56 | 0.003 | 1.70 | 0.01 | 1.64 | 0.02 |
| Age | 1.53 | 0.01 | | | | |
| Treatment-related mortality | | | | | | |
| GvHD† | 2.78 | <0.0001 | 2.41 | 0.01 | 3.15 | 0.001 |
| Year of BMT | 0.42 | 0.0005 | 0.39 | 0.006 | 0.45 | 0.03 |

ANLL: acute non-lymphoblastic leukemia; ALL: acute lymphoblastic leukemia; RR: relative risk; BMT: bone-marrow transplantation; GvHD: graft-vs.-host disease; *1st (value = 0) vs. 2nd (value = 1) complete remission; **age ≤ 40 (value = 0) vs. > 40 (value = 1); transplanted before or during 1985 (value = 0) vs. after 1985 (value = 1); † no GvHD (value = 0) vs. GvHD (value = 1).

MEDIUM, p = 0.43; MEDIUM vs. HIGH, p = 0.05). It was higher in patients treated with allogeneic BMT (30.7%) than in those treated with autologous BMT (18.7%), but the difference was not statistically significant (p = 0.16). In the allogeneic BMT group, among the patients with GvHD, the 5-year estimated IP incidence rate was 39.5% compared with 17.9% in those who had no such graft reaction (p = 0.04). The Cox stepwise multiple-regression model used to investigate the influence of fractionation, instantaneous dose rate, year of treatment (before or after 1985), type of BMT, type of conditioning chemotherapy (CY alone vs. other drugs ± CY), presence or not of GvHD, gender, and patient age revealed that GvHD was the only independent factor involved in the development of IP (p = 0.01).

*Cataracts*

A total of 25 (8%) cataracts developed after 19 to 72 months (median: 42 months) in 326 patients, with an estimated cataract incidence rate of 19% (95% CI, 12% to 26%) at 5 years. Of 190 patients in the STBI group, 20 (11%), and 5 (4%) of 136 patients in the FTBI group had cataracts (p = 0.04), with a 5-year estimated incidence of 29.2% and 8.5%, respectively (p = 0.003) (Figure 5a). When considering the instantaneous dose rate, none of 118 patients in the LOW group, 23 (12%) of 188 patients in the MEDIUM group, and 2 (10%) of 20 patients in the HIGH group had cataracts

(p = 0.0004), with a 5-year estimated incidence of 0%, 26.5%, and 33.3%, respectively (p < 0.0001) (Figure 5b). Among the patients who received steroids (n = 181), the 5-year cataract incidence rate was 19.4% compared to 29.6% in those who did not (p = 0.28). On the other hand, patients (n = 116) who received heparin as VOD prevention had significantly lower cataract incidence (10.3%) than those did not (23%, p = 0.03). The Cox stepwise multiple-regression model used to investigate the influence of fractionation, instantaneous dose rate, year of treatment, type of BMT, type of conditioning chemotherapy, presence or not of GvHD, use of steroids, use of heparin, gender, and patient age revealed that the only independent factor influencing the occurrence of cataracts was the instantaneous dose rate (p = 0.0008).

