

# Randomized Study to Evaluate the Use of High-Dose Therapy as Part of Primary Treatment for “Aggressive” Lymphoma

Ulrich Kaiser, Irmgard Uebelacker, Ulrich Abel, Josef Birkmann, Lorenz Trümper, Harald Schmalenberg, Tunca Karakas, Bernd Metzner, Dieter K. Hossfeld, Helge G. Bischoff, Astrid Franke, Marcel Reiser, Peter Müller, Luisa Mantovani, Marc Grundeis, Frank Rothmann, Cay-Uwe von Seydewitz, Rolf M. Mesters, Ernst U. Steinhauer, Dorothea Krahl, Kurt Schumacher, Michael Kneba, Michael Baudis, Norbert Schmitz, Rüdiger Pfab, Hubert Köppler, Reza Parwaresch, Michael Pfreundschuh, and Klaus Havemann

**Purpose:** This trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group compares the use of high-dose therapy (HDT) as part of primary treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus etoposide followed by involved-field (IF) radiotherapy in a randomized, multicenter, phase III study.

**Patients and Methods:** Three hundred twelve patients with “aggressive” non-Hodgkin's lymphoma aged  $\leq 60$  years with elevated serum lactate dehydrogenase levels were included from 1990 to 1997. Patients with at least a minor response after two cycles of CHOEP (CHOP + etoposide  $3 \times 100 \text{ mg/m}^2$ ) were to receive three further cycles of CHOEP followed by IF radiotherapy (arm A) or one further cycle of CHOEP followed by autologous stem-cell transplantation and IF radiotherapy (arm B).

**Results:** Among 158 patients randomized to arm B, 103 (65%) received HDT. The complete remission rate at the

end of treatment was 62.9% in arm A and 69.9% in arm B. With a median observation time of 45.5 months, overall survival for all 312 patients was 63% after 3 years (63% for arm A, 62% for arm B;  $P = .68$ ). Event-free survival was 49% for arm A versus 59% for arm B ( $P = .22$ ). Relapse in arm B was associated with a significantly worse survival rate than relapse in arm A ( $P < .05$ ). Relapse after HDT occurred early (median interval, 3 months). Six patients developed secondary neoplasia, three in arm A and three in arm B.

**Conclusion:** Results of the randomized trial comparing CHOP-like chemotherapy with early HDT do not support the use of HDT with carmustine, etoposide, cytarabine, and melphalan following shortened standard chemotherapy.

*J Clin Oncol* 20:4413-4419. © 2002 by American Society of Clinical Oncology.

WITH CONVENTIONAL chemotherapy, long-term remission can be achieved in approximately 50% of patients with disseminated “aggressive” lymphoma.<sup>1</sup> The landmark intergroup study revealed that cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) can still be regarded as the international standard.<sup>2</sup> Since the early 1980s, however, data have appeared that indicate that high-dose therapy (HDT) with autologous stem-cell transplantation may be superior to conventional therapy in selected younger patients with aggressive lymphoma. Phase I/II studies, initially performed with autologous bone marrow transplantation, suggested promising results with stable remissions in 70% to 80% of the patients.<sup>3</sup> Treatment-related mortality was around 5%. The use of autologous peripheral-blood stem cells and improvements in supportive care have further diminished treatment-related mortality. In patients with relapsed lymphoma, results of the trial conducted by the Parma study group have shown that high-dose chemotherapy in sensitive relapse may be superior to conventional salvage treatment.<sup>4</sup> However, in primary aggressive lymphoma, the role of HDT and its optimal timing have still not been determined.

In the German High-Grade Lymphoma Study Group, CHOEP (standard CHOP + etoposide) has been established as an effective regimen. In a phase II study recruiting patients from 1982 to 1985, CHOEP followed by involved-field radiation was shown to induce complete remission (CR) rates in 82% of 60 enrolled patients, leading to a 5-year event-free survival rate of 55%.<sup>5</sup> In the subsequent phase III study launched in 1986, four cycles of CHOEP were compared with a sequential therapy consisting of an escalating CHOP regimen alternating with ifosfamide, vincristine, etoposide, and prednisone, followed by involved-field radiation in both arms.<sup>6</sup> The CR rate was 85%, and event-free survival rates were 59% and 55% after 2 and 5 years,

respectively, for both groups without any statistically significant difference underlining the efficacy of the CHOEP regimen. Serum lactate dehydrogenase (LDH) was the strongest prognostic parameter. The 2-year survival rate was 84% for patients with normal LDH versus 55% for patients with elevated LDH ( $P < .001$ ).

These experiences led us to conceive the subsequent trial to determine the value of high-dose chemotherapy followed by

---

*From the Departments of Hematology and Oncology, Universitätsklinikum Marburg, Klinikum Nürnberg, Universitätsklinikum Homburg, Universitätsklinikum Jena, Universitätsklinikum Ulm, Klinikum Oldenburg, Universitätsklinikum Hamburg, Thoraxklinik Heidelberg-Rohrbach, Universitätsklinikum Magdeburg, Universitätsklinikum Köln, Zentralklinikum Augsburg, Universitätsklinikum Leipzig, Universitätsklinikum Leipzig, Klinikum Chemnitz, Klinikum Potsdam, Krankenhaus Hamburg-Altona, Universitätsklinikum Münster, Klinikum Kassel, Humboldt-Universität Berlin, Robert-Bosch Krankenhaus Stuttgart, Universitätsklinikum Göttingen, Universitätsklinikum Heidelberg, Universitätsklinikum Kiel, Klinikum Minden, Universitätsklinikum Rostock, Universitätsklinikum Zürich, Klinikum Karlsruhe, Klinikum Hagen, Klinikum Herford, Klinikum Lemgo, Universitätsklinikum Lund, Klinikum Mönchengladbach, Universitätsklinikum Uppsala, Universitätsklinikum Aachen, Diakonissenkrankenhaus Bremen, Klinikum Cottbus, Klinikum Darmstadt, Klinikum Eschweiler, Diakoniekrankenhaus Freiburg, Klinikum Münchberg, Klinikum Schweningen, Klinikum Schweinfurt, Klinikum Trier, and Klinikum Wolfsburg; the Institute of Medical Statistics, Universität Heidelberg; and the Institute of Hematopathology, Universität Kiel, Germany.*

