Treatment of Mantle Cell Lymphomas at Advanced Stages: Prospective Randomized Comparison of Myeloablative Radiochemotherapy followed by Blood Stem Cell Transplantation versus Maintenance with Interferon alpha in First Remission after Initial Cytoreductive Chemotherapy with an Anthracycline containing Combination

A European Intergroup Trial
of the
German Low Grade Lymphoma Study Group
EORTC Lymphoma Study Group
Groupe D'Etudes des Lymphomes De l' Adulte
Italian Lymphoma Intergroup

Study Coordinators:

Prof. Dr. W. Hiddemann
University Hospital Großhadern
Dept. of Medicine III
Marchioninistraße 15
81377 Munich

GERMANY

Phone-No.: (country code) -89-7095-2551
Telefax-No.: (country code) -89-7095-8875

Study Center:

German Low Grade Lymphoma Study Group
Prof. Dr. W. Hiddemann
Dr. M. Unterhalt
University Hospital Großhadern
Dept. of Medicine III
Tegernseer Landstr. 243
81549 Munich

GERMANY

Phone-No.: (country code) -89-6995-83-0 /-10 /-11
Telefax-No.: (country code) -89-6995-83-12
E-Mail: studyce@med3.med.uni-muenchen.de

Update 02/99

Pathology Review Panel:

Prof. Dr. F. Berger
Hopital Edouard Herriot
Laboratoire d'Anatormo-Pathologie
Place d'Arsonval
69437 Lyon
France

Prof. Dr. C. de Wolf-Peeters
Catholic University of Leuven
Dept. of Pathology
Minderbroederstraat 12
3000 Leuven
Belgium

Prof. Dr. A. C. Feller
Universitätsklinik
Dir. des Instituts für Pathologie
Ratzeburger Allee 160
23538 Lübeck

Prof. Dr. Hansmann
Universitätsklinik
Dir. des Instituts für Pathologie
Theodor-Stern-Kai 7
60590 Frankfurt
Germany

Dr. P. Kluin
University Hospital
Laboratory of Pathology
P.O. Box 9600, Bld. 1 Lr-Ch
2300 RC Leiden
The Netherlands

Prof. Dr. P. Möller
Abteilung f. Pathologie
Universität Ulm
Albert-Einstein-Allee 11
89081 Ulm

Prof. Dr. K. Müller-Hermelink
Universitätsklinik Würzburg
Institut für Pathologie
Josef-Schneider-Str. 2
97080 Würzburg
Germany

Prof. Dr. A. Norton
St. Bartholomew's Hospital
Dept. of Histpathology
West Smithfield
London EC1A 7BE
Great Britain

Prof. Dr. Parwaresch
Dr. M. Tiemann
Universitätsklinik Kiel
Inst. f. Hämatopathologie
Niemannsweg 11
24105 Kiel
Germany

Dr. E. Pedrinis
Istituto Cantonale di Patologia
Via in Selva 24
6600 Locarno
Switzerland

Prof. Dr. S. Pileri
Istituto di Ematologia "Seragnoli"
Policlinico S. Orsola
Via Massarenti 9
40138 Bologna
Italy

Prof. Dr. H. Stein
Universitätsklinikum Steglitz
Pathologisches Institut
Hindenburgdamm 30
12230 Berlin
Germany

Protocol Writing Committee:

Prof. Dr. W. Hiddemann (Chairman)
University Hospital Großhadern
Dept. of Medicine III
Marchioninistr. 15
81377 Munich
Germany

Prof. Dr. B. Coiffier (Co-Chairman)
Centre Hospitalier Lyon-Sud
Head Dept. of Hematology
69310 Pierre-Bénite
France

Prof. Dr. G. Brittinger
Georg-August-Universität
Med. Klinik u. Poliklinik
Abt. Hämatologie/ Onkologie
Robert-Koch-Str. 40
37075 Göttingen
Germany

Prof. Dr. F. Cavalli, M.D.
Ospedale San Giovanni
Head Division of Oncology
6500 Bellinzona
Switzerland

Prof. Dr. A. Hagenbeek
The Daniel Den Hoed Cancer Center
and Rotterdam Radio-Therapeutic Institute
Groene Hiltedijk 301
3075 EA Rotterdam
The Netherlands

Dr. J.C. Kluin-Nelemans
University Hospital Leiden
Bldg. 1, E1-Q-92
Rijnburgerweg 10
2333 AA Leiden
The Netherlands

Prof. Dr. A. Levis
Divisione di Ematologia
Ospedale Civile
Via Venezia 18
15100 Alessandria
Italy

Prof. Dr. E. Montserrat
Hospital i Provincia
Dept. of Hematology
Villarroel 170
08036 Barcelona
Spain

Dr. S. Pittaluga
Catholic University of Leuven
Dept. of Pathology
Minderbroederstraat 12
3000 Leuven
Belgium

Dr. A. van Hoof
AZ Sint Jan
van het O.C.M.W.
Ruddershove 10
8000 Brugge
Belgium

Dr. G.E.G. Verhoef
Univ. Ziekenhuis Gashuisberg
Afd. Haematologie
Herestraat 49
3000 B Leuven
Belgium

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1. Summary

1.1. Background

Among the malignant lymphomas mantle cell lymphomas (MCL) are characterized by an unfavorable prognosis with a moderate sensitivity to chemotherapy and a median survival of 3-4 years only. Attempts to improve the dismal outlook for the mostly elderly patients by more intensive and/or anthracycline containing combinations have resulted in somewhat higher rates of remissions but have not proven beneficial in terms of overall survival. First data of the German Low Grade Lymphoma Study Group and the EORTC Lymphoma Study Group indicate, that interferon alpha maintenance may prolong the disease free interval after successful chemotherapeutic cytoreduction. Furthermore, myeloablative radio-chemotherapy followed by stem cell transplantation appears as a promising approach.

