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E.O.R.T.C. NEWS

E.O.R.T.C. Protocol for the Treatment of Good-risk Patients with Chronic Myelogenous Leukemia. A Randomized Trial*

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1. BACKGROUND AND INTRODUCTION

THE MEDIAN survival of patients with chronic myelogenous leukaemia (CML) treated with busulfan or hydroxy-urea (3–3.5 yr), is not essentially better than that observed 50 yr ago in untreated patients (2–2.5 yr), when no antibiotics, allopurinol, transfusions and other supportive treatment facilities were available [1–3].

Therapy with mild acting cytostatic drugs improves the quality of life but should not be regarded as satisfactory since true remission is never achieved, merely an apparent control of the disease for a limited period. A number of theoretical reasons can be brought forward to introduce more intensive and cycle-specific cytostatic treatment schemes [4–8]. However the results of cyclic drug therapy, splenic irradiation, splenectomy and intensive chemotherapy till now are not essentially better than those obtained with traditional busulfan treatment. For this reason it seems at the moment not justified to institute a trial with intensive and potentially dangerous treatment in all CML-patients. It is important to realize that although the median survival of busulfan-treated patients is 3.5 yr, the scatter of survival is very broad. Even in Philadelphia chromosome (Ph^1) positive CML, patients with different prognosis can be distinguished. Signs of bad risk being: thrombocytosis, thrombocytopenia or hepatomegaly at presentation [1], or persistent leukocytosis, basophilia or splenomegaly after three months of busulfan therapy. [9].

The prognosis of the bad-risk group is a median survival of about 1–1.5 yr. The prognosis of the good-risk group is a median survival of about 40 months and may apparently not easily be improved by more intensive chemotherapy. For that reason for this group a study is proposed, which is not troublesome to the patients.

The study to be initiated in CML good-risk patients is a phase III trial about the effect of the immunostimulant Levamisole on the occurrence of metamorphosis and the total survival time. Sokal [10] reported a better survival in CML-patients, which received immunotherapy with intradermal B.C.G. mixed with cultured CML cells of patients in blastic crisis.

A number of observations have shown that Levamisole exerts an immunostimulant action by increasing phagocytic potency of polymorphonuclears and macrophages [11, 12] and T-lymphocyte reactivity in patients with depressed immunity [13–19] Fialkow [20] recently has shown that the number of normal T-lymphocytes which are undetectable during relapse of CML, increases during remission. It may be expected that Levamisole, which restores depressed T-cell function, at least improves the general condition in the relapse-phase and possibly prolongs the remission period in CML.

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Favourable effects of Levamisole on the survival time of patients with acute leukaemia, with breast cancer and lung cancer have been described [21–26]. Among neoplasias CML offers an unique opportunity for the simultaneous use of an immunostimulant and a cytostatic drug, since in contrast to other cytostatics, busulfan is known to have no or only a minimal immunosuppressive effect.

2. OBJECTIVES OF THE GOOD-RISK TRIAL

(a) To assess the effectiveness of Levamisole as adjuvant to busulfan-treatment in well-defined favourable forms of Ph^1-positive CML on the onset of the metamorphosis of the disease and on the overall survival time.
(b) To asses prognostic factors in ph^1-positive chronic myeloid leukaemia.
(c) To accurately assess the alternative forms of metamorphosis.

3. SELECTION OF PATIENTS

3.1 *Registration*

All patients who are diagnosed as suffering from chronic myelogenous leukaemia and who are positive for the presence of the Philadelphia chromosome (Ph^1-positive) are registered at diagnosis as patients potentially eligible for the trial.

3.2 *Entry into the CML-good-risk trial*

Patients suitable for the CML-good-risk trial must satisfy the following criteria:

1. Presence of Philadelphia (Ph^1) chromosome.
2. Immature white blood cells in the circulating blood.
3. W.B.C. $>80{,}000/\mu l$.
   If a patient has a W.B.C. $<80{,}000/\mu l$, but an increase of $20{,}000/\mu l$ over the following 2-months period, he becomes eligible.
   If a patient has a W.B.C. $<80{,}000/\mu l$, not increasing by $20{,}000/\mu l$ over the following 2 months, he becomes eligible on attaining W.B.C. $80{,}000/\mu l$.
4. Platelet counts between 100,000 and $450{,}000/\mu l$.
5. Age between 15 and 65 yr.
6. Treated for less than 3 months with busulfan or hydroxy-urea.

