Thirty-eight patients (median age, 21 years) with acute nonlymphoblastic leukemia (ANLL) (17 patients), acute lymphoblastic leukemia/lymphoma (ALL) (18 patients), chronic myelogenous leukemia (two patients), and refractory anemia received allogeneic bone marrow transplants from HLA-identical sibling donors or a one-antigen-mismatched brother (one patient) after a preparatory regimen consisting of fractionated total body irradiation and high-dose VP 16-213 (60 to 70 mg/kg body weight). Of the 33 patients with acute leukemia who received grafts from HLA-identical donors, three patients with ANLL received transplants in first remission and one patient with standard-risk ALL received a graft while in second remission. All other patients were in more advanced stages of their disease or exhibited other high-risk features. At the time of analysis, 20 of the 33 patients were alive, with 19 of them remaining in continued complete remission for 6 to 35 months (median, 18 months). The 3-year actuarial disease-free survival rate of 56.6% ± 9.7% (SE) and the actuarial relapse rate of 11.9% ± 6.8% (SE) demonstrate that the combination of fractionated total body irradiation and high-dose VP 16 is an effective mode of therapy in patients with advanced leukemias. Preliminary experience cautions against the use of VP 16 instead of cyclophosphamide in any clinical situation carrying an increased risk of graft rejection because the immunosuppressive potency of VP 16 is largely untested but may be inferior to that of cyclophosphamide.

From February 1985 through October 1987, 38 consecutive patients (median age, 21 years; range, 4 to 50 years) were eligible for this study and received an allogeneic marrow transplant after a preparatory regimen consisting of FTBI/VP 16. For one patient with ANLL in second CR his one-HLA-A antigen-mismatched brother served as the marrow donor while another patient with B-ALL in second CR was given a T-cell-depleted marrow graft from her HLA-identical sister. Of the remaining 36 patients who received unfractionated marrow from HLA-identical, mixed leukocyte culture-compatible sibling donors, 16 patients each received grafts for ANLL or ALL, respectively, two patients had marrow transplants for chronic myelogenous leukemia (CML) in accelerated phase, and in one patient each the underlying disease was an immunoblastic lymphoma with involvement of the marrow or refractory anemia (RA).

The pretransplant characteristics of the 33 patients with acute leukemias/lymphoma who received HLA-identical marrow grafts are listed in Tables 1 and 2. Except for two patients with ANLL, induction chemotherapy of all transplant candidates had followed German multicenter study protocols that were active at the time of diagnosis. Risk factors, as quoted in Tables 1 and 2, refer to results of the study in which the individual patient participated. Patients having received two courses of combination chemotherapy without achieving CR were termed induction failures. Refractory relapse refers to patients who after first or subsequent relapse of their original disease did not attain a further CR with one or more multiagent chemotherapies. Twelve of the 16 patients with ANLL were not in first CR when preparation for BMT was begun. The remission status of patient 13 was questionable because repeated marrow aspirations had revealed up to 12% blast cells in the marrow while receiving maintenance therapy. Sixteen of the 17 patients with ALL/lymphoma carried high-risk features before BMT. Patient 18 was the only transplant recipient in second CR who had relapsed more than 2 years after diagnosis and while not receiving maintenance therapy. Further details are given in Tables 1 and 2.

Materials and Methods

Patients. From February 1985 through October 1987, 38 consecutive patients (median age, 21 years; range, 4 to 50 years) were eligible for this study and received an allogeneic marrow transplant after a preparatory regimen consisting of FTBI/VP 16. For one patient with ANLL in second CR his one-HLA-A antigen-mismatched brother served as the marrow donor while another patient with B-ALL in second CR was given a T-cell-depleted marrow graft from her HLA-identical sister. Of the remaining 36 patients who received unfractionated marrow from HLA-identical, mixed leukocyte culture-compatible sibling donors, 16 patients each received grafts for ANLL or ALL, respectively, two patients had marrow transplants for chronic myelogenous leukemia (CML) in accelerated phase, and in one patient each the underlying disease was an immunoblastic lymphoma with involvement of the marrow or refractory anemia (RA).

