Bone Marrow Transplantation in Europe

Editor:
J. L. Touraine

BONE MARROW TRANSPLANTATION IN EUROPE

Proceedings of the Second European Symposium on Bone Marrow Transplantation, Courchevel, Savoie, France, March 27-30, 1978

Editor
Jean-Louis Touraine
Claude Bernard University, Lyon

Assistant Editors
R. Triau
General Secretary,
Fondation Mérieux, Lyon

F.E. Zwaan
General Secretary,
EBMT Group, Leiden

This publication was made possible by a grant from the Fondation Mérieux

1979

EXCERPTA MEDICA Amsterdam-Oxford-Princeton

ISBN Excerpta Medica 90 219 0399 7
ISBN Elsevier North-Holland 0 444 90113 2

Library of Congress Cataloging in Publication Data

European Symposium on Bone Marrow Transplantation,
2d, Courchevel, France, 1978.
Bone marrow transplantation in Europe.
Includes bibliographies and index.
1. Marrow--Transplantation--Congresses.
I. Touraine, Jean Louis. II. Triau, R.
III. Zwaan, F. E. IV. Title.
RD123.5.E92 1978 617'.44 79-23852
ISBN 0-444-90113-2

Publisher:
Excerpta Medica
305 Keizersgracht
1000 BC Amsterdam
P.O. Box 1126

Sole Distributors for the USA and Canada:
Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in The Netherlands by Groen, IJmuiden

Preface

Two decades ago, the pioneering efforts of several investigators (1–3) established the feasibility of bone marrow transplantation in man and its potential as a treatment for irradiation accidents, aplastic anaemias, immunodeficiencies and acute leukaemias. Significant progress in our knowledge of histocompatibility and transplantation immunobiology and in clinical experience were necessary before bone marrow transplantation could be regarded as a therapeutic measure of relatively wide use and value. In the present era of marrow transplant expansion, as in the past, collaboration between haematologists, immunologists, paediatricians, pathologists, microbiologists, etc. from all countries is of the utmost importance. The goal of the First (4) and the Second European Symposia on Bone Marrow Transplantation, held in Courchevel, was to bring together physicians and scientists from several neighbouring countries, thus giving them the opportunity to share their experience in human marrow transplantation.

Although marrow transplantation is being increasingly used (an estimated 1000 patients have already been treated with marrow transplantation worldwide), the experience of each group is still limited. Informal exchange of precise information, especially between specialists working in different fields, was felt to be useful, interesting and necessary. This informal meeting was not intended to compete in any way with the International Marrow Transplantation meetings with their larger audience but rather to set the stage for practical collaboration between easily connected clinics or laboratories.

Methods for marrow transplantation in immunodeficiencies, aplastic anaemias and acute leukaemias are somewhat different as far as the conditioning regimen, the subsequent treatment and laboratory monitoring are concerned. Rejection of a marrow transplant does not occur in severe combined immunodeficiencies. Incomplete immune reconstitution is a problem in haematology but more so in primary immunodeficiencies. However, most immunobiological aspects (histocompatibility, prevention and treatment of graft-versus-host disease), isolation measures, and anti-infection therapies are common preoccupations and justify common efforts.

The overall European experience, as worldwide results contained in the International Bone Marrow Transplant Registry (5), shows the best results in severe combined immunodeficiency diseases: 56% long-lasting success with apparently definitive reconstitution. In the absence of a compatible donor, fetal tissue transplantation has resulted in immunological reconstitution of several patients, but the data are still too scarce and recent to allow a general analysis. In aplastic anaemia, marrow transplantation has proved successful in 36% of cases (with more than one year follow-up) and encouraging results have been obtained with antilymphocyte globulin treatment whether given alone or in conjunction with marrow infusion. All results reported reflect some progress in preceding years (4) and the latest data show even better improvement. In acute leukaemia, allogeneic marrow transplantation has not yet provided comparable results but hopes are being raised by modifications in irradiation and chemotherapy. Infusion of autologous marrow, possibly treated in vitro, may prove to be an interesting alternative. More details on these various forms of therapies will be found in the following reports.