The current study, therefore, aims at further exploring the two currently most promising perspectives in the treatment of MCL in way of a prospective multinational controlled study.

1.2. Study Aims

The study addresses the following questions:

1. Impact of myeloablative radio-chemotherapy followed by blood stem cell transplantation on disease free and overall survival in comparison with historic controls of similarly selected patients.
2. Impact of early versus late myeloablative radio-chemotherapy followed by stem cell transplantation on overall survival.
3. Impact of interferon alpha maintenance on disease free survival in comparison with myeloablative radio-chemotherapy with stem cell transplantation and historic controls

1.3. Study Conduct

1. Initial cytoreductive chemotherapy with 4-6 cycles of an anthracycline containing combination such as CHOP, CNOP, MCP or similar regimens.
2. After achievement of a complete or partial remission according to the initial randomisation:

   Postremission Therapy - Arm 1: Intensified chemotherapy with Dexa BEAM followed by stem cell harvest and subsequent myeloablative radio-chemotherapy with TBI and cyclophosphamide followed by stem cell retransfusion.

   Postremission Therapy - Arm 2: Consolidation with 2 further cycles of chemotherapy and subsequent long term maintenance therapy with interferon alpha 2a (Roferon) until disease progression or untolerable toxicity.

At first relapse patients on interferon alpha maintenance should undergo cytoreductive chemotherapy again and in case of sensitive relapse procede to the myeloablative radio-chemotherapy with stem cell transplantation.

1.4. Eligibility criteria

- Histologic diagnosis of mantle cell lymphoma

- Clinical stage III or IV

- Age ≥ 18 ≤ 65 years

1.5. Statistics

The study is designed as a randomized prospective multicenter multinational trial to test whether myeloablative radio-chemotherapy with peripheral stem cell transplantation will improve relapse free survival in comparison to standard therapy followed by interferon alpha maintenance.

1.6. Randomization Procedure and Study Center

Before the start of therapy patients are centrally registered at the study data center in Munich by telephone or fax and are randomized for the treatment arms.

Randomisation will be stratified for risk factors and institution.

Telephone and Fax:

Dr. M. Unterhalt
Dept of Medicine III
University Hospital Großhadern
Tegernseer Landstr. 243
81549 Munich
Germany

Tel.: country code-89-6995-83-0 /-10
Fax: country code-89-6995-83-12

2. Background

2.1 Biology of Mantle Cell Lympoma

The increasing insights into the biology of the lymphatic system and the pathogenesis of malignant lymphomas, as provided by modern cell biologic and molecular techniques, have not only enlarged the understanding of lymphoma development but have also facilitated the classification of malignant lymphomas and the recognition of biologically and clinically distinct subtypes. Hence, the detection of the translocation t(11;14) in particular has supported the acceptance of mantle cell lymphoma as a separate entity, although this lymphoma was already described as centrocytic lymphoma by the Kiel classification and as mantle zone lymphoma by Weissenburger et al. more than 10 years ago (1,2). The recent general acceptance of mantle cell lymphomas as a separate entity and its extensive cyto-histologic characterization by the International Lymphoma Study Group and the European Lymphoma Task Force (3,4,5) has also renewed the interest in the clinical management of this disorder. Currently available data on clinical characteristics and therapeutic outcome are hampered by the preceding difficulties of classification and the fact that they are based on retrospective analyses and mostly small patient numbers. Still, the available data uniformly indicate a poor response to cytostatic therapy and a short survival time with a median of less than 3 years, questioning the clinical grouping of mantle cell lymphoma as a low malignant disorder (6,7,8,9,10,11,12). Attempts to improve the dismal outlook for the mostly elderly patients with mantle cell lymphomas by more intensive and/or anthracycline containing combination regimens have resulted in somewhat higher rates of complete and partial remissions but have not proven beneficial in terms of overall survival

(7,13,14,15). New approaches are therefore deeply warranted and pilot studies have been initiated investigating new agents such as the epipodophyllotoxins and purine analogues. In addition, interferon alpha maintenance after initial cytoreductive therapy has been explored by the EORTC and the German Low Grade Lymphoma Study Group (10,16). Preliminary data for the latter approach look promising and suggest that interferon alpha may prolong the disease free interval. Still, these results are not yet conclusive and need to be evaluated in way of a prospective randomized comparison with sufficient patient numbers.

A completely new perspectives has recently arisen through the introduction of myeloablative radio-chemotherapy followed by peripheral blood stem cell or bone marrow transplantation which may result in a substantial and potentially even complete reduction of the lymphoma cell mass. While this approach is already widely applied to patients with follicular lymphomas and poor risk high or intermediate lymphomas by several groups, experiences in mantle cell lymphoma are still limited (17,18).

The current study aims at further exploring the two currently most promising perspectives in the therapy of mantle cell lymphomas in way of a prospective multinational controlled study.

The first goal of this trial is the evaluation of the effect of myeloablative radio-chemotherapy followed by blood stem cell transplantation on the disfree free interval in comparsion to maintenance therapy with interferon alpha in patients achieving complete or partial remissions after initial cytoreductive chemotherapy with an anthracycline containing combination. Patients relapsing after interferon alpha maintenance will be transplanted in second remission thus providing the means to also compare the efficacy of myeloablative radio-chemotherapy followed by blood stem cell transplantation in first versus second remission.