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Preparative regimen. Patients enrolled in this study received strictly identical radiotherapy and chemotherapy at both institutions involved. TBI was administered from a linear accelerator in six doses of 200 cGy, each at a dose rate of 7 to 12 cGy/min. Fractions were given twice daily on three consecutive days (days -7 to -5) to a total dose of 1,200 cGy. With the aid of individual whole body compensators, lung doses of the 17 most recent transplant patients consisting of cytarabine (40 mg), methotrexate (8 to 12 mg), and prednisolone (50 mg) on days -8 and -3. For patients with more advanced disease and who had no history of severe mucositis. Patients with acute leukemia received triple intrathelial chemotherapy consisting of cytarabine (40 mg), methotrexate (8 to 12 mg), and prednisolone (50 mg) on days -8 to -3. For patients with ALL, these injections were resumed 1 month after BMI and then every 6 weeks until the end of the first year posttransplant. Starting with the VP 16 infusion, blood, urine, and CSF were collected from 15 patients administered 60 or 70 mg/kg of VP 16 to monitor plasma and CNS levels of the drug and to document clearance by renal excretion as described.25

Transplant procedure. Bone marrow was obtained from the donors and administered on day 0 as described previously. The donor marrow was not treated ex vivo except for one patient who received marrow that had been incubated with the monoclonal antibody Campath-1 and donor complement.27 In the case of blood group incompatibility, donor RBCs or plasma was removed from the marrow aspirates by centrifugation.

GVHD and posttransplant care. Prevention of GVHD was attempted by the administration of methotrexate plus methylprednisolone (three patients), cyclosporine A plus methylprednisolone (29 patients), or methotrexate plus cyclosporine A (five patients).28 Acute GVHD was diagnosed and graded according to the criteria of Glucksberg et al. and was primarily treated by steroids. Chronic GVHD was assessed according to previously published criteria and treated with methylprednisolone, cyclosporine A, and azathioprine, as necessary. Patients were nursed either in single-room reverse isolation or in rooms with laminar airflow on the sole basis of room availability. All patients received intravenous (IV) hyperalimentation, oral antifungal, and antibiotics were administered for selective or total GI decontamination.32

Toxicity. Acute toxicity of the FTBI/VP 16 regimen was judged according to the World Health Organization grading system.24 Cytogenetic studies. Thirty-one patients who were sex mismatched or showed differing fluorescent polymorphisms had cytogenetic analyses of direct bone marrow preparations. Eighteen patients also had chromosomal analyses of phytohemagglutinin (PHA)-stimulated peripheral blood cells or T-cell colonies grown early after BMT to document lymphoid chimerism.25

Statistical analyses. Actuarial survival in CCR and the proba-
Table 2. Characteristics and Outcome of 17 Patients With ALL/Lymphoma