*Veno-Occlusive Disease*

VOD was observed in 37 (11%) patients: in 23 (12%) patients in the STBI group, 14 (10%) patients in the FTBI group, 13 (11%) patients in the LOW group, 23 (12%) patients in the MEDIUM group, and 1 (5%) patient in the HIGH group (STBI vs. FTBI, p = 0.74; LOW vs. MEDIUM vs. HIGH, p = 0.62). VOD occurrence was influenced neither by its type of prevention (14% [16/116] in patients using heparin vs. 15% [21/142] in those receiving dinoprostone and pentoxifylline combination; p = 0.73), nor by the type of BMT (14%
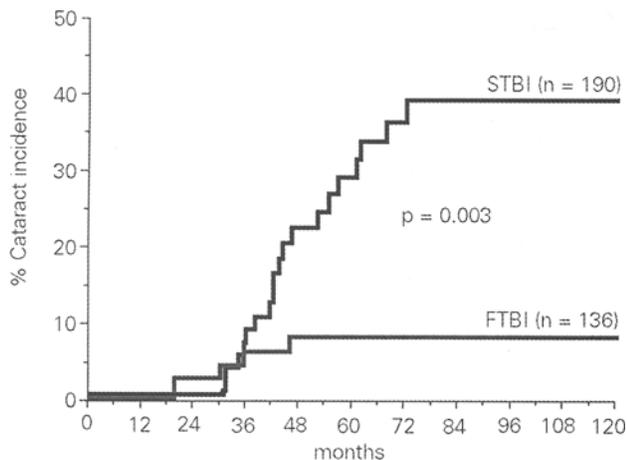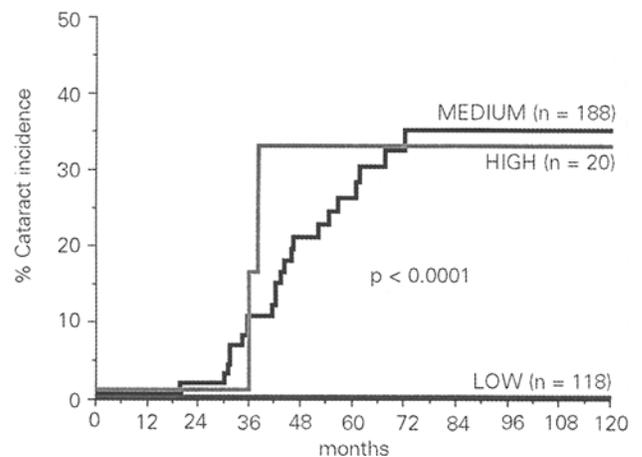


Figure 5a – Abbildung 5a

Figure 5b – Abbildung 5b

Figures 5a and 5b. Ten-year estimated cataract incidence in 326 patients with acute leukemia according to a) fractionation technique: single-dose (STBI: 10 Gy in 1 day, 8 Gy to the lungs) and fractionated (FTBI: 12 Gy in 6 fractions over 3 consecutive days, 9 Gy to the lungs) total-body irradiation, and b) 3 instantaneous dose rate groups: LOW (≤ 0.048 Gy/min), MEDIUM (> 0.048 and ≤ 0.09 Gy/min), and HIGH (> 0.09 Gy/min).

Abbildungen 5a und 5b. Die wahrscheinliche Zehn-Jahres-Kataraktinzidenz bei 326 Patienten mit akuter Leukämie in Abhängigkeit von der Fraktionierungstechnik: a) Einzeldosis (STBI: 10 Gy, 1 Tag mit 8 Gy Lungendosis) und Fraktionierung (FTBI: 12 Gy in sechs Fraktionen an drei Tagen mit 9 Gy Lungendosis). b) Drei Dosisgruppen: niedrige Dosisrate (≤ 0,048 Gy/min), mittlere Dosisrate (> 0,04 und ≤ 0,09 Gy/min), Hochdosisrate (> 0,09 Gy).

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[16/118] in allogeneic BMT vs. 10% [21/208] in autologous BMT; p = 0.44). On the other hand, VOD incidence was significantly lower (8%, 21/250) in patients whose conditioning chemotherapy consisted of CY alone than in those conditioned by other drugs ± CY (21%, 16/76; p = 0.005). Moreover, patients treated before or during 1985 had significantly higher incidence of VOD (15 of 79 patients) than those treated after 1985 (22 of 247 patients, p = 0.02). Multivariate logistic regression analysis revealed that the only independent prognostic factor influencing the occurrence of VOD was the type of conditioning chemotherapy (p = 0.003).

## Discussion

TBI, combined with high-dose chemotherapy and followed by allogeneic or autologous BMT, has become as a widely accepted and relatively effective treatment modality for acute leukemia [1, 3, 10, 24, 49, 54, 55]. TBI plays an important cytoreductive role in this treatment that may be associated with toxicity, especially with the development of IP, VOD, and cataracts [6, 11, 18, 20, 23, 31, 33, 35, 48, 51, 57, 65]. However, patients conditioned with busulfan instead of TBI have earlier toxicity and increased TRM, and especially in adults and patients with advanced disease TBI-containing conditioning regimens are reported to be better [41].