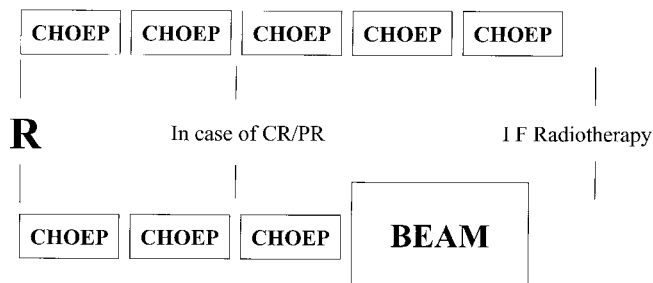
*Submitted July 16, 2001; accepted July 31, 2002.*

*Supported by grant no. 70-339 from the Deutsche Krebshilfe.*

*Address reprint requests to Ulrich Kaiser, MD, St Bernward Krankenhaus, Klinik für Hämatologie, Onkologie und Immunologie, Treibestr. 9, D-31134 Hildesheim, Germany; email: pd.dr.u.kaiser@bernward-khs.de.*

*© 2002 by American Society of Clinical Oncology.*

*0732-183X/02/2022-4413/\$20.00*



**Fig 1. Treatment schema: arm A, five cycles of CHOEP followed by involved-field (IF) radiotherapy; arm B, three cycles of CHOEP followed by high-dose BEAM therapy and IF radiotherapy**

autologous stem-cell transplantation. Patients under the age of 61 years with the elevated LDH risk factor were randomized to receive either five courses of CHOEP or three courses of CHOEP followed by high-dose chemotherapy and autologous bone marrow/peripheral stem-cell transplantation. In both arms, patients were to receive involved-field radiotherapy with a total dose of 36 Gy (single dose of 1.8 Gy/d). Here, we report the results of this prospective multicenter study.

## PATIENTS AND METHODS

### Patients

Eligible patients had to have a histologic diagnosis of a high-grade (aggressive) lymphoma according to the Kiel classification<sup>7</sup> (except for lymphoblastic lymphoma in patients under the age of 35 years; histologic diagnosis had to be confirmed by an expert panel), age 18 to 60 years, stage II to IV disease according to the Ann Arbor classification of malignant lymphomas, and serum LDH level above the normal value. They also had to provide informed consent. Staging included a physical examination, an assessment of laboratory status, a chest x-ray, computed tomography scan of the thorax and abdomen, and a bone marrow biopsy. Lumbar puncture was performed in patients with lymphoblastic or Burkitt's lymphoma or in case of suspected neurologic involvement. Serum LDH level had to be determined within 3 days before staging; hemolytic anemia had to be excluded. Further investigations (eg, bone scan, endoscopy) were to be performed if deemed necessary by the individual investigator.

### Treatment Plan

Patients were stratified according to age (< 50 v > 50 years), LDH level (< 400 v > 400 U/L), and disease stage (II/III v IV) and randomized before the first cycle to receive either five cycles of CHOEP (arm A) or three cycles of CHOEP plus HDT (arm B). The trial schema is outlined in Fig 1. Because a number of deaths occurred in patients with heavy tumor load during the first cycle, the steering committee recommended in 1994 that patients with serum LDH levels greater than two times normal undergo cytoreduction with vincristine (2 mg) and prednisone (100 mg/d) before the first cycle. CHOEP consisted of cyclophosphamide 750 mg/m<sup>2</sup> on day 1, doxorubicin 50 mg/m<sup>2</sup> on day 1, vincristine 2 mg on day 1, etoposide 100 mg/m<sup>2</sup> on days 1 to 3, and prednisone 100 mg on days 1 to 5. Treatment was repeated on day 22. Patients were restaged after two cycles in each treatment arm. If at least a minor response was achieved, treatment continued according to the protocol. In treatment arm A, patients received three additional CHOEP cycles. In arm B, patients received one additional cycle followed by HDT with carmustine 300 mg/m<sup>2</sup> on day -5, etoposide 100 mg/m<sup>2</sup> on days -5 to -2 (twice daily), cytarabine 200 mg/m<sup>2</sup> on days -5 to -2 (twice daily), and melphalan 140 mg/m<sup>2</sup> on day -5 (BEAM) followed by autologous stem-cell transplantation within 28 days after the third cycle. Patients were restaged after completion of chemotherapy. In both treatment arms, in case of at least partial remission (PR), patients were to receive involved-field radiotherapy to a total dose of 36 Gy.

### Stem-Cell Collection

Stem cells were collected by bone marrow aspiration according to standard procedure or by separation of peripheral stem cells after prior mobilization

with granulocyte colony-stimulating factor in a dosage of 10 μg/kg after treatment cycles 2 or 3. There were no recommendations concerning the source of stem cells. At the time of initiation in 1990, most patients received autologous bone marrow. Since 1994, peripheral stem cells have been the source of choice. No purging procedures were required or recommended.

### Evaluation of Response

Response after two cycles of CHOEP was defined as any reduction in tumor size. CR required the disappearance of all tumors detectable by clinical examination, imaging, biochemical analysis, or biopsy. PR was defined as a reduction of ≥ 50% in all measurable manifestations and the absence of new lesions. Stable disease was defined as less than PR but no signs of progression. Progressive disease required a greater than 50% increase of any previously identified abnormal node for PR or nonresponders or the appearance of any new lesion during or at the end of therapy.

### Study Design

The trial was planned as a phase III, randomized, multicenter trial. Seventy-one centers in Germany (n = 68), Switzerland (n = 1), and Sweden (n = 2) participated, among them 25 university hospitals, 37 teaching hospitals, and nine county hospitals. Randomization was carried out centrally by the Institute of Medical Statistics, University of Heidelberg. The patient recruitment was initiated in 1990 and concluded in June 1997. The original protocol called for a sample of 200 patients. In September 1995, based on a review of preliminary results and conditional power calculation, an independent advisory board consisting of four clinicians and biostatisticians not involved in the trial made the decision to extend the recruitment to 300 patients. Neither the interim results nor the reasons for the decision were disclosed to the members of the study group.

