Advances in the Treatment of Acute (Blastic) Leukemias

Edited by

Georges Mathé

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With 84 Figures

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Proceedings of the plenary session of the European Organization for Research on Treatment of Cancer (E.O.R.T.C.) and its cooperative groups. Paris, June 1969

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Fortschritte der Krebsforschung

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30

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Preface

The 1969 Proceedings of the Plenary Session of the European Organization for Research on Treatment of Cancer have been divided between two volumes of a completely different nature.

Volume 29, Aseptic Environments and Cancer Treatment, deals not only with the treatment of all types of cancer but also with aplastic treatment of bone marrow and certain other pathological conditions, such as immunological insufficiency, burns etc. Hence the volume will be of interest not only to carcinologists and haematologists but also to paediatricians, surgical units, intensive-care units, hospital administrators and architects and engineers who specialize in hospital design and equipment.

Volume 30, Advances in the Treatment of Acute (Blastic) Leukemias, deals with a particular form of cancer and will have a more restricted readership of carcinologists specializing in leukemia and all haematologists.

Paris, April 1970

GEORGES MATHÉ

Contents

D. Other Drugs

E. Immunotherapy

II. Strategy of the Treatment

III. Blastic Leukemias Secondary to Chronic Leukemias and Lymphomas

IV. Conclusions

Introduction

D. W. van Bekkum

President of the EORTC

The European Organization for Research on Treatment of Cancer (EORTC) has only a short history.

Nearly 7 years ago a small group of people, among them laboratory researchers as well as clinical oncologists from a number of European countries, came together and decided to start an effort towards European collaboration in the broad field of cancer treatment.

During the first few years the group's activities concentrated on the screening of chemical compounds for tumor-inhibiting properties and on the organization of clinical cooperative groups for the evaluation of new drugs in the treatment of various forms of cancer in patients.

Soon the group's adopted name, Groupe Européen de Chimiothérapie Anticancéreuse (GECA), became a widely recognized trademark, which had to be changed to EORTC in 1968, when it became clear that the potentialities of cooperation between the members and within the cooperative groups went beyond the limited field of cancer chemotherapy. Supportive cooperative groups engaged in more fundamental aspects of cancer research have been started and the members of the group have recognized the advantages of combining their efforts in other fields of research on the treatment of cancer, such as immunotherapy, radiotherapy and experimental oncology.

The present range of activities of EORTC and its associated cooperative groups can be summarized as follows.

1. Screening of substances for their anti-cancer activity using in vitro and in vivo screens. Secondary testing of specific compounds for other biological properties, such as immune suppression. More than 650 compounds have been processed so far.

2. Collaboration between clinical centers engaged in the treatment of cancer by way of the organization of clinical cooperative groups on a variety of forms of cancer. So far 10 clinical cooperative groups have been established and many of them have already produced important reports.

3. Organization of collaborative research between a number of research laboratories and departments of clinical medicine throughout Europe.

It should be mentioned here that the publication of the European Journal of Cancer, starting in 1965, has been an initiative of the EORTC and much of what is being achieved in the way of scientific research by EORTC associated workers can be found on the pages of that journal.

In looking back over the EORTC's achievements many inadequacies are still apparent, but it seems to me that we have succeeded in at least one direction, namely in abolishing various borders and barriers that have stood in the way of cancer research in Europe. I am not only referring to borders between the various nations, but also to barriers that separated the clinicians and the scientists and even different groups in one and the same country.

One tradition of the EORTC is that it attempts to organize once a year a meeting for all cancerologists at which its members and its cooperative groups present their results. This year is an important one for our organization. Not only will the meeting extend over two full days, but its program marks a serious attempt to abolish yet another barrier: that between the United States and Europe. Transatlantic cooperation will clearly be the next step in the collaborative investigation of cancer treatment.

Today, speakers from the leading centers in the United States as well as from Europe will compare and integrate their results and their visions, and, which is even more interesting, critically evaluate each other's conclusions.

It is my honour to express our thanks to Monsieur GALLEY, Minister of Scientific Research of France, for his kindness to sponsor our meeting.

We gratefully acknowledge the support of the CNRS in providing the present excellent meeting facilities and last but not least I wish to congratulate my friend GEORGES MATHÉ for his admirable achievement in the organization of the program and the many other activities that go with it. EORTC is lucky to have him, as one of the initiators of the group and its past president, continue to give us his unlimited interest and support.

I welcome all the participants and look forward to a fruitful and stimulating conference.

I. Means and Methods

A. Daunomycin

Present Results on Daunorubicine

(Rubidomycin, Daunomycin)

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With 1 Figure

We have treated 1299 patients with Daunorubicine between 1966 and 1969 (Table 1). Among those patients 785 were treated at the Hôpital Saint Louis with our personal protocols, 514 were treated according to protocols of ALGB. I am glad to have this opportinuty to thank Dr. J. F. HOLLAND for his chairmanship and for his friendship.