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Leukemia Subtype</th>
<th>Disease Status</th>
<th>Blasts in BM (%)</th>
<th>Additional Risk</th>
<th>Survival (d)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17*</td>
<td>22</td>
<td>Pre-B-ALL</td>
<td>1RL R</td>
<td>&gt;95</td>
<td></td>
<td>784+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>Pre-B-ALL</td>
<td>2CR</td>
<td>&lt;5</td>
<td></td>
<td>630+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>19</td>
<td>18</td>
<td>Common ALL</td>
<td>3CR</td>
<td>&lt;5</td>
<td></td>
<td>622+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>T-ALL</td>
<td>1RL R</td>
<td>7</td>
<td>High leucocyte count at diagnosis</td>
<td>615+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>21</td>
<td>16</td>
<td>Null ALL</td>
<td>1RL R</td>
<td>7</td>
<td></td>
<td>581+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>22</td>
<td>25</td>
<td>Common ALL</td>
<td>2RL</td>
<td>50</td>
<td></td>
<td>567+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>23</td>
<td>6</td>
<td>Common ALL</td>
<td>2CR</td>
<td>&lt;5</td>
<td>Early RL</td>
<td>497+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
<td>ALL (Burkitt)</td>
<td>IF</td>
<td>16</td>
<td></td>
<td>490+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>25</td>
<td>21</td>
<td>Common ALL</td>
<td>IF</td>
<td>&gt;95</td>
<td></td>
<td>427+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>26</td>
<td>4</td>
<td>Common ALL</td>
<td>2CR</td>
<td>&lt;5</td>
<td>Early RL</td>
<td>335+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>27</td>
<td>20</td>
<td>T-ALL</td>
<td>2RL</td>
<td>&lt;5</td>
<td>Relapsed in lymph nodes</td>
<td>182+</td>
<td>Alive in CCR</td>
</tr>
<tr>
<td>28</td>
<td>38</td>
<td>Common ALL</td>
<td>3CR</td>
<td>&lt;5</td>
<td></td>
<td>289</td>
<td>Idiopathic IP, death</td>
</tr>
<tr>
<td>29</td>
<td>20</td>
<td>Common ALL</td>
<td>1RL R</td>
<td>69</td>
<td>Ph'-positive</td>
<td>186</td>
<td>Relapsed day 151, death</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>T-ALL</td>
<td>2CR</td>
<td>&lt;5</td>
<td>Early RL</td>
<td>119</td>
<td>CMV-IP, death</td>
</tr>
<tr>
<td>31</td>
<td>23</td>
<td>Pre-B-ALL</td>
<td>1RL R</td>
<td>&gt;95</td>
<td></td>
<td>78</td>
<td>Graft rejection, death</td>
</tr>
<tr>
<td>32</td>
<td>34</td>
<td>Lymphoma†</td>
<td>6CR</td>
<td>&lt;5</td>
<td></td>
<td>62</td>
<td>GVHD, CMV-IP, death</td>
</tr>
<tr>
<td>33</td>
<td>4</td>
<td>T-ALL</td>
<td>1CR</td>
<td>&lt;5</td>
<td>High leucocyte count at diagnosis</td>
<td>12</td>
<td>Pseudomonas septicemia, death</td>
</tr>
</tbody>
</table>

Abbreviation: Ph', Philadelphia chromosome.
*Patients 19 through 21, 25 through 27, 29, and 31 through 33 received 60 mg/kg; patients 17, 18, 22, 24, 28, and 30 received 70 mg/kg of VP 16.
†Immunoblastic lymphoma with marrow involvement.

RESULTS

Toxicity of the preparatory regimen. FTBI/VP 16 is toxic to the mucous membranes. All patients developed severe stomatitis and pharyngolaryngitis necessitating the regular administration of IV narcotics. Abdominal pain and diarrhea lasting longer than two days were noticed in almost half of the patients. In four of them, diarrhea was bloody on at least one occasion. Patient 16 died of acute GI hemorrhage seven days after BMT. Nausea and vomiting were present in all but one patient. In 12 of the 38 patients a mild and transient rash developed that progressed to epidermal desquamation restricted to the palms and soles in four of them. There were two episodes of mild tachycardia or hypotension not requiring medical intervention. Patient 15 became somnolent approximately two hours after the VP 16 infusion had been stopped. He had no other neurologic signs or symptoms, but was noted to have a deterioration of his Karnofsky score from 100% to 70% in the course of his illness.