### Statistical Analysis

Data were analyzed using Statistical Analysis System software, version 6.12 (SAS Institute, Cary, NC). For failure-time distributions, such as the survival time or event-free survival time, we generated Kaplan-Meier curves and used log-rank statistics. In agreement with the study protocol, the *P* values reported for the comparison of survival or event-free survival data were one-tailed. All other *P* values were two-tailed.

Overall survival was the main end point. As described below, 19 patients were excluded after randomization. We believe the exclusion to be justified because (1) the reasons for exclusion had been specified in advance and did not create an arbitrary imbalance and (2) the exclusion reflected clinical reality, as the treatment protocol of this study, particularly HDT, did not apply to these patients. Therefore, all analyses were restricted to the subset of the remaining 312 patients.

## RESULTS

### Patient Characteristics

Between August 1990 and June 1997, 331 patients were registered onto the study. Before the start of therapy or during the first cycle, 19 of the randomized patients were found to violate the entry criteria of the study and were therefore excluded. Of these, 13 patients had been assigned to arm A and six to arm B. The protocol violations were as follows: change of histologic diagnosis by the reference hematopathologist (Hodgkin's disease, n = 4; solid tumor, n = 4; low-grade lymphoma, n = 1), diagnosis of a secondary high-grade lymphoma (n = 2), bone marrow infiltration greater than 25% (n = 3), diagnosis of secondary malignancies at the time of randomization (n = 1), age less than 18 years (n = 1), withdrawal of consent immediately after registration (n = 1), proven human immunodeficiency virus infection (n = 1), and treatment according to a leukemia protocol after randomization because of extensive bone marrow infiltration (n = 1). Among the remaining 312 patients, 154 were randomized to arm A and 158 to arm B. Patient characteristics are outlined in Table 1. Median age

**Table 1. Patient Characteristics**

	Arm A (n = 154)	Arm B (n = 158)
Sex		
Male	56	54
Female	44	46
Stage		
II	36	34
III	25	31
IV	38	35
Age		
< 50 years	63	65
51-60 years	37	35
LDH		
< 400 U/L	50	50
> 400 U/L	50	50
Performance status > 2	13	16
Bulky disease	58	61
Histologic diagnosis		
Centroblastic lymphoma	49	52
Immunoblastic lymphoma	12	6
Large-cell mediastinal lymphoma	16	9
Lymphoblastic lymphoma	3	5
Anaplastic large-cell lymphoma	10	9
Burkitt's lymphoma	2	6
T-cell lymphoma	4	3
Other	4	10

was 46 years (range, 19 to 60 years) in treatment arm A and 45 years (range, 19-60 years) in arm B. Median age of the whole study population was 46 years.

Patients were retrospectively classified according to the age-adjusted International Prognostic Index.<sup>8</sup> In arm A, 26% of the population were grouped as low intermediate, 55% as high intermediate, and 20% as high risk; in arm B, 26% were grouped as low intermediate, 50% as high intermediate, and 24% as high risk (Table 2).

The Revised European-American Lymphoma classification was retrospectively applied to all cases.<sup>9</sup> The distribution of the histologic subtypes was as follows (arm A v arm B): 61% versus 58% diffuse large B-cell lymphoma (centroblastic + immunoblastic), 16% versus 9% primary mediastinal large B-cell lymphoma, 10% versus 9% anaplastic large-cell lymphoma, 5% versus 11% lymphoblastic or Burkitt's lymphoma, and 4% versus 3% peripheral T-cell lymphoma.

#### Induction Treatment

After two cycles of CHOEP, a formal restaging was performed. In treatment arm A, the two cycles of CHOEP were given to 152 patients (98.7%); in arm B, they were given to 150 patients (94.9%). After two cycles of CHOEP, 298 patients (93%) achieved at least a minor response. Fourteen patients (7%), five in arm A and nine in arm B, had either no response or had progressive disease and were therefore taken off protocol.

During the induction phase, five patients died, four patients after the first cycle and one patient after the second cycle.

#### Consolidation Treatment

In treatment arm A, the three consolidation courses after two cycles of CHOEP were given in 137 patients (89%). In treatment arm B, HDT was administered to 103 (65%) of the 158 assessable patients. In 94 of these patients, HDT was administered according to protocol guidelines after a third cycle of CHOEP; in nine cases, there were deviations from the protocol (application of further CHOEP cycles in five patients, further cycles of dexamethasone, carmustine, etoposide, cytarabine, and melphalan in patients cases, and mobilization therapy with cyclophosphamide in one patient). In 54 patients (35%), HDT was not administered for the following reasons: lack of response or progressive disease before the planned HDT (n = 19 and therefore exclusion according to the protocol), patient denial (n = 14), concomitant diseases (n = 4), toxicity after previous chemotherapy (n = 5), failure to mobilize peripheral stem cells (n = 2), and other (n = 7). Three patients in arm B died during induction treatment. In 20 patients (19%), HDT was followed by reinfusion of autologous bone marrow; in 82 patients (81%), peripheral stem cells were used for transplantation. One additional patient received blood stem cells and bone marrow. The median number of CD34-positive cells was  $5.7 \times 10^6$  per kilogram of body weight (range, 1.4 to  $24.3 \times 10^6$  per kilogram of body weight).

#### Radiotherapy

Data on radiotherapy were available for 154 patients in arm A and 154 patients in arm B. Radiotherapy was completed in 107 patients (69%) randomized to arm A and in 82 patients (53%) randomized to arm B. In both arms, the main reason for not administering radiotherapy was treatment failure. In arm A, radiotherapy was not administered to 43 patients (28%). The main reason was insufficient response (23 patients) followed by patient's wishes or patient's refusal (four patients) and concomitant disease (four patients). In four patients (3%), radiotherapy was stopped because of disease progression or relapse (three patients) and side effects (one patient). In nine patients, radiotherapy was completed but interrupted because of toxicity. In the high-dose arm, radiotherapy was not administered to 55 patients (36%) and was stopped in 17 patients (11%). The major reasons for not administering radiotherapy were insufficient response (27 patients) followed by hematopoietic insufficiency (particularly thrombocytopenia, 15 patients) and patient denial (three patients). The main reason for abrogation of radiotherapy in treatment arm B was hematopoietic insufficiency (11 patients), particularly thrombocytopenia, followed by disease progression or relapse (five patients). In nine patients, radiotherapy was completed but it was interrupted because of toxicities. The median time interval between BEAM and radiotherapy had been planned to be 6 weeks after hematologic recovery, according to