It is the hope of all participants that the fruitful exchange of ideas on human marrow transplantation will continue to be very active and stimulating. It is their wish to gratefully acknowledge the help of the Fondation Mérieux. It is their goal to pursue the patient and international efforts which will make marrow transplantation a regularly successful form of treatment and leukaemia a curable disease. 'It is medicine's oldest dilemma, not to be settled by candor or by any kind of rhetoric; what it needs is a lot of time and patience, waiting for science to come in, as it has in the past, with the solid facts' (6).

Jean-Louis Touraine

References

1. Mathe, G., Schwarzenberg, L., Amiel, J.L. et al. (1959): Transfusions et greffes de moelle osseuse homologue chez des humains irradiés à haute dose accidentellement. *Rev. franç. Etud. clin. biol., 4,* 226.
2. Van Bekkum, D.W. and De Vries, M.J. (1967): *Radiation Chimaeras.* Academic Press, New York.
3. Thomas, E.D., Storb, R., Clift R.A. et al. (1975): Bone marrow transplantation. *New. Engl. J. Med., 292,* 832.
4. Bone Marrow Transplantation: Clinical Aspects (1978): Meeting of the Immunodeficiency Group and European Bone Marrow Transplantation Group, organized by E. Gluckman and J.L. Touraine. *Path. et Biol., 26,* 13.
5. Bortin, M.M. and Rimm, A.A. (1977): Severe combined immunodeficiency disease: Characterization of the disease and results of transplantation. *Transplantat. Proc., 9,* 169.
6. Thomas, L. (1978): Notes of a biology-watcher. On magic in medicine. *New. Engl. J. Med., 299,* 461.

ERRATUM

An error which crept in at the last minute has resulted in the transposition of pages 203 and 204. We regret this mistake and apologise for the inconvenience.

EXCERPTA MEDICA

Contents

I. Aplastic anaemia

The pattern of hemopoietic reconstitution after ALG and bone marrow infusion in severe aplastic anemia
P. Cornu, B. Speck, W. Weber, C. Nissen, J. Sartorius and P. Groff 3

Severe aplastic anaemia in adults: Histological observations in 13 patients under ATG treatment
J. Te Velde, H.L. Haak, F.E. Zwaan and P.J. Spaander 11

Bone marrow morphology after marrow transplantation, with special reference to erythroblastic islands and macrophagic reactions
A. Marmont 19

The effect of ATG on abnormal mitogen stimulation in patients with aplastic anemia
L.J.M. Sabbe, H.L. Haak, B.A. Bradley and J.J. Van Rood 31

Human-placenta-conditioned medium as source of colony-stimulating activity for human granulopoietic stem cell (CFU-C) cultures
H.-P. Lohrmann 39

Bone marrow transplantation in aplastic anemia: A new conditioning regimen using total irradiation and lung shielding
E. Gluckman, A. Devergie, A. Bussel and J. Bernard 42

Major ABO-incompatible bone marrow transplantation
A. Bussel, C. Schenmetzler, E. Gluckman, A. Devergie and J. Reviron 48

The detection of non-HLA antibodies and their significance in bone marrow graft rejection
F.H.J. Claas, J.J. Van Rood, R.P. Warren, R. Storb, P.L. Weiden and P.J. Su 57

II. Acute leukaemia

Current status and perspectives in the treatment of acute leukemia by bone marrow transplantation
B. Speck, W. Weber, P. Cornu, C. Nissen, P. Groff and J. Sartorius 65

Autologous bone marrow transplantation in acute leukemia: a review
U.W. Schaefer, J.H. Beyer, W.R. Boecker, M.R. Nowrousian, S. Oehl, C.G. Schmidt, E. Scherer, G. Schmitt, E. Haralambie, G. Linzenmeier, E. Hierholzer, E. Kuwert, W. Luboldt, L. Gerhard, L.D. Leder, V. Reinhardt, C. Stambolis and D. Hantschke 71

Cryopreservation of human bone marrow with a view to autologous bone marrow transplantation
P. Herve, E. Tamayo, C. Coffe, R. Lenus and A. Peters 80
High-dose combination chemotherapy (TACC) with and without autologous bone marrow transplantation for the treatment of acute leukemia and other malignant diseases. Kinetics of recovery of hemopoiesis: a preliminary study of the cases
N.C. Gorin, R. David, J. Stachowiak, F. Hirsch Marie, J.C. Petit, J.Y. Muller, G. Leblanc, Y. Parlier, Ch. Salmon and G. Duhamel 88
Bone marrow transplantation (BMT) in acute leukaemia with BACT conditioning: results in 7 cases
A. Grañena, C. Rozman, F. Casals, E. Felíu, J. Aranalde, E. Montserrat and L. Hernández 98
Autologous bone marrow transplantation in acute leukemia: case report and current problems
K.P. Hellriegel, W.D. Hirschmann, Ch. Gauwerky, D. Gerecke, H. Borberg and R. Gross 104