It is a generally accepted fact that leukemic cells and their normal counterparts are highly radiosensitive [27]. Although the data reported over the years generally confirm a high radiosensitivity and low repair capacity of leukemic stem cells, a number of exceptions have also been observed: decreasing the dose rate or increasing the number of fractions could affect the repair capacity of the leukemic cells [28, 39, 50]. The experimental data suggest that a fractionated scheme or low dose rate irradiation would probably be less effective against leukemia than STBI delivering the same dose, or high dose rate TBI [59–61]. However, clinical data do not show a higher incidence of relapse with the use of low dose rate and/or fractionated TBI [10, 26, 36, 55], with the exception of a few reports [44]. On the other hand, 15-Gy hyperfractionated TBI is reported to be more effective in terms of leukemic cell kill than 10-Gy (4 to 7 cGy/min) STBI [46]. Nevertheless, relatively small changes in the TBI dose have been reported to be an influencing factor on mixed hematopoietic chimerism following T-cell-depleted allogeneic BMT, which could influence the relapse rate [12]. Furthermore, it is even reported that hematopoietic recovery after 10-Gy acute TBI in a radiation accident was possible without

BMT [2]. Our data revealed that, when considering the influence of fractionation in all patients, no difference was observed between the STBI and FTBI groups in terms of RI. However, when considering the instantaneous dose rate, patients in the LOW group had higher 5-year RI than those in the MEDIUM (p = 0.03) or HIGH (p = 0.11) groups. Both in the ANLL and ALL group of patients, fractionation did not significantly influence the RI. When considering the instantaneous dose rate separately in the ANLL patients, the 5-year RI was significantly higher in the LOW group than in the MEDIUM group (p = 0.001), whereas the instantaneous dose rate did not seem to influence the RI in ALL patients (Table 2). Malignant cells in ANLL could be more sensitive to the changes in the TBI dose rate than those in ALL, which was also demonstrated by the experimental studies [39, 59]. However, following the adjustment with various prognostic factors, multivariate analyses revealed that the only independent factor significantly influencing the RI was the remission status, either in all patients or separately in ANLL and ALL patients.

Theoretically, the therapeutic index is increased with better preservation of healthy tissues when using low dose rate and/or fractionation [21, 22, 52]. The choice of an optimal TBI regimen depends on several factors, including the technical difficulties (e. g., type and energy of treatment machine, time spent in low dose rate TBI, fractionation taking up the machine time for more than 1 day). When considering the late complications and the TRM, fractionated or hyperfractionated TBI seems to be better than single-dose TBI [15, 20, 45, 47, 48, 51], as well as low dose rate TBI better than high dose rate TBI [3, 4, 40, 58]. In our study, the main causes of TRM were GvHD, IP, VOD, and infections. Animal experiments demonstrated clear improvement in dogs treated with autologous BMT conditioned with fractionated TBI [19]. TBI was reported to be an important factor influencing the TRM. According to Vriesendorp [62, 63], there is an important sparing of normal tissues like lung and intestines to be expected with more fractionated regimens. Clift et al. [13] reported that increasing the dose of fractionated TBI from 12 to 15.75 Gy increased the TRM. The Seattle group [55] observed a significant survival advantage in patients treated with fractionated TBI, with a lower death rate related to non-leukemia related causes. Sutton et al. [51] concluded that the only independent predictive factor influencing the TRM was the TBI regimen (fractionated vs. single dose) in their series of 184 adult acute leukemia patients in first CR trans-

planted with allogeneic BMT. In our series, stepwise multivariate analyses concluded that the TBI regimen was not a significant factor affecting survival and LFS when analyzing either all patients together, or ANLL and ALL patients separately. The same multivariate analysis revealed that the 2 independent predictive factors influencing the TRM rate were the year of BMT and the presence of GvHD, which was strongly related with allogeneic BMT (Table 4). One possible explanation for a lower incidence of TRM in patients treated after 1985 is the GvHD prophylaxis: after 1985, the majority of our patients transplanted with allogeneic BMT received a combination of cyclosporine and methotrexate, which is reported to decrease the incidence of GvHD in several studies [29].