2.2 Study Aims

The two arm approach of the current study will allow to evaluate the following questions:

1. Impact of interferon alpha maintenance on disease free survival in comparison with myeloablative radio-chemotherapy and stem cell transplantation
2. Impact of early versus late myeloablative radio-chemotherapy followed by stem cell transplantation on overall survival
3. Impact of myeloablative radio-chemotherapy followed by blood stem cell transplantation on disease free and overall survial when compared with historic controls of similarly selected cases

2.3 Patients

The current study is designed for previously untreated patients at 18 to 65 years of age with advanced stage mantle cell lymphomas who do not qualify for primary, potentially curative, radiotherapy.

2.3.1. Eligibility criteria

- histologic diagnosis of mantle cell lymphoma
- clinical stage III or IV
- age $\geq 18 \leq 65$ years

2.3.2 Exclusion criteria

- option of primary potentially curative radiotherapy
- age < 18 or > 65 years
- ECOG performance status > 2
- concommittent disease comprizing a medical contraindication against the study protocol
  - manifest heart failure
  - coronary heart disease
  - chronic lung disease with hypoxemia
  - severe, uncontrolled hypertension
  - severe, not sufficiently controlled diabetes mellitus
  - renal insufficiency (creatinine > 2,0 mg/dl)
  - impairment of liver function (unless caused by the lymphoma) with transaminase values ≥ three times of control values and/or bilirubin ≥ 2,0 mg/dl
  - pregnancy
  - previous therapy with cytostatic drugs or interferon
  - prior organ, bone marrow or peripheral blood stem cell transplantation

2.4. Randomization Procedure

After initial diagnosis and fulfillment of entry criteria patients are centrally registered at the study data center in Munich by telephone or fax.

They will then be randomized between two treatment arms:

Arm 1: Intensive consolidation with stem cell collection and subsequent myeloablative radio-chemotherapy followed by blood stem cell transplantation in first complete or partial remission after initial cytoreductive chemotherapy

Arm 2: Maintenance with interferon alpha 2a (Roferon) in first complete or partial remission after initial cytoreductive chemotherapy with the option for intensive retreatment as in arm 1 at first relapse or lymphoma progression

From all patients diagnostic material must be submitted for central pathologic review to one of the members of the pathology review panel as indicated below.

The randomization will be stratified for risk factors according to the international prognostic index and institution. For the randomization the following data must be submitted:

- initials and date of birth
- intitution and name of the responsible physician
- performance-status (ECOG-status)
- LDH serum level and normal range for the respective laboratory
- number of extranodal lymphoma involvements

- institution to which diagnostic material will be submitted for central pathologic review

3. Therapy

3.1. Induction Chemotherapy

Initial cytoreductive chemotherapy comprizes an anthracycline containing combination such as CHOP, CNOP, MCP or similar regimens. This treatment aims at the achievement of a complete or partial remission. For this purpose four cycles of chemotherapy will be performed initially. If a complete remission is achieved after four cycles, patients will proceed towards the intensification and myeloablative radiochemotherapeutic approach or will receive an additional two courses of chemotherapy for consolidation followed by interferon alpha maintenance as determined by initial randomization

Patients not achieving a complete remission after four treatment cycles will receive two further courses of chemotherapy. Patients achieving at least a partial remission with no microscopically detectable mantle cells in the blood and less than 20 % residual lymphoma cells in the bone marrow after six treatment cycles will then proceed to intensive consolidation with stem cell collection and subsequent myelo-ablative radio-chemotherapy with stem cell transplantation (arm 1) or to two further cycles of induction chemotherapy for consolidation followed by interferon alpha (arm 2) as determined by initial randomization.

Patients not experiencing at least a partial remission after six cycles of initial cytoreductive chemotherapy or with a higher degree of bone marrow or peripheral blood involvement are taken off study.

3.2. Treatment Protocols

The following protocols represent examples for regimens that can be applied for initial cytoreductive chemotherapy. Participating centers may choose other protocols of comparable intensity. At each center, however, a uniform treatment procedure must be followed and fixed before joining the study.

In the German Low Grade Lymphoma Study Group initial chemotherapy will be randomized between CHOP and MCP.

3.2.1. CHOP - Therapy

Cyclophosphamide	750 mg/m^2 i.v.	day 1
Doxorubicin	50 mg/m^2 i.v.	day1
Vincristine	1.4 mg/m^2 i.v. max. Dose: 2 mg	day 1
Prednisone	100 mg/m^2 p.o.	day 1-5
repetition every 21 days		

3.2.2. CNOP - Therapy

Cyclophosphamide	750 mg/m² i.v.	day 1
Mitoxantrone (Novantron)	12 mg/m² i.v.	day 1
Vincristine	1.4 mg/m² i.v. max. Dose: 2 mg	day 1
Prednisone	100 mg/m² p.o.	day 1-5
repetition every 21-28 days		

3.2.3. MCP - Therapy

Mitoxantrone (Novantron)	8 mg/m² i.v.	day 1 and 2
Chlorambucil	3 x 3 mg/m²	day 1-5
Prednisone	25 mg/m²	day 1-5
repetition every 28 days		

3.3. Postremission Therapy - Arm 1

After completion of initial cytoreductive chemotherapy with 4 to 6 cycles of CHOP or a similar regimen and achievement of a complete remission or a partial remission with no microscopically detectable mantle cells in the blood and less than 20% residual lymphoma cells in the bone marrow intensified chemotherapy will be initiated within a time period of six weeks to achieve a further reduction of the lymphoma cell mass and for stem cell mobilization.