III. Immunodeficiency diseases, osteopetrosis

Heterogeneity and pathophysiology of severe combined immunodeficiency diseases
J.-L. Touraine 111
Selective defect of precursor T-cells associated with apparently normal B-lymphocytes in severe combined immunodeficiency disease
C. Griscelli, A. Durandy and J.L. Virelizier 117
Correction of severe combined immunodeficiency by fetal liver transplant: report on 2 patients
M. Fiorilli, P. Ammirati, R. Paganelli and F. Aiuti 130
Bone marrow or fetal tissue transplantation in severe combined immunodeficiencies
J.-L. Touraine 135
Lymphoid cell transplantation in experimental and human osteopetrosis
J.J. Ballet, R. Moutier, C. Griscelli and K. Toyama 139

IV. Supportive care, isolation, decontamination

The influence of HLA matching and leukocyte cross-match tests upon platelet transfusion responses in highly alloimmunized patients
J. Gmür and A. Von Felten 149
HLA and non-HLA antibodies influencing platelet transfusion results
A. Brand, A. Van Leeuwen, J. Langerak, A. Niterink, J.G. Eernisse and J.J. Van Rood 159

Infectious complications in patients undergoing bone marrow transplantation
T.R. Rogers 164
Infections in granulocytopenia. The efficacy of partial antibiotic decontamination
H.F.L. Guiot and J.W.M. Van der Meer 167
Progress with tent isolators
J.G. Watson 173
The provision of sterile drugs for patients in isolators
A. Brown and J. Sloggem 175
Studies of cytomegalovirus in donors and recipients
R.S. Pereira, T. Rogers and J.G. Watson 180

V. Antilymphocyte globulins

Comparative studies with anti-human-thymocyte globulin preparations produced in different animal species
J.G. Kreeftenberg, M.F. Leerling, M.E.M. Geleijnse, B.C. Kruijt, J. Nagel and E.J. Ruitenberg 187
The relative toxicities of different preparations of antilymphocyte globulin
M.Y. Gordon and A.J. Barret 193
Potential usefulness of heterologous antilymphocyte globulins and of anti-HLA-DR allo-antibodies in human bone marrow transplantation
J.-L. Touraine, M. Bonneau, E. Gluckman, J. Brochier, J.P. Revillard and J. Traeger 201

VI. Graft-versus-host disease

Attempted characterization of the T-cell subset responsible for the induction of GVHR
J.-L. Touraine, M.B. Gojon, J. Navarro, C. Genin, R. Falchetti, F. Touraine and O. De Bouteiller 207
Skin antibodies produced by humans after a bone marrow graft react with epidermal cell differentiation antigens
J.H. Saurat, E. Gluckman and L. Didierjean 213

Author index 223

I. Aplastic anaemia

THE PATTERN OF HEMOPOIETIC RECONSTITUTION AFTER ALG AND BONE MARROW INFUSION IN SEVERE APLASTIC ANEMIA*

P. Cornu, B. Speck, W. Weber, C. Nissen, J. Sartorius° and P. Groff

Division of Hematology, Department of Internal Medicine, Kantonsspital Basel and Kinderspital Basel°, Switzerland

SUMMARY

Immunosuppression with ALG (anti-lymphocyte-globulin) with or without marrow infusion from a haploidentical family donor has become a real alternative in the treatment of severe aplastic anemia for patients without histocompatible sibling.

Nine of 13 patients of the reported series are long-term survivors with almost complete autologous reconstitutions. All these patients experienced reconstitution 1-4 months after conditioning and restarting of the androgens. All the patients who died had not been restarted on androgens after immunosuppression and bone marrow infusion. Time factor and androgens appear to be essential in autologous reconstitutions following immunosuppression with ALG followed by marrow infusion.

Immunosuppression with anti-lymphocyte-globulin (ALG) followed or not by bone marrow infusion in severe aplastic anemia (SAA) has now become a real alternative to bone marrow transplantation (BMT) in patients without histocompatible sibling. Survival with sustained remission has been observed in over 50% of the cases as described recently (1,2).