Interstitial pneumonitis is one of the most important post-BMT complications. It involves mostly the pulmonary interstitium as a mononuclear cell infiltration and relatively moderate fluid accumulation. GvHD seems to be the leading cause of IP in patients treated with allogeneic BMT [4, 14, 30, 51, 65]. There is also evidence that IP is influenced independently by the total TBI dose, total dose to the lungs, dose rate, and fractionation. However, irradiation is not the only cause. The International Bone Marrow Transplantation Registry data, in which doses delivered to the lungs and the use or not of pulmonary shielding were not thoroughly analyzed, showed no correlation between the type of TBI used and the incidence of IP [65]. CY given 24 h before or after TBI could also affect the incidence of IP [66], and the effect of CY on radiation pneumonitis seems to be dose dependent [37, 66]. In the randomized trial of the Seattle group [55], the IP incidence was not found to be significantly different between the single-dose (10 Gy in 1 day, 6 cGy/min) and fractionated TBI (2 Gy × 6 fractions, 1 fraction/day) groups. Shank et al. [47, 48] observed a clear decrease in IP incidence with hyperfractionated TBI (15 Gy, 6 to 19 cGy/min, 1.25 Gy 3 times a day) compared to single-dose TBI (10 Gy). Kim et al. [26] compared 2 different TBI regimens in ANLL patients treated with allogeneic BMT. Thirty-six patients were conditioned with STBI (7.5 Gy, 25 cGy/min), and 48 using hyperfractionated TBI (13.2 Gy, 1.65 Gy twice a day, 10 cGy/min). They did not find any difference in IP incidence between the 2 groups. Others have postulated that low dose rate STBI (about 5 to 6 cGy/min) is less toxic [3, 4, 40]. In our previously reported series [36], which was randomized on 2 different instantaneous dose rates in 157 patients with various hematological malignancies, neither dose rate (3 vs. 6 cGy/min in FTBI, 6 vs. 15 cGy/min in

STBI) nor fractionation (STBI vs. 6 × 2 Gy over 3 consecutive days) significantly influenced the IP incidence. GvHD remains an important complication following allogeneic BMT [64], and its incidence does not seem to be related with the TBI regimen. Our present study shows that the 5-year IP incidence was influenced neither by fractionation nor by the type of BMT, but its incidence seemed to be higher in the HIGH group (46%) compared to the MEDIUM (19%, p = 0.05) or LOW (25%, p = 0.15) groups. In the allogeneic BMT group, GvHD influenced significantly the 5-year IP incidence (40% in GvHD+ vs. 18% in GvHD- patients, p = 0.04), and it was the only independent factor involved in the development of IP (p = 0.01) in multivariate analysis. Moreover, in a recent analysis of an homogeneous series of 186 autologous BMT patients, which exclude the effect of GvHD, we reported a significant influence of instantaneous dose rate on the IP incidence, both in the univariate and in multivariate analyses [34].

Among the other numerous complications following BMT, VOD of the liver is an early life-threatening syndrome directly caused by the conditioning regimen, which usually consists of TBI and single- or multiagent high-dose chemotherapy [31]. Several factors like pretherapeutic hepatic condition, the use of different chemotherapeutical agents and the irradiation dose can influence the risk of VOD [31, 32, 34]. Deeg et al. [20] reported a VOD incidence of 52% after 10-Gy STBI vs. 19% after 12-Gy FTBI (p = 0.02). Cosset et al. [15], in their non-randomized comparison between single-dose and fractionated TBI, found a better therapeutic index favoring fractionated TBI in terms of VOD. Others report a decrease in the VOD incidence with a dose rate below 6 cGy/min both in animal experiments [58] and retrospective studies [3]. Ganem et al. [23], in their series of 151 allogeneic BMT patients conditioned with high-dose chemotherapy and STBI (10 Gy, 3 cGy/min), found that the only independent factors influencing the incidence of VOD were high serum transaminase levels before BMT, and female gender. Neither in our previous randomized [36] nor in our non-randomized [8] studies did we observe any influence of TBI regimen on VOD incidence. Furthermore, the type of medical prevention did not have an influence on the latter's incidence.