We would like in this presentation to recall already well known facts (activity of Daunorubicine on advanced acute lymphoblastic leukemias resistant to other drugs, induction of complete remissions in A. M. L. at a higher rate than with other drugs), we will also report results of more recent studies dealing with combinations of Daunorubicine with other drugs.

Two facts are well established. The risk of typical cardiac accidents with high doses (above 30 mg/kg within 5 months) (Table 2) and the relative rarity of such accidents at lower doses (Table 3).

However many questions remain unanswered. Is the cardiac risk as severe if total high doses are distributed within a long period of time 2 years, 3 years or more. This eventuality will be met in protocols including so called "reinduction".

Which is the responsability of Rubidomycine in the origin of equivocal accidents for which there may be other explanations (cardiac history—collapsus with sepsis). It should be outlined that these accidents are more frequent in elderly patients and are seen more often in males than in females.

That Daunorubicine may induce complete remissions in A. L. L. resistant to other drug has been confirmed since 1966 by many publications.

But the most striking feature of Daunorubicin is the ability to induce a relativity high rate of C. R. in A. M. L. as it has been already shown at the international symposium on Rubidomycin in Paris in 1967.

Table 1. *Number of patients treated by rubidomycine alone or combinated to other drugs*

Rubidomycine alone	AML	Phase 1	64		
	ALL	relapses	38		
	6706	ALGB		(27)	129
	6706 A	ALGB		(36)	211
	6806	ALGB		(12)	65
	LMC	Phase 1	16		
	Hodgkin	Phase 1	6		
Combinations	06 LA 66		130		
	6801	ALGB		(33)	109
	06 LA 66 01 LA 67 02 LA 67 02 LA 68	relapses of ALL	270		
	06 LA 66 LBS		50		
	Quintuple		50		
	RU+MTX		17		
	RU+Aase		9		
	Epitheliomas		135		
	Total		785	(108)	514 1299

June 1969.

Table 2. *Deaths from cardio toxicity. Observed in A. L. treated with rubidomycin*

Leukemia	Total dose (mg/kg)	Interval between beginning of treatment and first cardiac troubles
LAL, 6 y.	42	5 months
LAM, 10 y.	40	6 months
LAL, 6 y.	32	5 months
LAL, 10 y.	42	5 months
LAL, 8 y.	45	6 months

Table 3. *Cardiac toxicity*

	Number of patients	Unequivocal cardiac toxicity	Equivocal cardiac toxicity
> 30 mg/kg	13	5	
< 30 mg/kg	1010	2	22
Total	1023	7	22

Table 4. *Protocol Paris 06 LA 66*

Pred. 100 mg/m²/d.
Vinc. 2 mg/m²/w.
Rub. 60 mg/m²/w.
→ RC → Maintenance { 6MP 90 mg/m²/d. / Mtx 15 mg/m²/w. + Mtx IT/m 10 mg/m²
+ Reinductions { Pred. 100 mg/m² × 7 d. / Vinc. 2 mg/m²/d. 1 and 7 / Rub. 30 mg/m²/d. 1 and 7 / Mtx IT—2 Inj. 10 mg/m²
At 0.5, 1, 2, 4, 7, 11, 16 months
→ ev. 6 months

Table 5. *Results obtained with daunorubicin in induction. Treatment for acute myelocytic leukaemia*

Result	1st attack		1st relapse		2nd relapse		3rd relapse		Total
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	
Complete remission	6	20	3	3	1	1	1	0	35
Partial remission	0	4	1	1	0	1	1	0	8
No improvement	1	12	0	5	2	1	0	0	21
Total	7	36	4	9	3	3	2	0	64

In our experience, the maximum daily dose was 2 mg/kg; the number of doses and duration of treatment varied from one case to another depending on the decrease of white blood cells and the modifications of bone marrow smears, the percentage of blast cells and cellularity being especially taken in consideration. On the whole the mean number of doses was 7 and the mean total dose given was 12 mg/kg.

In the first 64 patients with acute granulocytic leukemias treated according to the protocol indicated on Table 4, 35 complete remissions were attained (Table 5); more remissions were obtained in children than in adults. All patients suffered a severe aplasia and most of the patients who did not attain remission died during induction phase from bleeding or still more frequently from sepsis. These aplasias are the main draw back of Daunorubicine.

In these 35 patients the median remission time has been 155 days; in four cases however it lasted more than two years and 2 of these patients are still in remission after two and half years: both were promyelocytic forms and we must emphasize the striking sensitivity to Daunorubicine of these forms formerly the most severe of all.

We shall now consider combinations with Rubidomycine: in A. L. L. Rubidomycine has been added since 1967 to the program that we apply at the Hôpital Saint Louis since 1963. This program combines an induction treatment with Vincristine and Prednisone, a maintenance treatment with continuous 6-MP and intermittent Methotrexate, and systematic "reinduction" courses at definite intervals.