Whether marrow infusion improves the results or not is still not clear. The answer should come from the randomized trial of the European Cooperative Group for BMT (EBMT) which is currently underway.

We would like to summarize here our experience with ALG and marrow infusion and try to emphasize some special aspects of autologous reconstitution.

MATERIAL AND METHODS

1. Patients

We have now treated 14 patients, who all fulfilled the criteria of SAA. All received ALG and marrow infusion as described later, 1 patient is too early for evaluation. The median age of the patient was 14.0 years with a range of 4-50 years. Median duration of the disease prior to ALG and

*Supported by the Swiss Cancer League Grants FOR 080.AK.75 and FOR 101.AK.77 (2) and the Swiss Science Foundation Grant 3.3320.74.

marrow was 6 months with a range of 2-38 months.

All the patients were on androgens, oxymetholone in most cases, prior to ALG. Two patients had an initial response, one of them under a very high dose of etiocholanolone. Both became refractory after 1½ year of treatment. The median duration of androgen therapy prior to immunosuppression with ALG was 3 months with a range of 1-30 months. Most of the patients received more than 20 transfusions from different donors. All patients with more than 20 transfusions were refractory to random platelets. One patient was not transfused at all. She maintained a hemoglobin of 4 g% for 1 year before a rapid deterioration began and all criteria of SAA were fulfilled.

2. Immunosuppression and marrow infusion

All the patients received 4 x 40 mg/kg body weight ALG (Lymphoser Berna, Schweiz. Serum- und Impfinstitut Bern) on consecutive days as an i.v. infusion over 3 hours under prophylactic platelet transfusion from unrelated best compatible donors. Marrow from a haploidentical family donor was infused 48 hours after the last ALG. Mean marrow cells number was 2.8 x 10^8/kg body weight (range: 1.8-4.9 x 10^8).

Supportive care was provided as for patients undergoing BMT after cyclophosphamide conditioning: platelets were transfused prophylactically by values under 20,000/mm^3, red cells were transfused in order to maintain hemoglobin levels between 8 and 10 g%. Granulocyte transfusions were performed in cases of resistent infections or septicemia, when granulocyte values were under 100/mm^3.

All blood products were irradiated in vitro with 1500 rad prior to transfusion for 6 weeks from the beginning of conditioning.

RESULTS

No patient died of conditioning toxicity. Four patients out of 14 died within 53-270 days after ALG and marrow infusion of marrow insufficiency with septicemia and hemorrhage. One patient is too early for evaluation.

The pattern of reconstitution of the 6 long-term survivors who have been followed long enough to be reasonably certain of the stability of their remission is shown in Figure 1 (5 patients 1 year and more after ALG + BM, 1 patient 6 months after remission). Three further patients are not recorded in this figure: 2 of them have now achieved a good remission and the 3rd continues to require platelet transfusions.

The time interval between ALG + BM and the moment where the criteria for SAA were not fulfilled anymore is recorded here. By now all these patients have achieved complete remissions. Most patients needed from 1 to 4 months before showing clearcut signs of reconstitution. Reticulocytes and granulocytes were seen first. Platelets came later. Hemo-