Cataract formation in the crystalline lens of the eye is a well-recognized complication in patients treated with TBI [7, 11, 18, 26, 33, 57]. Deeg et al. [18], in their series of 181 BMT patients conditioned with

TBI, observed 70 cataracts during a median follow-up period of 47 months for single-dose, and 30 months for fractionated TBI regimens using a dose rate from 4 to 8 cGy/min. The estimated cataract incidence (80% in STBI vs. 19% in FTBI) was significantly different between the 2 groups. Kim et al. [26] observed 15 cataracts from 10 to 60 months (12/36 in STBI, median follow-up: 107 months; 3/48 in hyperfractionated TBI, median follow-up: 27 months) in 84 patients, with a 3-year estimated incidence of 27% in STBI group compared with 12% in the hyperfractionated TBI group (p > 0.05). Calissendorff and Bolme [11] reported that, in their series of 43 pediatric leukemia patients, all children who were followed for at least 3 years (n = 37) developed cataracts following STBI (10 Gy, 4 cGy/min). The Basel group [57] concluded that lens opacification developed later in fractionated TBI patients than in STBI patients, and progression of the lens opacification was slower (p < 0.01). In our prospective study of 157 patients randomized according to instantaneous dose rate both in STBI and FTBI regimens, the instantaneous dose rate and fractionation significantly influenced the 5-year estimated cataract incidence, but multivariate analysis, which took into consideration the influences of fractionation, dose rate, and steroid therapy, revealed that the only independent factor influencing the cataractogenesis was the instantaneous dose rate (p = 0.04) [33]. In our recent evaluation of 494 BMT patients with various hematological malignancies conditioned with either STBI or FTBI, we observed statistically significant differences in terms of 5-year cataract incidence between the STBI (34%) and the FTBI (11%, p = 0.0004) groups, as well as low (3.5%), medium (30%) and high (54%; low vs. medium, p = 0.0001; low vs. high, p < 0.0001) instantaneous dose rate groups [7]. Nevertheless, multivariate analysis revealed the protective effect on eyes of low instantaneous dose rate and intravenous administration of heparin against VOD. In the present series, 25 patients developed cataracts (20 in 190 patients in the STBI group and 5 in 136 patients in the FTBI group) during a median follow-up period of 68 months. When considering the 5-year estimated cataract incidence, in univariate analyses, both fractionation and instantaneous dose rate were found to influence cataract development (Figure 5). The protective effect of heparin [7], which was an interesting finding, could not be observed after the evaluation in multivariate analysis, which revealed that the only independent factor influencing cataractogenesis was the instantaneous dose rate (p = 0.0008).

In this retrospective evaluation of 326 acute leukemia patients, who underwent allogeneic or autologous BMT in their first or second CR and who were conditioned with single-dose or fractionated TBI using different instantaneous dose rates, we conclude that the outcome was not significantly influenced by the TBI technique, and the TRM seemed to be lower in patients treated after 1985 and in those who did not experience GvHD. IP incidence was also significantly influenced by the presence of GvHD. The addition of other drugs to cyclophosphamide in conditioning chemotherapy has been related to increased incidence of VOD of the liver. On the other hand, the cataract incidence was significantly influenced by the instantaneous dose rate.