3.3.1. Intensified Chemotherapy with Dexa BEAM

Intensified Chemotherapy with Dexa BEAM will be performed within six weeks after the completion of initial cytoreductive treatment as follows:

Dexa BEAM

Dexamethasone	3 x 8 mg orally	days 1 - 10
BCNU	60 mg/m² i.v.	day 2
Melphalan	20 mg/m² i.v.	day 3
Etoposide	75 mg/m² i.v.	days 4, 5, 6, 7
Cytosine Arabinoside	2 x 100 mg/m² i.v. q 12 hours	days 4, 5, 6, 7

3.3.2. Application of Hematopoietic Growth Factors

For the regeneration of granulopoesis and mobilization of peripheral stem cells G-CSF will be started on the first day after the end of Dexa BEAM at a dose of 5-10 µg/kg bodyweight and will be continued until the completion of stem cell harvest.

3.3.3. Stem Cell Harvest and Asservation

Stem cell separation will be performed on at least two consecutive days following the WBC nadir and achievement of a WBC count > 1000/mm^3. Separation and asservation will be done according to the accepted practise at the participating institution.

No enrichment of stem cell subpopulations or in vitro purging should be performed.

In case of accumulating evidence for a beneficial effect of such procedures and the establishment of the respective techniques the study group retains the option to introduce such manipulations at all participating center uniformly.

3.3.4. Myeloablative Radiochemotherapy and Peripheral Stem Cell Transplantation

The myeloablative radiochemotherapy and peripheral stem cell transplantation should follow the Dexa BEAM intensification and stem cell harvest within a period of four to six weeks. This procedure depends on the following requirements:

- continuing complete or partial remission
- asservation of > 1,0 - 2,5 x 10^6/kg bodyweight CD34+ stem cells for transplantation and "back-up"
- no medical contraindications against myeloablative radiochemotherapy

The myeloablative treatment consists of a combined radiochemotherapy with fractionated total body irradiation with 12 Gy (2 fractions per day à 2 Gy) on days -6 to -4 and cyclophosphamide 60 mg/kg bodyweight/day on days -3 and -2.

The reverse sequence of myeloablative therapy with chemotherapy followed by irradiation may also be applied.

The retransfusion of peripheral stem cells will be done on day 0 and should contain at least 1,0 - 2,5 x 10^6/kg bodyweight CD34+ positive stem cells.

Following the retransfusion of peripheral stem cells the subsequent administration of G-CSF at a dose of 5 µg/kg bodyweight is recommended, but not mandatory, until a peripheral granulocyte count > 1000/mm^3.

After completion of therapy and recovery of blood counts no further antilymphoma therapy will be applied.

3.4. Postremission Therapy - Arm 2

3.4.1. Consolidation - Therapy

After completion of initial cytoreductive chemotherapy with 4 to 6 cycles of CHOP or a similar regimen and the achievement of a complete or partial remission two further courses of chemotherapy will be applied for consolidation and maintenance therapy with interferon alpha will be initiated within the following four weeks.

3.4.2. Interferon Alpha Maintenance

Interferon alpha 2a (Roferon) is given at a total dose of 6 Mill. U./d three times a week by s.c. injection. The dose of interferon alpha will be adjusted to side effects as follows:

- any side effects of WHO grades 0 and I - full dose
- any side effects of WHO grades II or greater except for fever - dose reduction to 3 Mill. U./d
- persistance or reccurrence of side effects of WHO grades II or greater - further dose reduction to 1,5 Mill. U./d
- persistance or recurrence of side effects of WHO grades II or greater - treatment termination

Interferon therapy will be adminstered without timely limitation until relapse or disease progression or the occurenec of side effects requiring treatment termination.

3.5. Treatment at First Relapse

Patients with first relapse or lymphoma progression during interferon alpha 2a maintenance should be offered the option to undergo the intensified therapeutic approach according to protocol arm 1. Before intensification with DexaBEAM salvage chemotherapy of moderate intensity should be applied for the achievement of a second remission. In case of late relapse i.e. after a progression free interval ≥ 12 months it is recommended to repeat the initially applied regimen again.

4. Diagnostic Procedures

4.1. Initial Diagnosis

a) Histology

The initial histologic diagnosis will be done at the local department of pathology at the participating institutions. An additional tissue specimen must be sent to one of the reference pathology centers for central pathologic review. Central pathology review should be completed before the start of postremission therapy. The histologic diagnosis of mantle cell lymphoma is based on the criteria developed by the European Lymphoma Task Force (5)

The histologic diagnosis should be performed within 3 months prior to the initiation of therapy

b) Staging Procedures

- history and physical examination
- chest X-ray and computed tomography
- ultrasound examination of abdomen and computed tomography
- bone marrow aspiration and biopsy
- complete laboratory investigation including peripheral blood values, LDH, beta 2 microglobuline, creatinine, uric acid, transaminases, bilirubin, serum protein, urine analysis

4.2. Diagnostic Evaluation of Treatment Response after two, four or six Cycles of Initial Cytoreductive Chemotherapy

- history and physical examination

- chest X-ray and computed tomography (to be done only if a partial or complete remission is achieved by clinical examination)
- ultrasound examination of abdomen and computed tomography (to be done only if a partial or complete remission is achieved by clinical examination)
- bone marrow histology and aspiration (to be done only if a partial or complete remission is achieved by clinical examination)
- complete laboratory investigations as above

4.3. Diagnostic Procedures Prior to Myeloablative Radiochemotherapy and Peripheral Stem Cell Transplantation

- history and physical examination
- chest X-ray and computed tomography
- ultrasound examination of abdomen and computed tomography
- bone marrow aspiration and biopsy
- complete laboratory investigation including peripheral blood values, LDH, beta 2 microglobuline, creatinine, uric acid, transaminases, bilirubin, serum protein, urine analysis
- echocardiography
- pulmonary function