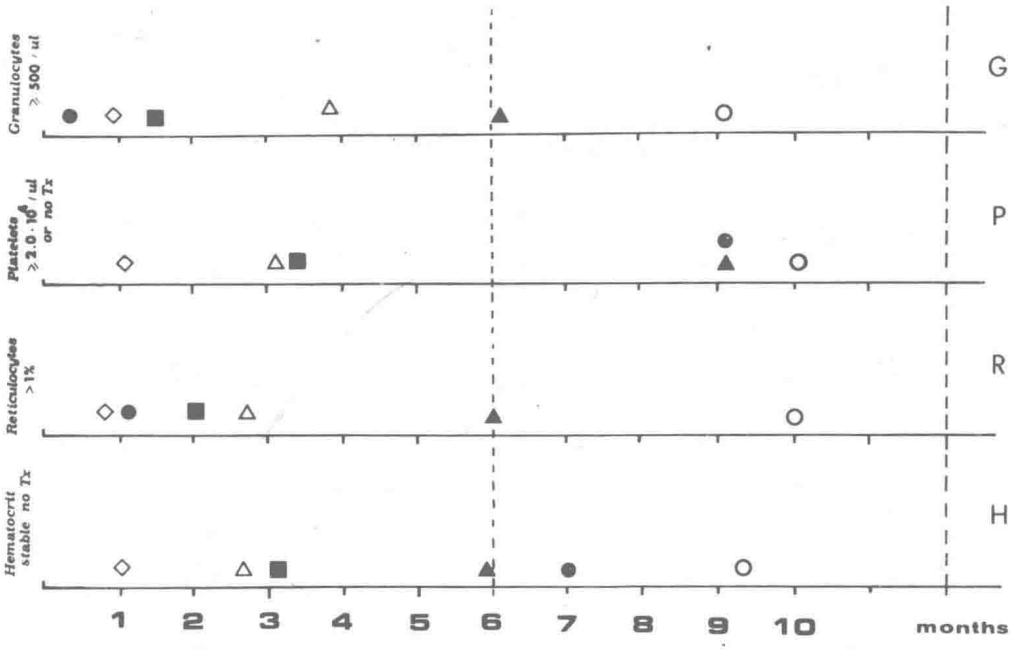

Fig. 1. Time interval between ALG + BM and the moment where the criteria of aplastic anemia were not fulfilled anymore. Symbols represent the different patients.

globin stabilized relatively late and all these patients showed initially signs of very ineffective erythropoiesis with distinct dyserythropoietic features in the bone marrow.

Three patients recovered 6-10 months only after ALG and bone marrow, so that the relation to treatment appears somewhat doubtful.

The course of such a patient with late recovery is shown in Figure 2. After ALG + BM the peripheral blood showed a transient amelioration of the reticulocytes without correction of the anemia. Nine months later the values suddenly ameliorated and the blood picture normalized. Three months before, androgens, which were stopped prior to ALG because the patient was refractory to them, were started again.

Figure 3 showed the same phenomenon in a second patient. He came into remission only 3 months after restarting on androgens, having been refractory to them prior to ALG + BM. Both patients are still androgen dependent. They both need about 10 mg oxymetholone on alternate days. The first patient was documented twice to experience relapse after androgen withdrawal. Restarting was followed by complete restoration in about 6 weeks. Considering the time interval between treatment and reconstitution corrected for androgen beginning after ALG (Fig. 4), all our long-term survivors recovered a sufficient marrow function between 1 and 4½ months after ALG + BM, as did the 2 later patients not

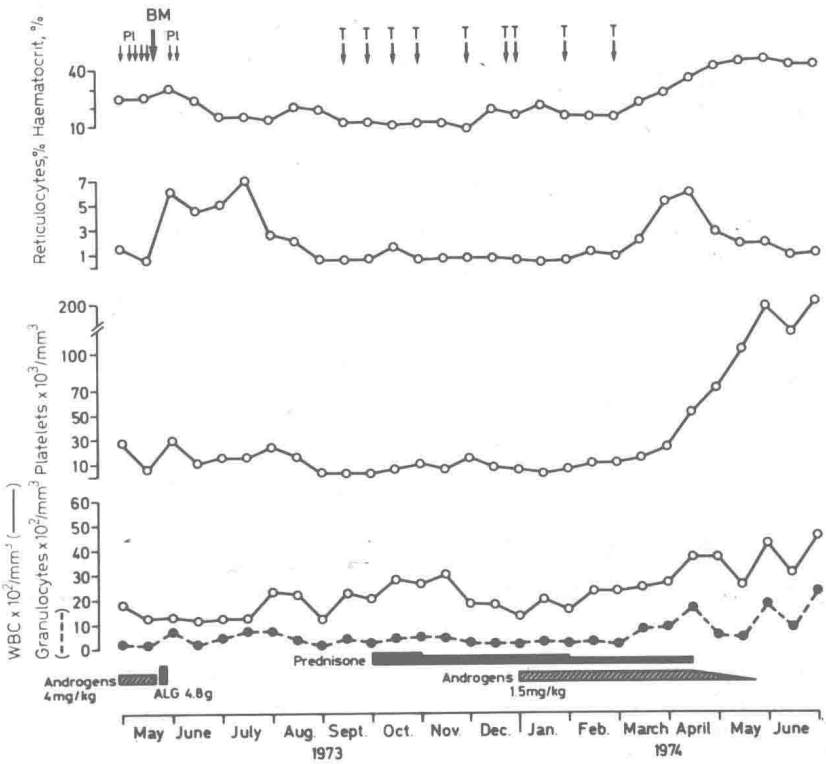

Fig. 2. Hematological course of a patient with late recovery (C.J-L. 1961).

recorded here.