### References

1. Appelbaum F, L Fisher, ED Thomas. Chemotherapy vs. marrow transplantation for adults with acute nonlymphoblastic leukemia: a five-year follow-up. Blood 1988;72:179–84.
2. Baranov AE, GD Selidovkin, A Butturini et al. Hematopoietic recovery after 10-Gy acute total body irradiation. Blood 1994;83:596–9.
3. Barrett A. Total body irradiation (TBI) before bone marrow transplantation in leukemia: a co-operative study from the European Group for Bone Marrow Transplantation. Br J Radiol 1982;55:562–7.
4. Barrett A, MH Depledge, RL Powles. Interstitial pneumonitis following bone marrow transplantation after low dose rate total body irradiation. Int J Radiat Oncol Biol Phys 1983;9:1029–33.
5. Barrett A, J Nicholls, B Gibson. Late effects of total body irradiation. Radiother Oncol 1987;9:131–5.
6. Baume D, JM Cosset, JL Pico et al. Maladie veino-occlusive du foie après greffe de moelle osseuse: intérêt possible du fractionnement de l'irradiation corporelle totale. Presse Méd 1987;16:1759.
7. Belkacémi Y, M Ozsahin, F Pène et al. Cataractogenesis after total-body irradiation. Int J Radiat Oncol Biol Phys 1996;10:53–60.
8. Belkacémi Y, M Ozsahin, B Rio et al. Is veno-occlusive disease influenced by the total-body irradiation technique. Strahlenther Onkol 1995; 171:694–7.
9. Brauner R, M Fontoura, JM Zucker et al. Growth and growth hormone secretion after bone marrow transplantation. Arch Dis Child 1993; 68:458–63.
10. Brochstein JA, NA Kernan, S Groshen et al. Allogeneic bone marrow transplantation after hyperfractionated total-body irradiation and cyclophosphamide in children with acute leukemia. N Engl J Med 1987; 317:1618–24.
11. Calissendorff BM, P Bolme. Cataract development and outcome of surgery in bone marrow transplanted children. Br J Ophthalmol 1993;77:36–8.
12. Chalmers EA, AM Sproul, KI Mills et al. Effect of radiation dose on the development of mixed haemopoietic chimerism following T cell-depleted allogeneic bone marrow transplantation. Bone Marrow Transplant 1992;10:425–30.
13. Clift RA, CD Buckner, FR Appelbaum et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens. Blood 1991;77:1660–65.
14. Cordonnier C, JF Bernaudin, P Bierling et al. Pulmonary complications occurring after allogeneic bone marrow transplantation: a study of 130 consecutive transplanted patients. Cancer 1986;58:1047–54.
15. Cosset JM, D Baume, JL Pico et al. Single dose versus hyperfractionated total body irradiation before allogeneic bone marrow transplantation: a non-randomized comparative study of 54 patients at the Institut Gustave-Roussy. Radiother Oncol 1989;15:151–60.
16. Cox D. R. Regression models and life tables. J R Stat Soc 1972;34: 187–220.
17. Deeg HJ. Interstitial pneumonitis. In: : Deeg HJ, Klingemann HG, Phillips GL, eds. A Guide to Bone Marrow Transplantation, 2nd edn, Berlin: Springer-Verlag, 1992:175–86.
18. Deeg HJ, N Flournoy, KM Sullivan et al. Cataracts after total body irradiation and marrow transplantation: a sparing effect of dose fractionation. Int J Radiat Oncol Biol Phys 1984;10:957–64.
19. Deeg JH, R Storb, G Longton et al. Single dose or fractionated total body irradiation and autologous marrow transplantation in dogs: effects of exposure rate, fraction size and fractionation interval on acute and delayed toxicity. Int J Radiat Oncol Biol Phys 1988;15:647–53.