3.3 *Excluded from the CML-good-risk trial are patients*

1. Who have been treated for >3 months with cytoreductive drugs.
2. Who present with platelet counts $<100{,}000/\mu l$ or $>450{,}000/\mu l$ before start of therapy.*
3. Who present with skin involvement, with enlarged lymph nodes, with lytic bone lesions, spinal cord compression or other manifestations of tissue localization.*
4. Who do not arrive at apparent haematological remission within three months after the start of busulfan therapy as defined in paragraph 5.*
5. Who have been splenectomized.

4. DESIGN OF THE TRIAL

Patients who fulfil the criteria for diagnosis and selection in the category Good-Risk CML, Ph^1-positive are registered for the trial and are subsequently treated with busulfan (Section 5.1) to induce remission. If they achieve apparent haematological and clinical remission (Section 5.2) within three months of therapy, they are randomized to receive either busulfan alone or busulfan + levamisole for maintenance treatment.

The time which elapses from the date of randomization to the occurrence of metamorphosis (Section 7.2) and the total survival time will be compared between the two treatment groups.

5. THERAPEUTIC REGIMENS AND SIDE EFFECTS

5.1 *Remission induction by busulfan is obligatory*

Busulfan is given at a dosage of $3\,mg/m^2$/day. The dosage may be increased to $4\,mg/m^2$/day if after 4 weeks the response is inadequate.

When the rate of WBC-fall is very steep busulfan is discontinued as soon as WBC arrives at $30{,}000/\mu l$.

Busulfan dosage is diminished when the WBC reduces slowly to $20{,}000/\mu l$.

If the WBC drops to $<20{,}000/\mu l$ busulfan should be stopped or the dosage should be modified to 2 mg once, twice or three times weekly in order to maintain the WBC between 10,000 and $20{,}000/\mu l$. If the WBC is falling $<10{,}000/\mu l$ then busulfan treatment must be stopped.

*Such patients are considered as "Bad Risk" patients.

If the platelet count drops below 100,000/μl busulfan treatment must be stopped. Mostly this drop is associated with an impending onset of metamorphosis rather than the effect of busulfan itself. In case of severe leukocytosis (>150,000/μl) at the start of therapy the following modes of treatment are advocated:

1. Administration of allopurinol (300–600 mg/day).
2. Hydration of the patient orally or intravenously to establish a brisk diuresis.
3. Alkalinization of the patient's urine by oral or intravenous administration of sodium bicarbonate.
4. Optionally leukapheresis, which may be repeated 4–6 times in the first 14 days during which 10^{11}–5×10^{11} granulocytes are removed to decrease the dangerous hyperviscosity of the blood.

Note: Centres which have facilities to perform leukapheresis and cryopreservation of mononucleated cells may perform this procedure before the start of therapy in order to have stem-cells at disposal at the time of metamorphosis.

5.2 *Apparent remission is defined as follows*

1. WBC < 30,000/μl.
2. < 5% blast cells, < 15% immature cells (promyelocytes, myelocytes) and < 5% basophils in the peripheral blood.
3. Platelet count between 100,000/μl and 400,000/μl.
4. Hemoglobin level > 11 g/dl.

5.3 *Maintenance treatment*

Maintenance therapy with either busulfan or with busulfan and levamisole should continue until metamorphosis occurs.

1. *With busulfan.* After randomization the busulfan drug dosage can be adjusted individually varying from 0 to 2 mg/day for 1–7 days weekly, aiming at WBC < 30,000/μl. When WBC gradually increases, the dosage of busulfan may be temporarily augmented to 4–6 mg/day (see Section 7.2).

2. *With busulfan–levamisole.* If the patient is randomized into the group busulfan + levamisole, the busulfan is given as indicated under maintenance treatment with busulfan.

Levamisole is given orally 100 mg/m^2 in one dose per week, preferably monday evening with the last meal. Fifty milligram tablets are provided and the dose for each patient should be adjusted upwards to give a dose which is a multiple of 50 mg.

Even if busulfan has to be temporarily interrupted the therapy with levamisole should be continued.