4.4. Diagnostic Procedures during Interferon alpha Maintenance and in the Post Transplantation Period

(every 3-6 months)

- history and physical examination (every 3 months)
- chest X-ray (every 6 months)
- ultrasound examination of abdomen (every 3 months)
- bone marrow aspiration and biopsy (every 6 months)
- complete laboratory investigation including peripheral blood values, LDH, beta 2 microglobuline, creatinine, uric acid, transaminases, bilirubin, serum protein, urine analysis (every 3 months)

5. Evaluation of Results

5.1. Complete Remission

A complete remission requires the disappearance of all lymphoma manifestations including hepatomegaly and splenomegaly for at least four weeks, a normal bone marrow histology, the normalization of peripheral blood counts with granulocytes > 1500/mm^3, Hb > 12,0 g/dl and thrombocytes > 100 000/mm^3 and the absence of circulating abnormal cells

5.2. Partial Remission

A partial remission is defined as a 50% reduction or more in the sum of the sizes of all measurable lymphoma manifestations for at least four weeks and a normalization of peripheral

blood counts. In addition, no single manifestation may show an increase of 25% or more in size and no new lesions must appear during the four week period.

5.3. Stable Disease

No measurable change in lymphoma manifestations, i.e. absence of criteria for complete or partial remission or progression, respectively.

5.4. Progression

- increase in frequency and severity of disease associated symptoms
- occurance of new nodal or extranodal lesions
- increase in the size of one or more lymphoma manifestations > 25 %
- increase in splenomegaly > 25 %

5.5. Relapse

Occurence of parameters defining progression in patients in remission.

5.6. Remission Duration

Interval between the achievement of complete or partial remission and relapse.

5.7. Event Free Interval

Interval between the end of sucessfull induction therapy with PR or CR (before start of DexaBeam or consolidation therapy) and relapse or death.

5.8. Survival

Interval between initial randomization and death.

5.9. Evaluation of Toxicity

Toxicity will be evaluated according to WHO criteria.

6. Declaration of Helsinki and Approval by Ethic Committee

The current study design follows the updated declaration of Helsinki. Prior to its initiation the study must be approved by the ethic committees at the participating institutions.

7. Publication

The study will be published as a joined effort of all participants mentioning every investigator and participating institution. Except for the study chairman and co-chairman who will take the position of first or senior author, the number of entered patients will determine the sequence of authorship.

8. Statistics

8.1. Evaluation of the Event Free Interval

All randomized patients who finish the induction therapy with a complete remission or a partial remission with no microscopically detectable mantle cells in the blood and less than 20% residual lymphoma cells in the bone marrow and who start with the therapy of postremission arm 1 or arm 2 according to the randomization are evaluable for the randomized group. Patients with histology other than MCL according to central pathologic review are excluded from the evaluation. Patients who do not start treatment according to the randomized arm are also excluded. Patients with serious protocol violations (e.g. additional therapy, PBCT with purging) during the event free interval are censored at the time of protocol violation.

8.2. Stratification

The initial randomization will be stratified for risk factors according to the international prognostic index and the participating institution. Risk factors are:

- performance-status (ECOG-status) >1
- LDH serum level over normal range of the respective laboratory
- more than one extranodal lymphoma involvement

Institutions are grouped into:

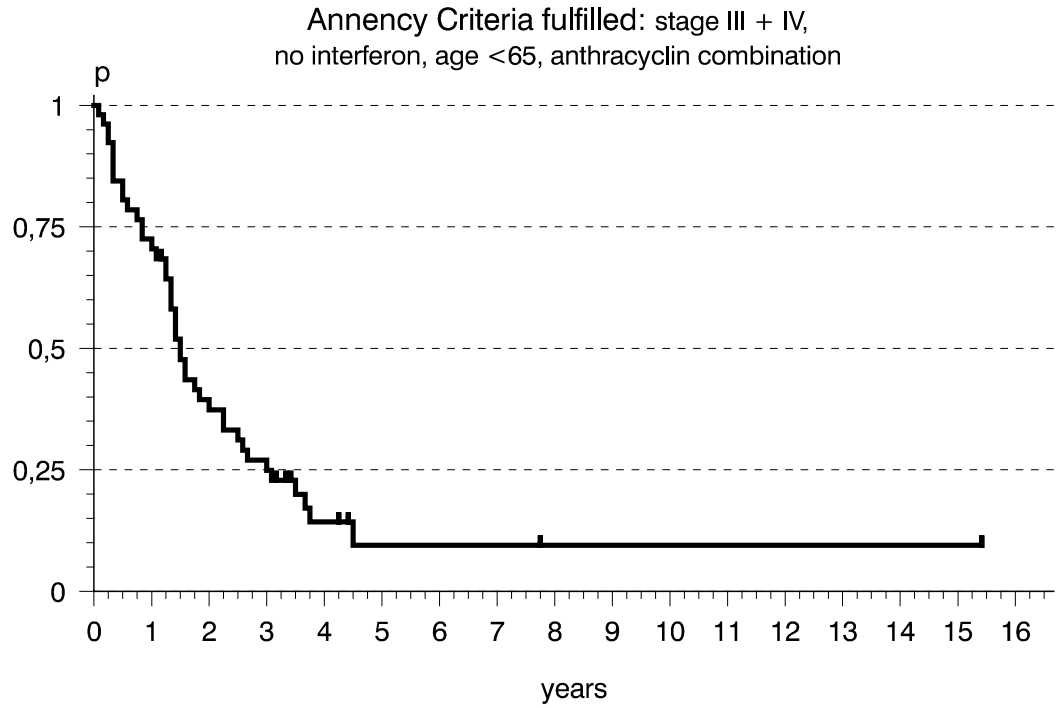
- centers of the Netherlands and Belgium
- centers of the German Study Group
- centers of Switzerland, Italy and Spain
- centers of Great Britain
- centers of France

8.3. Statistical Test and Sample Size

8.3.1 Sample Size Calculation for a Fixed Sample

The central aim of the study is to show that there is a significant improvement by myeloablative radio-chemotherapy followed by stem cell transplantation compared to interferon alpha maintenance for the event free interval. For this purpose the log rank test is applied.