**Table 2. Classification of Patients According to the International Prognostic Index**

Risk	Arm A		Arm B		Total	
	No.	%	No.	%	No.	%
Low intermediate	39	26	41	27	80	26
High intermediate	83	55	69	45	152	50
High	30	20	43	28	73	24

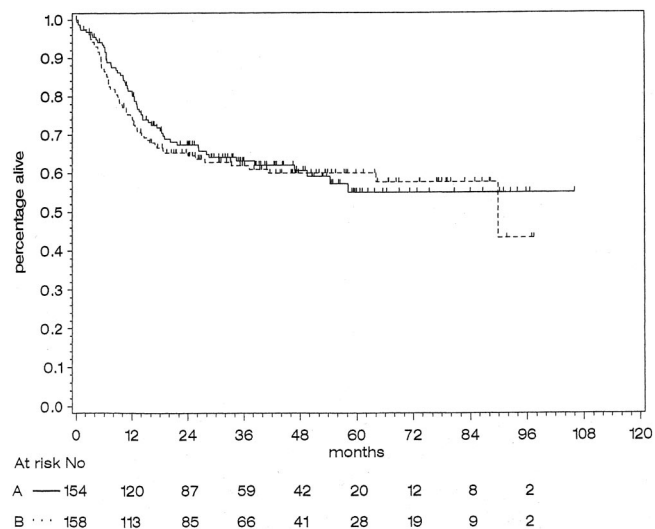


Fig 2. Overall survival after 3 years for all patients.

the protocol. In fact, it was 59 days (range, 14 to 154 days). Overall, 102 patients (66%) in arm A and 73 patients (47%) in arm B received radiotherapy without interruption.

#### Treatment Results

The median observation time was 45.6 months.

**Response.** For the entire patient population ( $n = 312$ ), the CR rate at the end of treatment was 66.3% ( $n = 207$ ) and the PR rate was 16.6% ( $n = 42$ ). In arm A, the CR rate was 62.9% ( $n = 97$ ) and the PR rate 22.7% ( $n = 35$ ); in arm B, the CR rate was 69.9% ( $n = 110$ ) and the PR rate was 10.7% ( $n = 17$ ).

**Survival.** The 3-year survival rate was 63% in arm A versus 62% in arm B. The difference was not statistically significant ( $P = .68$ , one-tailed log-rank test, Fig 2). The 3-year event-free survival rate was 49% in arm A versus 59% in arm B (Fig 3). The difference was not statistically significant ( $P = .22$ , one-tailed log-rank test). Event-free survival and overall survival for patients with high intermediate and high risk factors according to the International Prognostic Index did not reveal statistically significant differences (Figs 4 and 5). After patients with

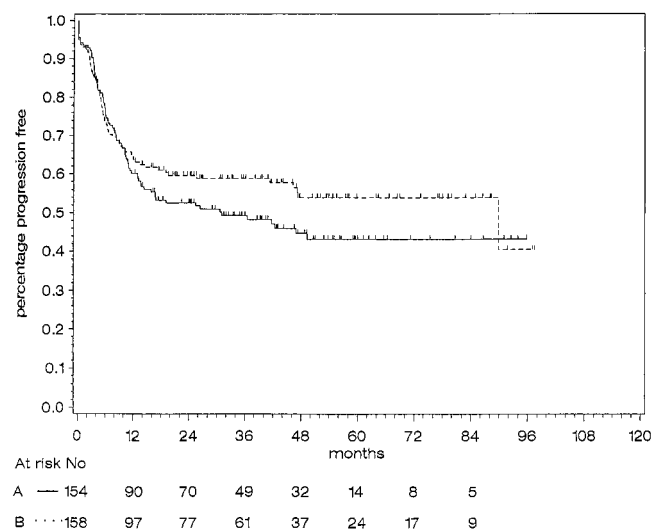


Fig 3. Event-free survival after 3 years for all patients.

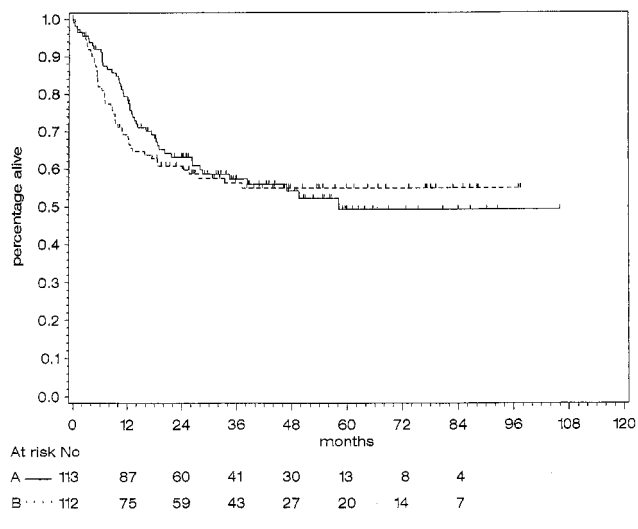


Fig 4. Overall survival after 3 years for patients classified as high intermediate and high risk according to the International Prognostic Index.

Burkitt's lymphoma and lymphoblastic lymphoma were excluded, there was still no advantage for the HDT with regard to survival ( $P = .95$ ) and event-free survival ( $P = .12$ ). Survival curves for this subgroup of 290 patients is shown in Figs 6 and 7.

Among patients who received HDT, the median time to neutrophil recovery greater than  $500/\mu\text{L}$  was 10 days (range, 5 to 56 days); the median time to platelet recovery  $20,000/\mu\text{L}$  was 11 days (range, 0 to 150 days). Median stay in hospital after HDT was 16.5 days (range, 10 to 78 days).

**Relapse pattern.** Among the 132 patients in arm A who received the whole chemotherapy protocol and reached PR or CR, relapse or disease progression was documented in 61 patients (46%). In 16 (28%) of these patients, relapse or progression occurred exclusively in sites of previous tumor involvement; in 16 (28%) of the patients, it occurred exclusively in previously noninvolved sites; and in 26 (45%) of the patients, it occurred in new and previously involved sites. In three patients, the relapse pattern could not be determined conclusively.