Almost complete reconstitution followed the phase of self-sustaining marrow function with low counts.

Considering further the patients of our series who died we find that none of them had androgens after ALG + BM, because to that time they were considered as refractory and we did not recognize the value of androgens after immunosuppression with ALG.

Figure 5 showed the survival curve of our 13 patients. The overall survival is 69%. If we consider only the patients who received androgens after ALG + BM we have a survival of 100%. Eight of these 9 patients are now off transfusion with self-sustaining hemopoiesis and have virtually complete reconstitutions. The 9th patient has a good reconstitution of the granulocytes and of the erythrocytes but still needs platelet support.

Figure 6 shows the latest granulocyte and platelet values of all the patients. Most patients have now granulocytes over 1000/mm^3 and platelets over 50,000/mm^3. They have self-sustaining erythropoiesis.

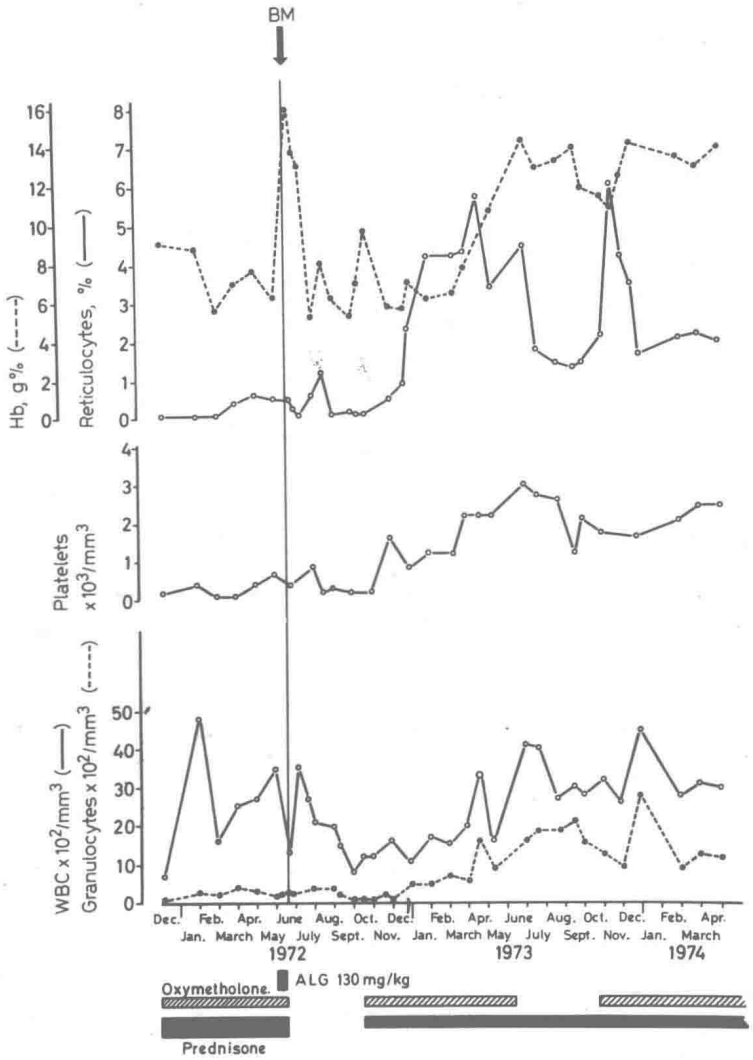

Fig. 3. Hematological course of a second patient with late recovery (H.H. 1964).

DISCUSSION

In our patients there is a clear relation between success and androgen therapy after ALG conditioning and bone marrow infusion, even if the patient was refractory to androgens prior to ALG.