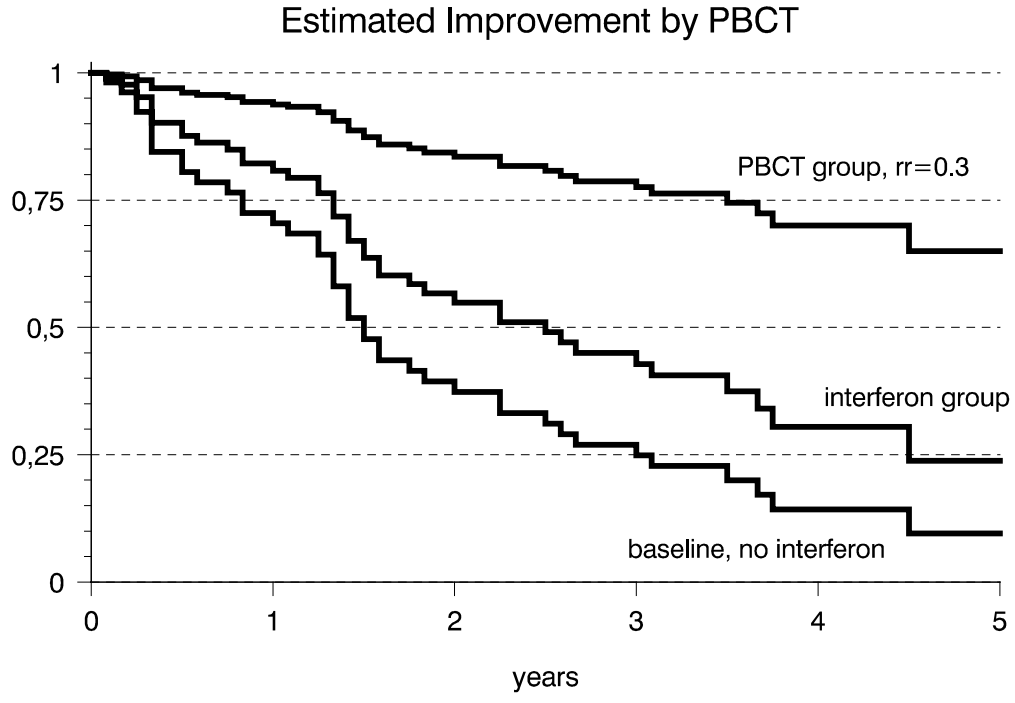
As basis for this evaluation the product-limit estimate for the event free interval after treatment with anthracycline containing combinations in patients younger than 65 years in the European retrospective mantle cell survey was calculated.



Using this data as baseline in a proportional hazard model, the improvement of treatment can be expressed by reduction of relative risk (*rr*) compared to the respective control.

Furthermore, the effect of interferon alpha maintenance was estimated according to the data of the German Low Grade Lymphoma Study Group. This data suggests a reduction of relative risk to 60% of a control without interferon alpha maintenance.

First non randomized studies in mantle cell lymphomas suggest a relapse free survival after PBCT of about 90%. This improvement would imply a relative risk of less than 30% when compared to the interferon group. Hence, a reduction of relative risk to 30% by PBCT will be used as upper attainable value for further planing.



For a working significance level α=0.05 and a power of 1-α the number *k* of events (relapse or death) necessary for a one sided fixed sample trial can be estimated by the following formula:

$$k \approx \frac{16\, u_{1-\alpha}^{2}}{\Theta_{R}^{2}} \qquad \Theta_R = -\ln(rr) \qquad u_{1-\alpha} = 1.64$$

rr	0.6	0.5	0.45	0.4	0.35	0.3
k	166	91	68	52	40	30

Provding a continous entry of patients into the study, the number of observed events will be a function of the recruitment rate, the observation time and the improvement reached by IFN and PBCT. Using the described baseline observations the following estimates for the percentage of observed events are obtained.

years of observation		***rr* for PBCT**					
	IFN	**0.6**	**0.5**	**0.45**	**0.4**	**0.35**	**0.3**
2	21%	13%	11%	10%	9%	8%	7%
2.5	26%	17%	14%	13%	12%	10%	9%
3	31%	20%	17%	16%	14%	13%	11%
3.5	35%	23%	20%	18%	16%	15%	13%
4	38%	26%	23%	21%	19%	17%	15%
4.5	42%	29%	25%	23%	21%	19%	16%
5	45%	32%	28%	25%	23%	21%	18%
6	50%	36%	31%	29%	26%	24%	21%
7	54%	39%	34%	32%	29%	26%	23%
8	57%	41%	36%	34%	31%	28%	24%
9	59%	43%	38%	35%	32%	29%	25%
10	60%	44%	39%	36%	33%	30%	26%