The computed tomography scan of the brain was normal, and he recovered slowly over the next day. This patient concurrently had developed bronchospasm that may have been caused by VP 16. Five of six patients with grade 2 or greater hepatoxicity had transient elevations of levels of liver enzymes and/or bilirubin. The patient who received a graft for RA experienced irreversible hepatoxicity, with maximum levels of SGPT (1140 U/L) and bilirubin (52 mg/dL) being reached on days 42 and 111, respectively. Liver biopsy specimens taken on day 36 showed cholestasis with minimal hepatocellular damage. This picture, thought to be most compatible with drug-induced hepatoxicity, persisted at necropsy. Thirty patients developed clinical sepsis, ie, temperatures >38°C on two consecutive days, during the first 2 weeks posttransplant. In four cases, the infections became life-threatening, and patients 15 and 33 along with one of the patients who received a graft for CML died 12, 13, and 20 days after BMT of pneumonia of unknown origin (two patients) or Pseudomonas septicemia. The acute toxicity data are summarized in Table 3. Toxicity did not significantly differ between patients receiving 60 or 70 mg/kg of VP 16, although there was a tendency for the more severe side effects to occur in patients administered 70 mg/kg. So far, long-term regimen-specific toxicities have not been encountered.

Informed consent. The treatment protocol was approved by institutional review boards at the Universities of Kiel and Ulm. The transplant procedure and the attendant risks were explained in detail to the patients and their families, after which a signed consent form was obtained from the patient and the donor or their legal guardians.
with CML could not be evaluated for engraftment because they died before day 20 after BMT. Three of the remaining 34 patients rejected their marrows: patient 31, who received a graft for refractory ALL; the patient who was administered T-depleted marrow; and the patient who received unmanipulated marrow from his one-antigen–mismatched brother. Thirty-one patients showed complete and sustained engraftment. They achieved a WBC level of 0.5 and 1.0 × 10^9/L at a median of 12 days (range, 10 through 23) and 14 days (range, 11 through 29), respectively. The median time to reach a self-sustaining platelet count of 20 × 10^9/L was 18 days (range, 11 through 31).

The degree of chimerism was assessed primarily by chromosomal analyses. Thirty-one evaluable patients had one to five cytogenetic analyses of bone marrow cells aspirated between 13 and 465 days posttransplant. PHA-stimulated peripheral blood cells and/or T-cell colonies were analyzed in 18 patients between days 23 and 465. In the marrow of patients 23 and 32, one of 21 and one of 61 mitoses, respectively, were found to be of host origin 15 or 56 days posttransplant. Follow-up studies of these patients as well as repeated analyses of all other evaluable patients showed exclusively donor cells. The cytogenetic analyses of peripheral blood cells showed host cells in nine of 18 patients (days 14 to 171; median, 43 days). This included the patient receiving a T-depleted marrow graft and patient 31, who both ultimately rejected their grafts. Four of the remaining patients had cleared their peripheral blood of residual host cells on subsequent testing, one patient relapsed shortly after the first analysis, and the other two patients have not yet been reevaluated. In the recipient of mismatched marrow, transient engraftment of donor cells was documented by HLA typing of peripheral blood cells.

**Engraftment.** Patients 15, 16, 33, and one of the patients with CML could not be evaluated for engraftment because they died before day 20 after BMT. Thirty of the remaining 34 patients rejected their marrows: patient 31, who received a graft for refractory ALL; the patient who was administered T-depleted marrow; and the patient who received unmanipulated marrow from his one-antigen–mismatched brother. Thirty-four patients showed complete and sustained engraftment. They achieved a WBC level of 0.5 and 1.0 × 10^9/L at a median of 12 days (range, 10 through 23) and 14 days (range, 11 through 29), respectively. The median time to reach a self-sustaining platelet count of 20 × 10^9/L was 18 days (range, 11 through 31).

Fifteen of 28 patients (54%) surviving more than 100 days after BMT developed chronic GVHD. It was graded as limited disease in nine patients; extensive disease was diagnosed in six patients. Chronic GVHD has resolved without sequelae in six patients, while eight patients are currently responding to low-dose steroids and/or cyclosporine A. Patient 3 is severely disabled by extensive chronic disease involving the skin and joints but is slowly improving with cyclosporine A, steroid, and symptomatic treatment.