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20. Deeg HJ, KM Sullivan, CD Buckner et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission: toxicity and long-term follow-up of patients conditioned with single dose or fractionated total body irradiation. Bone Marrow Transplant 1986;1:151–7.
21. Dutreix J, E Gluckman, JM Brule. Biological problems of total body irradiation. J Eur Radiother 1982;3:163–73.
22. Evans RG, CL Wheatley, JR Nielsen. Modification of radiation-induced damage to bone marrow stem cells by dose rate, dose fractionation, and prior exposure to Cytoxan as judged by the survival of CFUs: Application to BMT. Int J Radiat Oncol Biol Phys 1988;14:491–5.
23. Ganem G, MF Saint-Marc Girardin, M Kuentz et al. Venocclusive disease of the liver after allogeneic bone marrow transplantation in man. Int J Radiat Oncol Biol Phys 1988;14:879–84.
24. Gorin NC, P Aegerter, B Auvert et al. Autologous bone marrow transplantation for acute myelocytic leukemia in first remission: a European survey of the role of marrow purging. Blood 1990;75:1606–14.
25. Kaplan EL, P Meier. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
26. Kim TH, PB McGlave, N Ramsay et al. Comparison of two total body irradiation regimens in allogeneic bone marrow transplantation for acute non-lymphoblastic leukemia in first remission. Int J Radiat Oncol Biol Phys 1990;19:889–97.
27. Kimler BF, CH Park, D Yakar et al. Radiation response of human normal and leukemic hematopoietic cells assayed by in vitro colony formation. Int J Radiat Oncol Biol Phys 1985;11:809–16.
28. Laver J. Radiobiological properties of human hematopoietic and stromal marrow cells. Int J Cell Cloning 1989;7:203–12.
29. Lazarus HM, GB Vogelsang, JM Rowe. Prevention and treatment of acute graft-versus-host disease: the old and the new. A report from the Eastern Cooperative Oncology Group (ECOG). Bone Marrow Transplant 1997;19:577–600.
30. Maraninchi D, JP Vernant, E Gluckman et al. Greffes de moelle allogéniques dans les leucémies aiguës myéloïdes: étude rétrospective chez 111 malades greffés en première rémission complète. Presse Méd 1986;1:2093–96.
31. McDonald GB, P Sharma, DE Matthews et al. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence and predisposing factors. Hepatology 1984;4:116–22.
32. McDonald GB, P Sharma, DE Matthews et al. The clinical course of 53 patients with venocclusive disease of the liver after marrow transplantation. Transplantation 1985;39:603–8.
33. Ozsahin M, Y Belkacémi, F Pène et al. Total-body irradiation and cataract incidence: a randomized comparison of two instantaneous dose rates. Int J Radiat Oncol Biol Phys 1994;28:343–7.
34. Ozsahin M, Y Belkacémi, F Pène et al. Interstitial pneumonitis following bone-marrow transplantation conditioned with cyclophosphamide and total-body irradiation. Int J Radiat Oncol Biol Phys 1996;34:71–7.
35. Ozsahin M. F Pène, JM Cosset et al. Morbidity after total body irradiation. Semin Radiat Oncol 1994;4:95–102.
36. Ozsahin M, F Pène, E Touboul et al. Total-body irradiation before bone marrow transplantation: results of two randomized instantaneous dose rates in 157 patients. Cancer 1992;69:2853–65.
37. Ozsahin M, LH Schwartz, F Pène et al. Is body weight a risk factor of interstitial pneumonitis after bone marrow transplantation? Bone Marrow Transplant 1992;10:97.
38. Peto P, MC Pike, P Armitage et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient: Part II. Br J Cancer 1977;35:1–39.
39. Rhee JG, CW Song, TH Kim et al. Effect of fractionation and rate of radiation dose on human leukemic cells, HL-60. Radiat Res 1985;101:519–27.
40. Ringdén O, I Baryd, B Johansson et al. Increased mortality by septicemia, interstitial pneumonitis and pulmonary fibrosis among bone marrow transplant recipients receiving an increased mean dose rate of total body irradiation. Acta Radiol Oncol 1983;22:423–8.
41. Ringdén O, T Ruutu, M Remberger et al. A randomized trial comparing busulfan with total-body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: A report from the Nordic Bone Marrow Transplantation Group. Blood 1994;83:2723–30.
42. Ryalls M, HA Spoudeas, PC Hindmarsh et al. Short-term endocrine consequences of total body irradiation and bone marrow transplantation in children treated for leukemia. J Endocrinol 1993;136:331–8.