Table 6. *Treatment of AML with rubidomycin Paris protocol*

Induction	Maintenance	Reinductions
		1, 2, 4, 7, 11 months
Ru. 60 mg/m²	6-MP 90 mg/m²/d.	Ru. 30 mg/m²/days 1 and 8
2—7 days	Mtx 15 mg/m²/w.	M. GAG. 350 mg/m²/days 3 and 5

Table 7. *Protocole 06 LA 66 (Paris). Mars 1967, coloque international sur la rubidomycine*

	Enfants	Adultes	Total
R. C.	17	8	25
R. I.			
Echecs		3	3
Total	17	11	28

Table 8. *Results of combination of L-asparaginase. Vincristine rubidomycine prednisone in ALL*

Number of cases	1st attack	1st relapse	2nd relapse	3rd relapse	4th or 5th relapse	Total
Complete remissions		13 (6)	4 (3)	2	2 (1)	21 (10)
Partial remissions			1			1
Partial failure		1				1
Total failure		1 (1)				1 (1)
Death on treatment		3 (2)				3 (2)
Total		18 (9)	5 (3)	2	2 (1)	27 (13)

Between brackets figure the patients with prior treatment of Prednisone—Vincristine—Rubidomycine. June 1969.

The interest of these inducer doses is proved by our results and also by those of two independant protocols of ALGB; ALGB 6413 and ALGB 6601.

It is not our intention to detail these results but 25% of the patients treated according to he protocol initiated in 1964 are still in remission between the forth and the fifth year. Those datas are impressive if one considers that until now the frequency of remissions lasting more than 5 years was evaluated approximately at 1%.

Protocol Paris 6606 is indicated on Table 6.

The first results, presented at the "International Symposium on Rubidomycin" in March 1967 showed a high rate of remissions. Complete remissions are obtained with high frequency in adults, in very young people (less than 1 year) and in forms with high leucocytosis. In one patient who attained complete remission, white blood cells count was 1 600 000 (Table 7).

Fig. 1 shows the initial comparison of protocols 02 LA 64 and 04 LA 65 (which differ only by the frequency of induction doses) and protocol 6606.

Studies on the combination of Vincristine, Daunorubicine, Asparaginase and Prednisone are pursued on relapses as well as on first attacks and complete remissions are

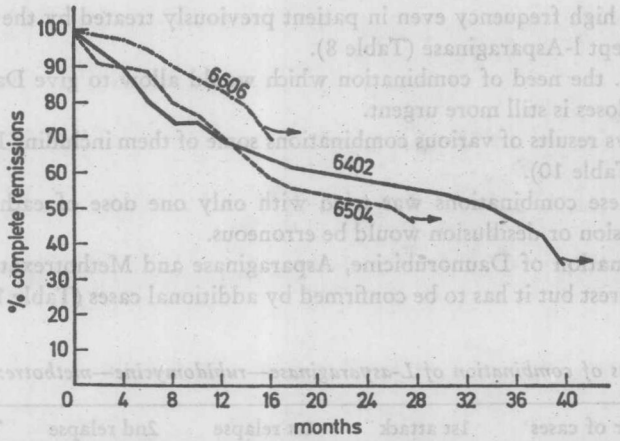

Fig. 1. Duration of first complete remission in children ≤ 15 years. — 6402 (41 c.), - - - 6504 (38 c.); —·—·— 6606 (87 c.)

Table 9. *Acute granulocytic leukemias*

Induction treatment	Years	No. of cases	No. of C. R.	% of C. R.
Pr+MTX	1956—1960	118	17	14
6-MP+GAG	1963	45	14	33
6-MP+GAG+MTX	1964	24	9	35
Ara-C	1965	39	12	30
Ara-C+GAG+6-MP+Pr	1966	37	13	35
Total	1956—1966	263	65	23

> 4 years, 7 cases. June 1969.

Table 10. *Acute granulocytic leukemias*

Rubidomycine	Years	No. of cases	No. of C. R.	% of C. R.
	1967	64	35	54
ALGB A (3 days)		45	13	29
6706 B (5 days)	1968	49	11	22
C (7 days)		31	7	22
ALGB A (5 days)		61	21	34
6706 A B (b; w.)	1968	62	13	21
C (o. w.)		75	12	16
Ara-C+GAG+ 6-MP+RU+Pr	1968	32	13	40
6-MP+GAG +RU+Pr	1968	18	6	35
RU+MTX	1969	17	6	35
RU+MTX+Aase	1969	9	5	55
Total	1967—1969	463	142	32

June 1969

obtained with high frequency even in patient previously treated by the drugs already mentioned except l-Asparaginase (Table 8).