In arm B, 28 patients (27%) relapsed among the 103 patients who received the whole treatment plan including HDT. Among

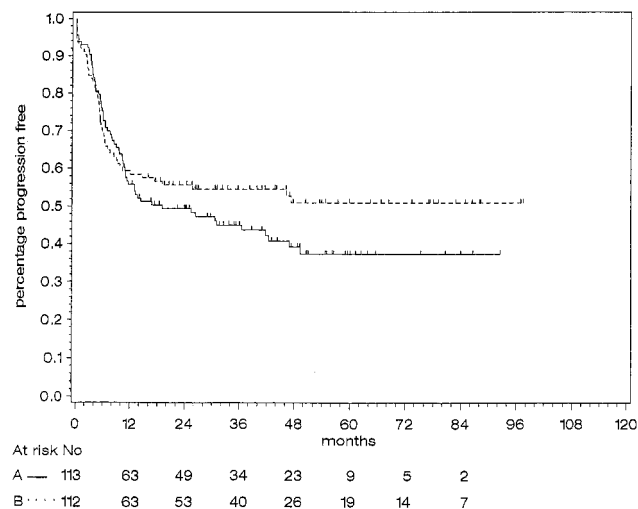


Fig 5. Event-free survival after 3 years classified as high intermediate and high risk according to the International Prognostic Index.

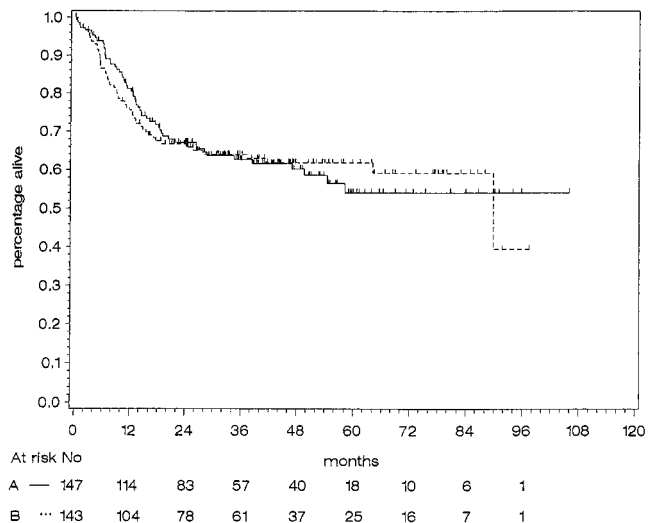


Fig 6. Overall survival after 3 years for all patients except patients with Burkitt's and lymphoblastic lymphoma.

these 28 patients, the relapse pattern was as follows: five patients (18%) had a relapse in a previously involved site, 11 patients (39%) had a relapse in a previously uninvolved site, and 12 patients (43%) had relapses in both new and previously involved sites. Relapse after HDT occurred early, with a median interval of 3 months. Median survival after relapse was 7.5 months for patients who relapsed after HDT (n = 28) and 38 months for patients who relapsed after conventional treatment (n = 58). The duration of survival after relapse is shown in Fig 8. The differences between these groups are statistically significant (P = .0022, log-rank test). Salvage HDT after relapse was administered to 26 patients (24 patients who relapsed in arm A and two patients in arm B who relapsed after initial denial of primary HDT). Median survival of patients receiving salvage HDT was 15 months.

*Treatment-Related Mortality, Side Effects, and Secondary Neoplasia*

Thirty-nine patients died during the course of treatment. Thirty-one patients died due to progressive disease. In eight

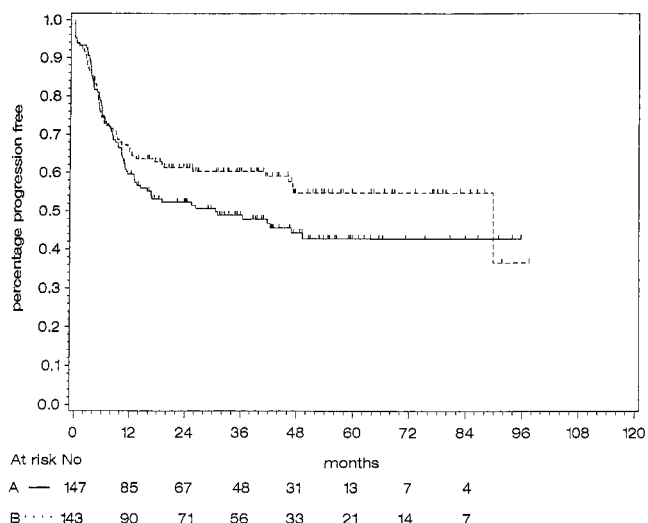


Fig 7. Event-free survival after 3 years for all patients except patients with Burkitt's and lymphoblastic lymphoma.

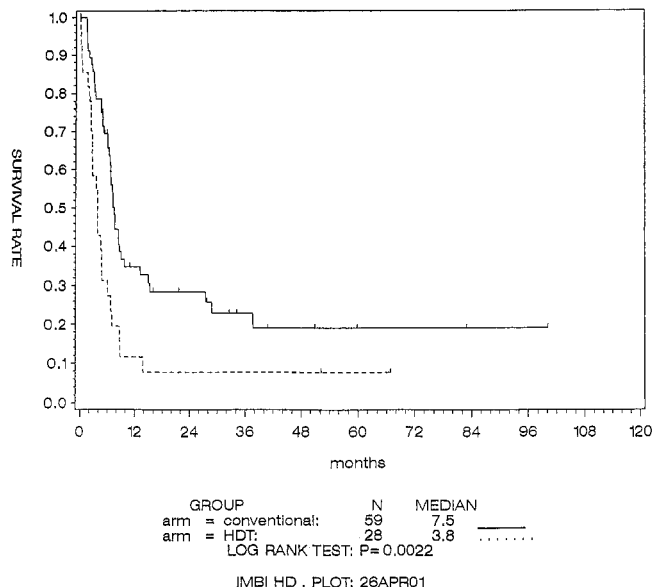


Fig 8. Survival after relapse: relapse after prior HDT (n = 28) versus relapse after conventional treatment (n = 59).

patients (2.6%) who died during treatment, death was judged as possibly treatment related. Patient characteristics are listed in Table 3. Among these eight patients, five died during the first or second cycle of CHOEP, two died within the third cycle of CHOEP, and one patient died after having received five cycles of CHOEP. Six of the eight patients had serum LDH levels that were two times the normal value at diagnosis, which indicates a high tumor load. This led us to implement a cytoreductive treatment with prednisone and vincristine in high-risk patients. No patient died due to HDT, but the 100-day mortality rate after HDT was 5%. All patients died due to disease progression.