**Antileukemic effect.** Bone marrow aspirations were carried out 14, 28, 56, 100, and 356 days after BMT and at any time when a deteriorating peripheral blood count suggested the recurrence of leukemia. CR was documented in all 34 patients who had at least one marrow aspiration after BMT. This includes 13 patients who were refractory to either primary treatment or to later attempts to reinduce remission before BMT. Two patients with ANLL (patients 9 and 11) relapsed on days 69 and 106, respectively. The latter patient succumbed to his disease on day 122, while patient 9 currently is alive with symptomatic therapy. Of the 17 patients who received grafts for ALL, patient 29 with refractory Ph1-positive common ALL relapsed 151 days posttransplant and died of infection on day 186. This added to an actuarial relapse rate of 11.9% ± 6.8% (SE) for all 33 patients with acute leukemia who received grafts from HLA-identical donors (Fig 1). In addition, one of the patients who received a graft for CML in accelerated phase relapsed 371 days after BMT. Thus, the actuarial relapse rate for the entire group of 36 recipients of unmanipulated marrow from HLA-identical donors was 17.2% ± 4.0% (SE) (Kaplan-Meier plot not shown).

**Survival and causes for failure.** As of February 1, 1988, 20 of the 33 patients with acute leukemias listed in Tables 1 and 2 were alive, with 19 of them remaining in CCR for 6 to more than 35 months (median, 18 months). As shown in Fig 1, the actuarial disease-free survival (DFS) rate for this group was 56.6% ± 9.7% (SE). Exclusion of patients 4, 7, and 10, who received grafts for ANLL in first CR, and patient 18 with standard-risk ALL did not alter the DFS rate (56.8% ± 11.0%). Patients who received grafts for ALL had an actuarial DFS rate of 63.7% ± 14.3% (SE) as opposed to...
54.2% ± 13.2% in patients with acute myelogenous leukemia (P > .05). DFS did also not significantly differ for patients administered 60 or 70 mg/kg of VP 16 (P > .05). Thirteen patients died between seven and 289 days after grafting. Six patients died of interstitial pneumonia, which was associated with CMV infection in five cases. Three patients experienced lethal infections (septicemia, pneumonia, and meningitis), two patients died of recurrent leukemia, and one patient died of intractable GI bleeding. Patient 31 rejected the graft and eventually died of pneumonia.

Of the three patients with HLA-identical donors who did not receive grafts for acute leukemia, one patient with CML relapsed 371 days after BMT but is alive with standard chemotherapy, and the other patient with CML as well as the patient with RA died of pulmonary problems (IP and acute respiratory distress syndrome [ARDS]) 20 and 113 days posttransplant. The actuarial DFS rate for all 36 patients receiving unfractionated marrow from HLA-identical donors was 51.1% ± 9.7% (SE) (Kaplan-Meier plot not shown). The patients receiving T-depleted marrow or marrow from an HLA partially mismatched donor both rejected their grafts and died of IP and aspergillosis of the brain, respectively.

**Pharmacokinetics of high-dose VP 16.** A linear relationship between the total administered dose of VP 16 and the peak plasma level as well as the total area under the curve has been established.

It is noteworthy that extremely high plasma levels, >200 μg/mL, were detected in patients given 60 or 70 mg/kg body weight of VP 16. CSF levels determined between one and 24 hours after the VP 16 infusion ranged from 0.7% to 1.0% of the corresponding plasma level. A report describing the full pharmacokinetics of VP 16 in 15 patients administered 60 or 70 mg/kg of the drug is in preparation (Holthuis et al).