The reason for this is not clear but does not seem to be depending on the kind of androgen used (3 patients had oxymetholone, 3 norethandrolone). One possibility could be some kind of further immunosuppression by a side effect of

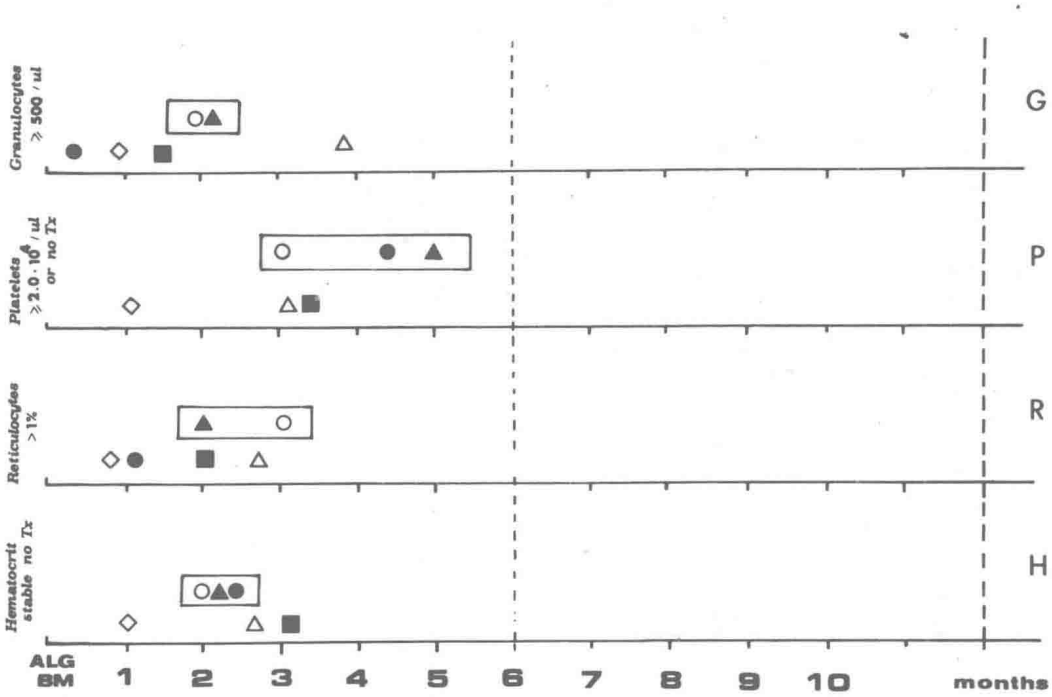

Fig. 4. Time interval between ALG + BM and beginning of reconstitution corrected for restarting on androgens after marrow infusion. Symbols in frames represent patients who were restarted on androgens late and had a 'late recovery'.

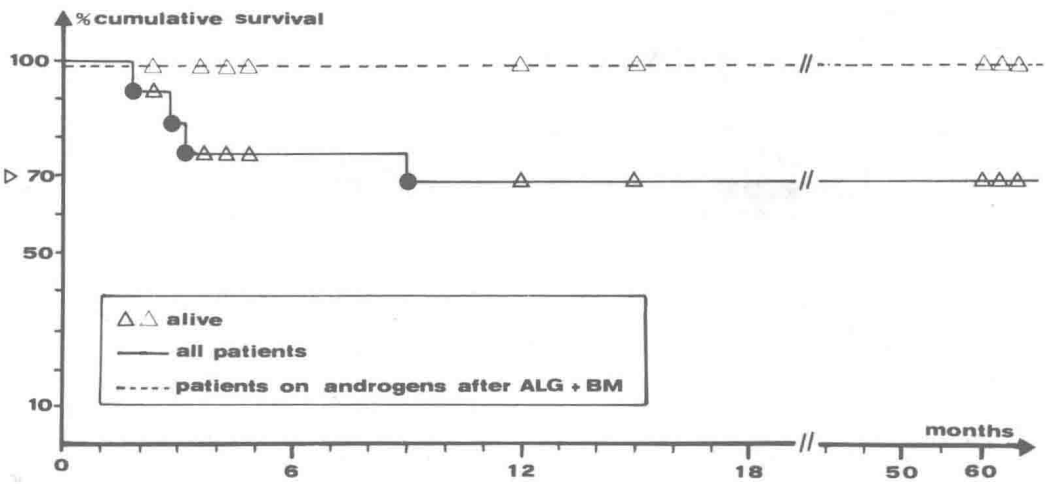

Fig. 5. Survival curves of the 13 evaluable patients. Open symbols represent living patients. The dotted curve represents survival of the patients having been restarted on androgens after marrow infusion. The other curve represents the overall survival.