Following HDT in treatment arm B, 39% of patients experienced grade 3/4 stomatitis, 27% experienced grade 3/4 infection, and 17% had grade 3/4 diarrhea. In treatment arm A during the corresponding fourth and fifth cycles of CHOEP, no patient experienced grade 3/4 stomatitis or diarrhea, 1% of patients experienced grade 3/4 infection, 73% experienced grade 3/4 leukopenia, and 9% experienced grade 3/4 thrombocytopenia.

With a median observation time of 45.6 months, six secondary neoplasias (1.9%) were reported. A case of acute myeloid leukemia (AML) of French-American-British type M2 occurred 8 years after HDT, another patient developed AML of French-American-British type M1 4 years after HDT, a case of AML occurred 3 years after five cycles of CHOEP, and a case of myelodysplasia (refractory anemia with excess blasts in transformation) occurred 1 year after five cycles of CHOEP. One patient developed breast cancer and

Table 3. Possibly Treatment-Related Mortality (n = 312)

Age (years)	LDH (U/mL)	No. of Cycles	Cause of Death
51	462	2	Leukopenic sepsis
59	308	1	Cerebral infarction
55	523	1	Leukopenic sepsis
58	271	3	Hemorrhagic shock due to peptic ulcer
37	634	1	Acute abdomen, sepsis
58	4,500	1	Neutropenic colitis
53	1,311	5	Heart failure
53	1,440	3	Pneumonia during leukopenia

another patient developed an adenocarcinoma of the bile duct, 2 years after five cycles of CHOEP in both cases.

## DISCUSSION

The aim of this study was to compare HDT as part of the primary treatment to conventional chemotherapy in patients with newly diagnosed, disseminated, aggressive lymphoma and the risk factor of elevated LDH. Thus far, the study has failed to show any benefit of intensive treatment until now in an intent-to-treat evaluation.

In previous studies, CHOEP followed by involved-field radiotherapy was proved to be an effective regimen in the treatment of patients with aggressive lymphoma, and this treatment resulted in stable remission in the majority of patients in this study. It can be administered without major toxicities and with tolerable long-term side effects. The German High-Grade Lymphoma Study Group has conducted a randomized study comparing CHOEP with standard CHOP in 890 patients  $\leq$  60 years of age with low risks; the study is currently under evaluation.

Why did three cycles of CHOEP followed by BEAM not prove to be superior to five cycles of CHOEP in this patient group? Patients were randomized up front. One third of the patients randomized to treatment arm B did not receive HDT, mainly because of induction failure and patient's choice. According to the study protocol, the interval between CHOEP cycles was to be 21 days. In fact, the fourth cycle in the conventional treatment arm was given after a median period of 63 days after the first cycle. However, in the high-dose arm, BEAM could only be administered after a median period of 78 days. Patients in the conventional arm therefore received more chemotherapy during that period than patients in the HDT arm. Involved-field radiotherapy was administered in both treatment arms. However, radiotherapy could only be completely administered in 53% of the patients in the high-dose arm compared with 69% in the conventional treatment arm. Major reasons for deletion of radiotherapy were induction failure and hematologic toxicities, predominantly persistent thrombocytopenia. The median interval between the last chemotherapy cycle and radiotherapy was 40 days in arm A; the median interval between HDT and radiotherapy was 59 days in arm B. Therefore, radiotherapy may have been more effective in treatment arm A. These data further illustrate the limited value of administering radiotherapy immediately after HDT.

An additional reason why there was no difference in survival between the two treatment groups may be that salvage therapy for patients who relapsed after primary treatment was more effective in patients treated in arm A than in arm B, with increased 2-year survival rates for relapsed patients in arm A (26%) compared with arm B (11%). Twenty-six of the 61 relapsed patients in arm A received salvage high-dose treatment leading to a median survival time of 15 months, whereas relapse after front-line HDT was associated with a median survival time of only 3.8 months. These data suggest that salvage therapy is more effective after conventional therapy than after HDT.

Seventy-five percent of the patients were classified as high intermediate or high risk according to the International Prognostic Index. In a subgroup analysis of these patients, there was no difference in event-free survival or overall survival.

A number of trials have evaluated HDT as part of front-line therapy. In the LNH87-2 trial of the Groupe d'Etude des

Lymphomes de l'Adulte (GELA), patients who had achieved CR after four courses of induction therapy were randomized to receive HDT or conventional consolidation treatment.<sup>10</sup> Survival and event-free survival did not reveal any difference, but subgroup analysis demonstrated a benefit in terms of event-free survival and overall survival for high-risk patients.<sup>11</sup> The follow-up trial, which evaluated early intensification with BEAM after a shortened induction therapy compared with the conventional GELA arm, demonstrated a benefit for conventionally treated patients.<sup>12</sup> The Genova group randomized patients to receive complete conventional therapy versus complete conventional therapy followed by autologous bone marrow transplantation; they did not see any benefit for the high-dose arm.<sup>13</sup> The Milan group used a different approach, in which HDT was part of a sequentially escalated treatment regimen.<sup>14</sup> With small patient numbers, sequential HDT was superior to conventional treatment with methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in terms of event-free survival after 7 years. The European Organization for the Research and Treatment of Cancer performed a trial in which patients were randomized after three cycles of a CHOP-like regimen to receive either five more cycles of the same regimen or three more cycles followed by HDT. In contrast to the German trial, 70% of the 311 registered patients belonged to the low or low intermediate risk groups of the International Prognostic Index. Estimated 5-year survival rates did not differ between the two treatment groups.<sup>15</sup> Two randomized trials addressed HDT in patients with delayed response after induction therapy.<sup>16,17</sup> Both studies included only small patient numbers and failed to show an advantage of HDT for this patient population.