43. Sanders JE, CD Buckner, D Amos et al. Ovarian function following marrow transplantation for aplastic anemia or leukemia. J Clin Oncol 1988;6:813–8.
44. Scarpati D, F Frassoni, V Vitale et al. Total body irradiation in acute myeloid leukemia and chronic myelogenous leukemia: influence of dose and dose-rate on leukemia relapse. Int J Radiat Oncol Biol Phys 1989;17:547–52.
45. Schmidt GM, JC Niland, SJ Forman et al. Extended follow-up in 212 long-term allogeneic bone marrow transplant survivors. Transplantation 1993;55:551–7.
46. Shank B. Hyperfractionation versus single dose irradiation in human acute lymphocytic leukemia cells: application to TBI for marrow transplantation. Radiother Oncol 1993;27:30–5.
47. Shank B, FCH Chu, R Dinsmore et al. Hyperfractionated total body irradiation for bone marrow transplantation: results in seventy leukemia patients with allogeneic transplants. Int J Radiat Oncol Biol Phys 1983; 9:1607–11.
48. Shank B, RJ O'Reilly, I Cunningham et al. Total body irradiation for bone marrow transplantation: the Memorial Sloan-Kettering Cancer Center experience. Radiother Oncol Suppl 1990;1:68–71.
49. Sierra J, A Grañena, J García et al. Autologous bone marrow transplantation for acute leukemia: results and prognostic factors in 90 consecutive patients. Bone Marrow Transplant 1993;12:517–23.
50. Song CW, TH Kim, FM Khan et al. Radiobiological basis of total body irradiation with different dose rate and fractionation: repair capacity of hematopoietic cells. Int J Radiat Oncol Biol Phys 1981;7:1695–1701.
51. Sutton L, M Kuentz, C Cordonnier et al. Allogeneic bone marrow transplantation for adult acute lymphoblastic leukemia in first complete remission: factors predictive of transplant-related mortality and influence of total body irradiation. Bone Marrow Transplant 1993;12:583–9.
52. Tarbell NJ, DA Amato, JD Down et al. Fractionation and dose rate effects in mice: a model for bone marrow transplantation. Int J Radiat Oncol Biol Phys 1987;13:1065–69.
53. Tarbell NJ, EC Guinan, C Niemeyer et al. Late onset of renal dysfunction in survivors of bone marrow transplantation. Int J Radiat Oncol Biol Phys 1988;15:99–104.
54. Thomas ED. The use and potential of bone marrow allograft and whole-body irradiation in the treatment of leukemia. Cancer 1982;50:1449–54.
55. Thomas ED, RA Clift, J Hersman et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission using fractionated or single-dose irradiation. Int J Radiat Oncol Biol Phys 1982;8:817–21.
56. Thomas ED, R Storb, CD Buckner. Total body irradiation in preparation for marrow engraftment. Transplant Proc 1976;8:591–3.
57. Tichelli A. Late ocular complications after bone marrow transplantation. Nouv Rev Fr Hematol 1994;36:Suppl 1:S79–82.
58. Travis EL, LJ Peters, J McNeill et al. Effect of dose-rate on total body irradiation: lethality and pathologic findings. Radiother Oncol 1985;4:341–51.
59. Uckun FM, M Chandan-Langlie, W Jaszcz et al. Radiation damage repair capacity of primary clonogenic blasts in acute lymphoblastic leukemia. Cancer Res 1994;53:1431–6.
60. Uckun FM, CW Song. Lack of CD24 antigen expression in B lineage acute lymphoblastic leukemia is associated with intrinsic radiation resistance of primary clonogenic blasts. Blood 1993;81:1323–32.
61. van Os R, H Thames, AWT Konings et al. Radiation-dose fractionation and dose-rate relationships for long-term repopulating hemopoietic stem cells in a murine bone marrow transplant model. Radiat Res 1993; 136:118–25.
62. Vriesendorp HM. Prediction of effects of therapeutic total body irradiation in man. Radiother Oncol Suppl 1990;1:37–50.
63. Vriesendorp HM. Radiobiological speculations on therapeutic total body irradiation. Crit Rev Oncol Hematol 1990;10:211–24.
64. Wagner JE Jr, GB Voselgang, WE Beschorner. Pathogenesis and pathology of graft vs. host disease. Am J Pediatr Hematol Oncol 1989;11:196–212.
65. Weiner RS, MM Bortin, R P Gale et al. Interstitial pneumonitis after bone marrow transplantation: assessment of risk factors. Ann Intern Med 1986;104:168–75.
66. Yan R., LJ Peters, EL Travis. Cyclophosphamide 24 hours before or after total body irradiation: effects on lung and bone marrow. Radiother Oncol 1991;21:149–56.

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