**DISCUSSION**

FTBI/VP 16 exerts an excellent antileukemic effect in patients proceeding to allogeneic marrow transplantation. An actuarial relapse rate of 11.9% at 3 years is unexpectedly low for a group of patients mostly suffering from advanced and partly refractory acute leukemias. After a similar observation period, Blume et al reported a relapse rate of 32% for a cohort of 33 patients with ANLL and ALL in late remission or relapse who were prepared by hyperfractionated or single-dose TBI and escalating doses of VP 16 of 25 to 70 mg/kg. A meaningful comparison with our results surely is not possible because the pretransplant characteristics of the patients, the TBI regimens, and the VP 16 dose differed in both studies. Despite these shortcomings, it is tempting to speculate that the higher doses of VP 16 used in most of our patients contributed to the lower relapse rate observed. In this context it was important to realize that not only were very high peak plasma concentrations of VP 16 achieved but also elimination of the drug was relatively slow, with effective plasma levels (>1 μg/mL) being preserved for approximately 32 hours. Furthermore, although the CSF levels found in our patients appear relatively low, they may be active against residual CNS leukemia because clear responses have been documented in patients with brain metastases of small cell lung cancer with even lower CSF levels.

Patients with acute leukemia who did relapse after preparation with FTBI/VP 16 were in frank relapse, with 35%, 69%, and >95% of blast cells in the marrow before grafting. Moreover, they were refractory to conventional chemotherapy or had achieved CR for a very short period of time after previous attempts had failed. Although three or four patients with relapse suffered from myelogenous leukemias, the small numbers preclude a definite statement as to whether the FTBI/VP 16 regimen might be especially effective in patients with lymphocytic leukemia.

Of the 33 patients who received grafts for acute leukemias, 57% are alive in CCR. This, on the one hand, reflects the high antileukemic potency of the FTBI/VP 16 regimen and, on the other hand, demonstrates that this effect was achieved without unacceptably high toxicity. Nevertheless, toxicity in this heavily pretreated group of patients was apparent. Apart from the nonlethal complications summarized in Table 3, four of 38 patients (11%) died within the first 20 days after BMT of infectious complications or GI bleeding. Another patient dying 113 days posttransplant of ARDS suffered from irreversible liver failure, presumably due to the preparatory regimen. Patients who receive grafts early in the course of their disease tolerate the FTBI/VP 16 regimen much better (unpublished observation, 1987). In such instances it may well be possible to administer 70 mg/kg of VP 16 without major toxicity. For patients with advanced leukemias who most urgently need a regimen with vigorous antileukemic properties, we cannot, however, recommend the use of doses exceeding 60 mg/kg because increasing toxicity may outweigh the benefits of a presumably stronger antileukemic effect.

Both patients receiving either T-cell–depleted marrow from an HLA-identical donor or an unmanipulated graft from a mismatched donor rejected their marrow and died of infectious complications. We are aware of at least two further transplant recipients at the West German Tumor Center Essen who failed to show engraftment with partially mismatched unfractionated marrow (U.W. Schäfer, personal communication, 1987) after preparation with the FTBI/VP 16 regimen. If the results of this and Blume’s study are combined, two of 83 patients given unmanipulated marrow from matched sibling donors have also rejected their grafts. This might indicate an increased risk of graft failures with the FTBI/VP 16 regimen even in the HLA-identical situation. The animal data generated by our group, which clearly demonstrate that the immunosuppressive potency of VP 16 is inferior to that of cyclophosphamide when both drugs are administered at clinically relevant doses to the busulfan-treated rat, add to this suspicion. Therefore, clinical and experimental data would at the moment argue against the use of the FTBI/VP 16 regimen in any clinical setting bearing an increased risk of graft rejection, eg, mismatched marrow transplants, T-cell–depleted marrow grafts, or transplants from unrelated donors.

Although the results of this study are encouraging, it cannot be stated that the FTBI/VP 16 protocol is superior to the standard combination of TBI and cyclophosphamide. More recent studies of alternative regimens using hyperfrac-
tiated TBI and cyclophosphamide or combinations of busulfan and cyclophosphamide also deserve further attention. Only prospective randomized trials comparing the FTBI/VP 16 regimen with the standard combination of cyclophosphamide and TBI or any of the newer preparatory regimens will result in an unbiased evaluation of the antileukemic efficacy of either protocol.

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Fractionated total body irradiation and high-dose VP 16-213 followed by allogeneic bone marrow transplantation in advanced leukemias

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