When physicians consider the value of up-front high-dose chemotherapy as front-line treatment, the option of salvage HDT has to be taken into account. The PARMA study demonstrated that patients who relapse after conventional treatment can benefit from salvage HDT.<sup>4</sup> Our results suggest that patients who relapse after HDT have a worse prognosis than patients who relapse after conventional treatment. In any HDT protocol that is part of primary treatment, this effect has to be considered. This study, as well as previous ones, underscores that outside of clinical trials, there is no indication for up-front HDT. Until now, no prospective randomized trial has proven a survival benefit of high-dose chemotherapy applied after a shortened induction therapy, like the trial outlined above. Trials that have evaluated HDT after a complete course of standard chemotherapy have shown a benefit for a subgroup of patients in retrospective analysis. Is there any role for front-line HDT? A number of clinical trials are presently addressing this issue, including the European MISTRAL trial (Multicenter International Studies on the Treatment of Aggressive Lymphomas) conducted by the Swiss Group for Clinical Cancer Research, which is incorporating the sequential Milan schema, and the German High-Grade Lymphoma Study Group trial, which is evaluating the role of sequential up-front HDT.

## ACKNOWLEDGMENT

We are indebted to C. Klose, U. Haag, and I. Eschenbach for their excellent assistance and to A. Neubauer and U. Datan for critical revision of the manuscript.

## REFERENCES

1. Armitage JO: Treatment of non-Hodgkin's lymphomas. *N Engl J Med* 328:1023-1030, 1993
2. Fisher RI, Gaynor ER, Dahlborg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 328:1002-1006, 1993
3. Nademee A, Schmidt GM, O'Donnell MR, et al: High dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: A pilot study. *Blood* 80:1130-1134, 1992
4. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 333:1540-1545, 1995
5. Köppler H, Pflüger KH, Eschenbach I, et al: CHOP-VP16 chemotherapy and involved field irradiation for high grade non-Hodgkin's lymphomas: A phase II multicentre study. *Br J Cancer* 60:79-82, 1989
6. Köppler H, Pflüger KH, Eschenbach I, et al: Randomised comparison of CHOEP versus alternating hCHOP/IVEP for high-grade non-Hodgkin's lymphomas: Treatment results and prognostic factor analysis in a multicentre trial. *Ann Oncol* 5:49-55, 1994
7. Stansfeld AG, Diebold J, Noel H, et al: Updated Kiel classification for lymphoma. *Lancet* 1:292-293, 1988 (letter)
8. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 329:987-994, 1993
9. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 84:1361-1392, 1994
10. Haioun C, Lepage E, Gisselbrecht C, et al: Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: A study of 464 patients. *J Clin Oncol* 12:2543-2551, 1994
11. Haioun C, Lepage E, Gisselbrecht C, et al: Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: Final analysis of the prospective LNH-87-2 protocol—A Groupe d'Etude des Lymphomes de l'Adulte study. *J Clin Oncol* 18:3025-3030, 2000
12. Gisselbrecht C, Lepage E, Molina T, et al: Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. *J Clin Oncol* 20:2472-2479, 2002
13. Santini G, Salvagno L, Leoni T, et al: VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: Results of a prospective trial by the Non-Hodgkin's Lymphoma Cooperative Study Group. *J Clin Oncol* 16:2796-2802, 1998
14. Gianni AM, Bregni M, Siena S, et al: High dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med* 336:1290-1297, 1997
15. Kluin-Nelemans H, Zagonel V, Anastasopoulou A, et al: Standard chemotherapy with or without high-dose chemotherapy for aggressive Non-Hodgkin's lymphoma: Randomized phase III EORTC study. *J Natl Cancer Inst* 93:22-30, 2001
16. Martelli M, Vignetti M, Zinzanni P, et al: High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: A prospective randomized Italian multicenter study. *J Clin Oncol* 14:534-542, 1996
17. Verdonck LF, van Putten WLJ, Hagenbeek A, et al: Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *N Engl J Med* 332:1045-1051, 1995

---

# Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 20, No 22

CONTENTS

November 15, 2002

---

## EDITORIAL

### Autologous Stem-Cell Transplantation as a Component of Initial Treatment for Poor-Risk Patients With Aggressive Non-Hodgkin's Lymphoma: Resolved Issues Versus Remaining Opportunity

Richard I. Fisher 4411

## ORIGINAL REPORTS

### Hematologic Malignancies

#### Randomized Study to Evaluate the Use of High-Dose Therapy as Part of Primary Treatment for

“Aggressive” Lymphoma ..... Ulrich Kaiser, Irmgard Uebelacker, Ulrich Abel, Josef Birkmann,

Lorenz Trümper, Harald Schmalenberg, Tunca Karakas, Bernd Metzner, Dieter K. Hossfeld, Helge G. Bischoff,

Astrid Franke, Marcel Reiser, Peter Müller, Luisa Mantovani, Marc Grundeis, Frank Rothmann,

Cay-Uwe von Seydewitz, Rolf M. Mesters, Ernst U. Steinhauer, Dorothea Krahl, Kurt Schumacher,

Michael Kneba, Michael Baudis, Norbert Schmitz, Rüdiger Pfab, Hubert Köppler, Reza Parwaresch,

Michael Pfreundschuh, and Klaus Havemann 4413

#### Phase I Trial of the Proteasome Inhibitor PS-341 in Patients With Refractory Hematologic Malignancies

Robert Z. Orlowski, Thomas E. Stinchcombe, Beverly S. Mitchell, Thomas C. Shea, Albert S. Baldwin,

Stephanie Stahl, Julian Adams, Dixie-Lee Esseltine, Peter J. Elliott, Christine S. Pien, Roberto Guerciolini,

Jessica K. Anderson, Natalie D. Depcik-Smith, Rita Bhagat, Mary Jo Lehman, Steven C. Novick,

Owen A. O'Connor, and Steven L. Soignet 4420

### Pediatric Oncology

#### Children From Ethnic Minorities Have Benefited Equally as Other Children From Contemporary Therapy for Rhabdomyosarcoma: A Report From the Intergroup Rhabdomyosarcoma Study Group

K. Scott Baker, James R. Anderson, Thom E. Lobe, Moody D. Wharam, Stephen J. Qualman, R. Beverly Raney,

Frederick B. Ruymann, Richard B. Womer, William H. Meyer, Michael P. Link, and William M. Crist 4428

---

*Journal of Clinical Oncology* (ISSN 0732-183X) is published 24 times a year, twice monthly, by Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Periodicals postage paid at Hagerstown, MD, and at additional mailing offices. The GST number for Canadian Subscribers is 895524239.