In A. M. L. the need of combination which would allow to give Daunorubicin at the less toxic doses is still more urgent.

Table shows results of various combinations some of them including Daunorubicine (Table 9 and Table 10).

Each of these combinations was tried with only one dose of each drug so that definite conclusion or desillusion would be erroneous.

The combination of Daunorubicine, Asparaginase and Methotrexate appeared to have some interest but it has to be confirmed by additional cases (Table 11).

Table 11. *Results of combination of L-asparaginase—rubidomycine—methotrexate in A. M. L.*

Number of cases	1st attack	1st relapse	2nd relapse	Total
C. R.	4+1 [a]	1		5+1 [a]
Partial remission				
Partial failure			1	1
Total failure	1			1
Total				8

[a] Death in C. R. on day 30. June 1969.

One may thus conclude that Rubidomycine is a significant aquisition in the treatment of acute leukemias. Its major toxic threat is marrow aplasia rather than cardiac toxicity which is important only at high doses, in elderly patients or in those who have a cardiac history.

Its future lies mainly in active combinations.

Summary

The present status of daunorubicin results is summarized.

This drug, given alone, induces a relatively high rate of complete remissions in A. M. L.

Cardiac toxicity does not seem to offer an excessive threat if daunorubicin administration is avoided in patients with a cardiac history and in elderly patients, and if total doses are below 30 mg/kg.

The major drawback of daunorubicin is the risk of severe irreversible aplasias.

Given in combination with vincristine and prednisone, daunorubicin induces a high rate of complete remissions in A. L. L. even in poor-risk patients.

Studies of combinations, of daunorubicin, vincristine, prednisone and L-asparaginase in A. L. L. are in progress.

In A. M. L. combinations of daunorubicin with the other active drugs (ara-C, méthyl-GAG, etc.) were tried.

A study of the combination of L-asparaginase and daunorubicin is in progress.

Rubidomycin (or Daunomycin): A Clinicial Evaluation

"Leukemia and Hematosarcoma" Cooperative Group [1] of the European Organisation for Research on the Treatment of Cancer (E.O.R.T.C.)

Secretaryship: Institut de Cancérologie et d'Immunogénétique, Hôpital Paul-Brousse 14, avenue Paul-Vaillant Couturier, 94-Villejuif

With 3 Figures

Since Rubidomycin or Daunomycin has been used in the treatment of acute leukemias its effectiveness and toxicity have been differently evaluated. It might be profitable to point out a few conclusions drawn from therapeutic trials carried out by the Leukemia Group of E.O.R.T.C. and by MATHÉ's group.

On Table 1, we can see that Daunomycin used alone is less effective than Prednisone or Vincristine.

Table 1. *Value of efficient drugs in acute lymphoblastic leukaemia to induce complete remissions*

Drugs	Frequency of complete remissions
Prednisone	58%
Vincristine	43%
Daunomycin	25%

[1] President: W. F. STENFERT-KROESE; Responsible for the E.O.R.T.C.: G. MATHÉ; Secretary: M. HAYAT. Members who have cooperated to this trial: ALLEMAGNE: S. WITTE, K. TH. SCHRICKER (Medizinische Klinik mit Poliklinik der Universität Erlangen-Nürnberg, Erlangen); BELGIQUE: H. TAGNON, Y. KENIS (Institut Jules Bordet, Bruxelles); P. BASTENIE, CH. CAUCHIE (Hôpital Saint-Pierre, Bruxelles); FRANCE: J. BOUSSER, G. BILSKI-PASQUIER, A. BERNADOU, C. M. BLANC, R. ZITTOUN (Hôpital de l'Hotel-Dieu, Paris); P. CROIZAT, L. REVOL, J. J. VIALA (Hôpital Edouard-Herriot, Lyon); G. MATHÉ, J. L. AMIEL, A. CATTAN, M. HAYAT. F. DE VASSAL, CL. JASMIN, CL. ROSENFELD, J. R. SCHLUMBERGER, M. SCHNEIDER, L. SCHWARZENBERG (Service d'Hématologie de l'Institut Gustave-Roussy et Institut de Cancérologie et d'Immunogénétique, 94-Villejuif; GRANDE-BRETAGNE: G. HAMILTON FAIRLEY, R. B. SCOTT, M. LIPSEDGE (Saint Bartholomew's Hospital, Londres); HOLLANDE: W. H. STENFERT-KROESE (Rotterdamsch Radiotherapeutisch Instituut, Rotterdam); IRLANDE: J. B. HEALY (Saint-Luke's Hospital, Dublin); ITALIE: R. BULGARELLI, L. MASSIMO (Istituto G. Caslini, Gênes); L. BUSSI, D. CIPRINANI (Ospedale Maggiore Ca'Grande, Milan); E. POLLI, G. SALA (Istituto de Semeiotica Medica, Milan).