5.4 *Possible side effects of Levamisole*

Careful follow up is essential. Because cases of levamisole-induced reversible agranulocytosis (pyrazolone type, [27]) have been reported, it is recommended to control WBC every 2 weeks (see Section 6.2).

If once agranulocytosis occurs levamisole must be stopped definitely.

Other reversible side-effects of levamisole which have been described at dosages > 50% higher than those proposed in this trial include:

(a) gastro-intestinal upset.
(b) flu-like syndrome (fever, sweats, myalgia, arthralgia).
(c) skin-rash, urticaria.
(d) central nervous system disturbances (headache, metallic taste, dysosmia).
(e) lethargy, weakness.

6. CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW UP

1. *Physical examination* (*at diagnosis and every* 3 months *thereafter*)

Enlargement of spleen in cm below costal margin.
Enlargement of liver in cm below costal margin.
Enlargement of lymph nodes and areas involved.
Tissue involvement.
Ambulatory status (Karnofski index).

2. *Laboratory investigations*

WBC (every 2 weeks).
RBC, differential count, platelets (every 4 weeks).
Leukocyte alkaline phosphatase (at diagnosis and every 6 months).
Uric acids (mg/dl) (every 3 months).
LDH (i.u./l) (every 3 months).
Bone marrow aspiration (at diagnosis and at metamorphosis) (see Section 11).
Bone marrow biopsy (at diagnosis and optionally at metamorphosis) (see Section 11).
Cytogenetic studies (at diagnosis and optionally at metamorphosis).

3. *X-rays*

Chest X-ray (at diagnosis and if indicated during course of disease).

If indicated skeletal X-ray of vertebral column and pelvis or other bones at diagnosis or during the course of illness in case of local pain or tenderness.

7. CRITERIA OF EVALUATION AND DEFINITION OF METAMORPHOSIS

7.1 *Criteria of evaluation*

1. Duration of disease till onset of metamorphosis (see Section 7.2).
2. Type of metamorphosis (Blastic crisis, Resistance, Aplasia).
3. Type of blastic crisis (Cytomorphology, Immunologic cell type determination if available).
4. Total survival time.
5. Relative frequency of good and bad risk CML patients.

7.2 *Metamorphosis of CML is defined as follows*

1. *Blastic crisis.* Blast transformation of CML is defined by increase of blasts and early promyelocytes:
$>25\%$ of peripheral WBC and/or
$>40\%$ of bone marrow cells.
Cytomorphologically these blasts may have features, characteristic for myeloblasts, lymphoblasts or may be undifferentiated. It is optional to repeat cytogenetic studies during this phase.

2. *Resistant phase.* Resistant phase is defined by progressive increase of busulfan dosage (>6 mg daily >2 months) needed to keep the WBC $<30{,}000/\mu l$, (re-)occurrence of anemia, thrombocytopenia, splenomegaly, lymph node swelling, lytic bone lesions or tissue-involvement.

3. *Aplastic phase/myelofibrosis.* Pancytopenia with dry tap and a bone marrow biopsy which is almost a-cellular or which shows an increase of fibrous tissue.

8. REGISTRATION AND RANDOMIZATION PROCEDURES

8.1 *First registration*

The first registration is made at diagnosis when the suitability criteria have been confirmed (Section 3) by means of a telephone call to the E.O.R.T.C. Data Center (tel: Brussels 538.65.33) from 9.00 a.m. to 6.00 p.m. Monday–Friday. The date of registration is the date of making this telephone call. At this time, the following information is requested:

1. Protocol number (06771).
2. Institution's name.
3. Good- or bad-risk patient.
4. Patient's name.
5. Physician's name.
6. Caller's name.

The Data Center will at this time remind the caller that if the patient is a good-risk patient the busulfan induction treatment should commence when the WBC satisfy the criteria of Section 3.2.

8.2 *Second registration and randomization*

Second registration is made with the Data Center at the end of the induction period. If the patient has achieved a remission (see Section 5.2) he will be randomized to one of two maintenance arms: busulfan alone or busulfan + levamisole.

If the patient has not achieved remission within 3 months, he will then be classified as a bad-risk.

At this time the following information is requested:

1. Protocol number (06771).
2. Institution's name.
3. Has induction phase been completed.
4. Good- or bad-risk patient.
5. Patient's name.
6. Physician's name.
7. Caller's name.