Providing a balanced distribution between the two therapy arms, the necessary rate of evaluable patients per year can be calculated:

duration of the Study (years)	***rr* for PBCT**					
	0.6	**0.5**	**0.45**	**0.4**	**0.35**	**0.3**
2	484	339	218	172	138	107
2.5	309	214	139	110	88	68
3	218	149	98	77	62	48
3.5	164	112	74	58	46	36
4	128	86	57	45	36	28
4.5	104	70	47	37	29	23
5	86	57	38	30	24	19
6	64	42	29	23	18	14
7	51	33	23	18	14	11
8	42	28	19	15	12	9
9	36	23	16	13	10	8
10	32	20	14	11	9	7

In the European retrospective mantle cell survey the rate of remissions (PR+CR) for anthracycline combinations was 76%. In the German Low Grade Lymphoma Study Group early termination of induction therapy was 7%. In the PBCT pilot of the German Low Grade Lymphoma Study Group study about 13% of the patients terminated therapy after induction before PBCT. So only 60% of the initially randomized patients will be evaluable for the eventfree interval. The necessary rates of randomizations per year can therefore be calculated as follows:

duration of the	***rr* for PBCT**					
Study (years)	**0.6**	**0.5**	**0.45**	**0.4**	**0.35**	**0.3**
2	807	565	363	287	229	179
2.5	515	357	231	183	146	114
3	363	249	163	129	103	80
3.5	274	186	123	97	77	60
4	214	144	96	76	60	47
4.5	174	116	78	61	49	38
5	144	95	64	51	40	32
6	107	70	48	38	30	23
7	85	56	38	30	24	19
8	71	46	31	25	20	15
9	60	39	27	21	17	13
10	53	34	23	19	15	12

The expected rates for randomizations per year were estimated by the number of patients that were submitted to the European mantle cell survey and the pilot study of the German Low Grade Lymphoma Study Group. The following randomization rates will be attainable in the study:

-	centers of the Netherlands and Belgium:	15/year
-	centers of the German Study Group	11/year
-	centers of Switzerland, Italy and Spain	9/year
-	centers of Great Britain	4/year
-	centers of France	3/year
		42/year

So a total of 42 randomizations per year can be realized. Using a fixed sample size, a 5 year recruitment period is required to show a significant reduction of relative risk of 35 % by PBCT at a working significance level of 0.05 and a power of 0.95.

8.3.2 Sample Size Calculation for a Sequential Evaluation

For ethical reasons it will not be possible to do this trial without planed interim analyses. The most effective way for planed interim analyses is a sequential procedure as described by Jones and Whitehead (19). The stopping rules for a triangular test (described in (20)) will be applied for the log rank statistic. The statistics Z and V will be calculated after each reported event according to the following formulas:

$$Z = n - \sum_{i=1}^{k} o_i \left(\frac{r_{i/IFN}}{r_i}\right) \qquad V = \sum_{\{i:r_i>1\}} \frac{o_i(r_i - o_i)}{(r_i - 1)} \frac{r_{i/PBSCT}}{r_i} \frac{r_{i/IFN}}{r_i}$$

$d_1 < d_2 < ... < d_k$: *sequenz of values of observed uncensored event free intervals*

o_i := *number of observed uncensored event free intervalls* $= d_i$

r_i := *number of observed event free intervalls* $\geq d_i$

n := *number of observed events in the IFN – group*

$r_{i/IFN}$:= *number of observed event free intervalls* $\geq d_i$ *in the IFN – group*

$r_{i/PBCT}$:= *number of observed event free intervalls* $\geq d_i$ *in the PBCT – group*

Stopping Rule :

The test will continue for $Z \in (-a + \lambda V, a + \mu V)$

with values $a = 4{,}126 \lambda = 0{,}787 \mu = 0{,}262.$

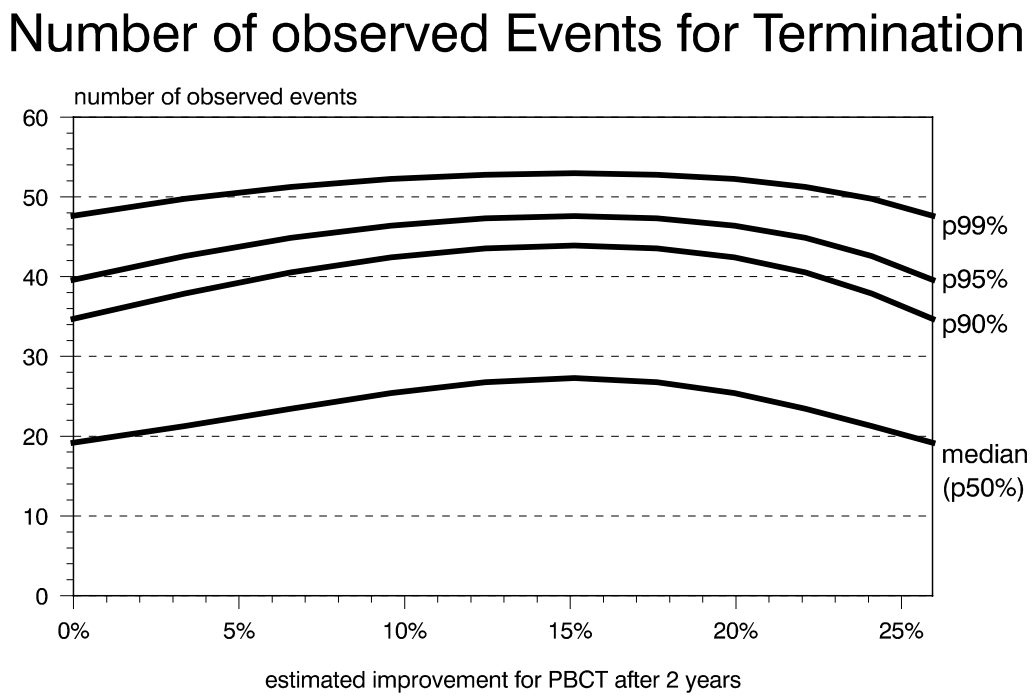
For $Z \geq a + \mu V$ *the procedure decides for a significant improvement by PBCT*,

while for $Z \leq -a + \lambda V$ *no significant improvement can be stated*.