Editorial correspondence should be addressed to Daniel G. Haller, MD, *Journal of Clinical Oncology*, 330 John Carlyle St, Suite 300, Alexandria, VA 22314. Telephone: (703) 797-1900; FAX: (703) 684-8720. Email: [jco@asco.org](mailto:jco@asco.org). Internet: <http://www.jco.org>

**POSTMASTER:** ASCO members send change of address to American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Non-members send change of address to *Journal of Clinical Oncology*, c/o Lippincott Williams & Wilkins, PO Box 1550, Hagerstown, MD 21740.

Yearly subscription rates: United States and possessions: individual, \$325.00; institution, \$452.00; single issue, \$25.00. Canada and Mexico: individual, \$456.00; institution, \$583.00; single issue, \$25.00. All other countries: individual, \$496.00; institution, \$623.00; single issue, \$25.00. Student and resident: United States and possessions: \$127.00. Canada and Mexico: \$153.00, all other countries: \$193.00. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription rate are on a prorated basis. Subscriptions are accepted on a calendar year basis. Prices are subject to change without notice. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. Publication Mail Agreement Number 863289.



## Lung Cancer

- U **Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Marimastat After Response to First-Line Chemotherapy in Patients With Small-Cell Lung Cancer: A Trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer** ..... Frances A. Shepherd, Giuseppe Giaccone, Lesley Seymour, Channa Debruyne, Andrea Bezjak, Vera Hirsh, Michael Smylie, Sheldon Rubin, Heidi Martins, Alan Lamont, Maciej Krzakowski, Anna Sadura, and Benny Zee 4434
- Safety and Pharmacokinetic Effects of TNP-470, an Angiogenesis Inhibitor, Combined With Paclitaxel in Patients With Solid Tumors: Evidence for Activity in Non–Small-Cell Lung Cancer** ..... Roy S. Herbst, Timothy L. Madden, Hai T. Tran, George R. Blumenschein, Jr, Christina A. Meyers, Lee F. Seabrooke, Fadlo R. Khuri, Vinay K. Pudevalli, Victoria Allgood, Herbert A. Fritsche, Jr, Leslie Hinton, Robert A. Newman, Elizabeth A. Crane, Frank V. Fossella, Margaret Dordal, Thomas Goodin, and Waun Ki Hong 4440

## Genitourinary Cancer

- Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis**  
Padraig Warde, Lena Specht, Alan Horwich, Tim Oliver, Tony Panzarella, Mary Gospodarowicz, and Hans von der Maase 4448

## Gastrointestinal Cancer

- Efficacy of Fluorine-18-Deoxyglucose Positron Emission Tomography in Detecting Tumor Recurrence After Local Ablative Therapy for Liver Metastases: A Prospective Study** ..... B.S. Langenhoff, W.J.G. Oyen, G.J. Jager, S.P. Strijk, Th. Wobbes, F.H.M. Corstens, and T.J.M. Ruers 4453
- Therapeutic Efficacy of Transcatheter Arterial Chemoembolization as Compared With Hepatic Resection in Hepatocellular Carcinoma Patients With Compensated Liver Function in a Hepatitis B Virus–Endemic Area: A Prospective Cohort Study** ..... Hyo-Suk Lee, Kang Mo Kim, Jung-Hwan Yoon, Tae-Rim Lee, Kyung Suk Suh, Kuhn Uk Lee, Jin Wook Chung, Jae Hyung Park, and Chung Yong Kim 4459

## Sarcoma

- U **Efficacy and Safety of Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas** ..... Tadashi Kamada, Hirohiko Tsujii, Hiroshi Tsuji, Tsuyoshi Yanagi, Jun-etsu Mizoe, Tadaaki Miyamoto, Hirotohi Kato, Shigeru Yamada, Shinroku Morita, Kyousan Yoshikawa, Susumu Kandatsu, and Akio Tateishi for the Working Group for the Bone and Soft Tissue Sarcomas 4466
- Function and Health Status Outcomes in a Randomized Trial Comparing Preoperative and Postoperative Radiotherapy in Extremity Soft Tissue Sarcoma** ..... A.M. Davis, B. O'Sullivan, R.S. Bell, R. Turcotte, C.N. Catton, J.S. Wunder, P. Chabot, A. Hammond, V. Benk, M. Isler, C. Freeman, K. Goddard, A. Bezjak, R.A. Kandel, A. Sadura, A. Day, K. James, D. Tu, J. Pater, and B. Zee 4472

## Clinical Trials

- Randomized Discontinuation Design: Application to Cytostatic Antineoplastic Agents** ..... Gary L. Rosner, Walter Stadler, and Mark J. Ratain 4478

## Genetic Testing for Cancer

- BRCA1/2 Genetic Testing in the Community Setting** ..... Wendy Y. Chen, Judy E. Garber, Suzanne Higham, Katherine A. Schneider, Katie B. Davis, Amie M. Deffenbaugh, Thomas S. Frank, Rebecca S. Gelman, and Frederick P. Li 4485

**REVIEW ARTICLE**

**Limb Salvage and Amputation in Survivors of Pediatric Lower-Extremity Bone Tumors: What Are the Long-Term Implications?** ..... *Rajaram Nagarajan, Joseph P. Neglia, Denis R. Clohisy, and Leslie L. Robison* 4493

**SPECIAL DEPARTMENTS**

**Announcements**


**Information for Contributors**

**Current Abstracts**

**Books Received**

**Internet Access**

JCO Homepage ..... [www.jco.org](http://www.jco.org)  
ASCO OnLine ..... [www.asco.org](http://www.asco.org)

 Online supplementary information  
Available at <http://www.jco.org>

★ Article was published online ahead of print at <http://www.jco.org>