The maintenance treatment assigned by randomization will then be given for good-risk patients only. If registration by telephone is not feasible, patients may also be registered by telex: 22773, or telegram: E.O.R.T.C. Data Center, rue Héger-Bordet 1, 1000 Brussels, Belgium, by including the information requested above.

9. FORMS AND PROCEDURES FOR COLLECTION DATA

All of the data obtained on each registered patient should be sent to: E.O.R.T.C. Data Center, Institut Jules Bordet, rue Héger-Bordet 1, 1000 Bruxelles, Belgium.

The required forms for recording the data and the schedule for sending them are as follows:

Form
1. On-Study (Form II)
Schedule
Within one week after registration with the Data Center.

Form
2. Flow sheet (Form VII)

Schedule

1. Within one week after registration together with the On-Study Form.
2. At the end of the induction treatment.
3. Three months after randomization and thereafter every 3 months until appearance of metamorphosis or death.

Form

3. Summary (Form IX)

Schedule

1. At the end of the induction period if the patient fails to achieve apparent remission.
2. At metamorphosis.
3. At death or when lost to follow-up or when patient leaves protocol.

Regardless of the reasons, all patient taken off protocol treatment while still alive, should continue to be followed and the E.O.R.T.C. Data Center should be notified of their survival status at least once a year.

10. STATISTICAL CONSIDERATIONS

The primary objective of this study is to compare the duration of the disease stage following remission induced by busulfan until onset of metamorphosis. In a pairwise comparison of patients treated with busulfan only after remission and patients treated with busulfan and levamisole, a total of 76 patients followed until relapse is required on each treatment group in order to detect a ratio of 1.5:1 in the median (or mean) remission duration (assumed to follow an exponental distribution) of the two treatment groups (error probabilities $\alpha=0.05$, $\beta=0.20$). Thus a total of 152 good-risk patients are to be followed until the onset of the metamorphosis.

11. ADMINISTRATIVE RESPONSIBILITIES

This study is a co-operative effort between the members of the E.O.R.T.C. Leukaemia and Haematosarcoma Co-operative Group.

Belgium

Antwerpen, Universiteit d'Antwerpen (U.I.A.).
Bruxelles, Institut Jules Bordet, Hôpital Universitaire de St. Pierre.
Leuven, Academisch Ziekenhuis, St. Raphaël.
Liège, Hôpital Bavière, Université de Liège.
Verviers, Hôpital Civil de Verviers.

France

Bordeaux, Fondation Bergonié.
Paris, Hôtel Dieu, Paris.
Reims, Institut Jean-Godinot.
Rouen, Centre H. Becquerel.
St. Etienne, Hôpital de Bellevue.
Toulouse, Centre Cl. Regoud.

Italy

Milano, Ospedale Maggiore Ca' Grana.

The Netherlands

Amsterdam, Academisch Ziekenhuis.
Gravenhage, Leyenburg Ziekenhuis.
Nijmegen, Universiteits Ziekenhuis.
Rotterdam, Radio-Therapeutisch Instituut.
Utrecht, Academisch Ziekenhuis.

West Germany

Bonn, Medizinische Universitäts-Poliklinik.
Düsseldorf, Medizinische Universitäts-Klinik.
Giessen, Zentrum für Inne Medizin der Universität.
Hannover, Abt. Hämatologie-Onkologie der Medizinische Hochschule.
Köln, Medizinische Universitätsklinik.
Mainz, Klinikum der Kohannes Gutenberg Universität.

Bone marrow samples together with peripheral blood smears (one May-Grünwald Giemsa and three unstained respectively), and bone marrow biopsies at diagnosis and optionally at metamorphosis should be sent to: K.-P. Hellriegel, Medizinische Universitätsklinik, Joseph Stelzmannstrasse 9, D. 5000 Köln-41 (FRG), Bundesrepublik Deutschland. Tel: 0221-478.44.58 Telex: 8882426.

All questions concerning the statistical or data processing aspects of this study should be addressed to: E.O.R.T.C. Data Center, Institut Jules Bordet, 1, Rue Héger-Bordet, 1000 Bruxelles, Belgium, Tel: 02-538.65.33 Telex: 22773.

All other questions should be addressed to: C. Haanen, Division of Haematology, University of Nijmegen, Geert Grooteplein Zuid 10 P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: 080-514762 Telex: 48232.

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