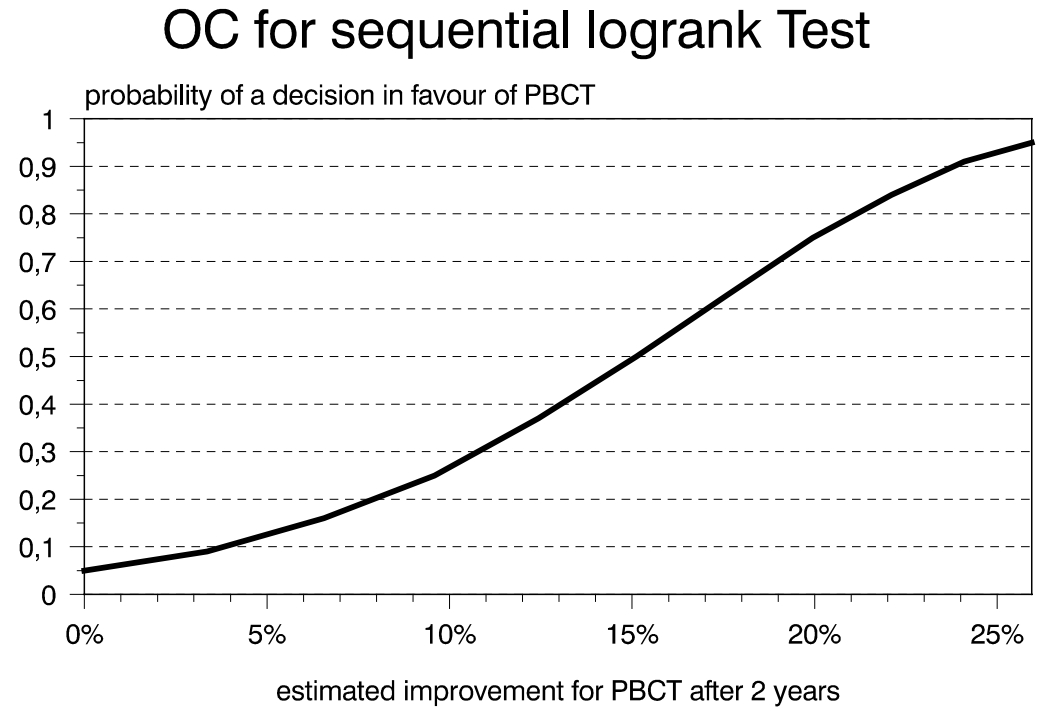
The sample size until termination of this procedure depends on observed results and will grow to a maximum value for a relative risk of about 60% (*rr* = 0.591, difference of 15% to the estimated IFN-baseline) for the PBCT-group compared to IFN. The following values can be calculated for the triangular test, a continous balanced randomization of 42 patients per year provided:

parameter	**number of events**	**estimated duration of observation**
expected terminal sample size for *rr* = 1.0 (no improvement)	22	3 years
expected terminal sample size for *rr* = 0.35	22	3.5 - 4.0 years
expected terminal sample size for *rr* = 0.591	29	4 years
p50% for rr = 0.591 (p50: probability of termination 50%; median)	28	4 years
p90 for *rr* = 0.591	44	4.5 - 5.0 years
p95 for *rr* = 0.591	48	5 years
p99 for *rr* = 0.591	53	5.0 - 5.5 years
absolute possible maximum:	63	6 years

A description of the parameters with respect to the estimated IFN-baseline is given by the following graph:



For a smaller improvement by PBCT than *rr* = 0.35 (26% after two years) the expected numbers of events necessary for termination will increase while the probability of detecting the improvement will decrease. For an improvement to *rr* = 0.43 (22% after two years) the probability of detection will be about 84%, while for an improvement to *rr* = 0.48 (20% after two years) the probability of detection is 75%. The following plot shows the operational characteristic of the planed seqential test:



Following these considerations, the timed sequential evaluation procedure will be applied for the current study. At the basis of a working significance level of 0.05 with a detection power of 0.95 and the assumption that the relative risk of relapse is reduced to 60% in the group receiving

myeloablative radio-chemotherapy in first remission as compared to interferon alpha maintenance a five year duration is anticipated to complete the current study.

8.4. Documentation

Therapy and observation after therapy or during interferon maintenance are documented on special forms of which two copies have to be submitted to the study center. The documentation about a patient is finished with the death of the patient or lost to follow up. Each death during the study has to be documented on a special form. In case of death of a patient during initial therapy, consolidation therapy or PBCT the study center should be informed at once by fax or phone.

The documentation of the trial is stored in a database at the study center. The evaluation of the documentation and the sequential evaluation of the statistic test will be done by J. Ohnesorge and Dr. M. Unterhalt Munich, Germany.

8.5. Evaluation during the Trial

Data about response to initial therapy, side effects of therapy and overall response will be evaluated every three month and reported to the study chairman and co-chairman. They will also be reported at the meetings of the study group. Data about the event free interval and survival in the therapy groups will not be disclosed before decision of the sequential procedure.

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Study Design