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A Survey of the Anthracycline Derivatives in Hematology

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Summary. *The anthracyclines, of which daunorubin (DNR), rubidazone (RBD), and adriamycin (ADR) are the most commonly used in cancer chemotherapy, belong to the group of intercalating agents capable of inhibiting the replication and transcription of DNA, and of fragmenting DNA and inhibiting the mitochondrial respiratory chain. Their experimental antitumoral activity varies according to the product, the type of tumor, and the route of administration. Following intravenous (IV) injection, they are distributed throughout all body tissues except those of the central nervous system and are metabolized principally in the liver, 90% of the metabolites being excreted in the bile. Excretion is slow, permitting intermittent high-dose therapy. Their principal toxicity is cardiac, presenting as congestive cardiac failure, which occurs when a specific cumulative dose of anthracycline is exceeded. This effect may be due to the formation of free semiquinone radicals from the anthracycline nucleus by the capture of electrons from the mitochondrial respiratory chain.*

Only a few of the most active derivatives have been studied in man and the search continues for active agents devoid of cardiotoxicity. The therapeutic indications vary according to the derivative. DNR, which we have utilized since 1967, is remarkably effective in induction therapy for acute myeloblastic leukemia, is the only agent which is effective in acute promyelocytic leukemia, and increases the number of complete remissions in acute lymphoblastic leukemia in the adult and in severe childhood forms of this disorder. ADR is active against solid tumors (thyroid, breast, osteosarcoma) and also against lymphomas. RBD induces a complete remission in two-thirds of the cases of acute monoblastic leukemia, is equally as effective as DNR in acute myeloblastic leukemia, and is significantly more manipulable. This agent may similarly induce a remission in the severe lymphomas (lymphosarcoma and Hodgkin's disease). A new semisynthetic compound, DEA.14.DNR, appears promising. Experimentally it compares favorably with the other anthracyclines and clinically demonstrates potential against solid tumors.

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Introduction

The most significant discoveries in cancer chemotherapy during the last 10 years have concerned the anthracyclines and, in particular, daunorubicin (DNR), doxorubicin or adriamycin (ADR), and rubidazone (RBD). Although several hundreds of products obtained by fermentation or semisynthesis have been investigated in the laboratory, only a few have been studied in man.

The object of the clinical and experimental research up to the present time has been to find a compound combining a high antitumoral activity with a low toxicity and, in particular, a low cardiotoxicity. All of these compounds contain an anthracycline nucleus and an amino sugar in their chemical structure. The majority of agents in this family differ only at the C13-C14 side chain (Fig. 1).

Differences in the metabolism and perhaps in the immunosuppressive activity of these closely related chemical compounds may explain the superiority of one or the other or their preferential activity against differing types of human tumor (Jolles, 1975). Recent studies have advanced our understanding of the mechanism of action of these agents. They infiltrate the deoxyribonucleic acid (DNA) helix ('intercalating agents'), thus inhibiting replication and transcription. They fragment DNA, inhibit the mitochondrial respiratory chain, and may generate free radicals and also act on the cell membrane.

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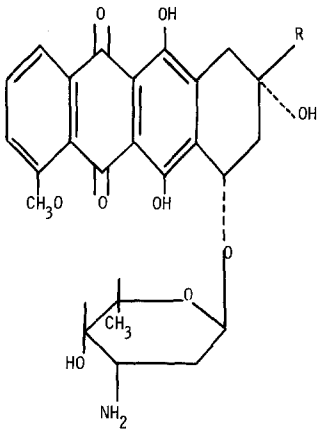

Compound	R
Daunorubicin (DNR)	$-CO-CH_3$
Daunorubicinol (Duborimycin)	$-CHOH-CH_3$
Benzoyl hydrazone DNR or Rubidazone (RBD)	$-C(CH_3)=N-NH-CO-C_6H_5$
Doxorubicin or Adriamycin	$-CO-CH_2OH$
14-Diethoxyactetoxy DNR (14DEA.DNR)	$-CO-CH_2-O-CO-CH(OC_2H_5)2$

Fig. 1. Product: daunorubicin (DNR), daunorubicinol-duborimycin, benzoyl hydrazone derivative of DNR or rubidazone (RBD), doxorubicin or adriamycin, diethoxyacetoxy-14-DNR (DEA.14.DNR)

Results and Discussion

The principal experimental characteristics of these agents may be summarized as follows (Maral, 1978).

They are *cytotoxic* and act principally in the G1 and especially the S phase of the cellular cycle, but would be equally effective in G0. The investigation of drug concentrations resulting in 100% killing of KB cells in culture has demonstrated that rubidazone is 4–8 times less cytotoxic than the other compounds.

They inhibit *DNA synthesis* (studied by the incorporation of tritiated thymidine into KB cells), this action being slower with rubidazone and most rapid with daunorubicin.

They inhibit *RNA synthesis* (studied by the incorporation of tritiated uridine into KB cells), but to a lesser degree than that of DNA; this effect is most marked with daunorubicin.

These products have no effect on protein synthesis. Mutagenic activity studied by the Ames test (*Salmonella typhimurium* his-) is least marked with rubidazone at corresponding molar concentrations.

Investigation of the 50% *lethal dose* (LD_{50}) and the *maximum tolerated dose* (MTD) of these products has revealed that rubidazone is the least toxic.

Cardiotoxicity may be studied by a number of techniques: using the method of Zbinden (1975), the prolongation of the QRS interval is observed in rats treated by intraperitoneal (IP) administration; using that proposed by Jaenke (1974), the development of congestive cardiac failure and the appearance of abnormalities in the myocardial cells (demonstrated extremely early by electron microscopy) are followed in the rabbit treated by IV administration. Cardiotoxicity has also been studied by Schmidt (unpublished results), using the monkey (development of cardiomegaly, anatomical study). In man, the surveillance of cardiotoxicity by means of myocardial biopsy (Stanford technique), electrocardiography, or sphygmomanometry is strongly recommended. It appears that rubidazone is 4–5 times less cardiotoxic than the other compounds.

Table 1. DEA.14.DNR, ADR, and DNR classified according to activity (administered at maximum tolerated doses, MTD)

	DEA.14.DNR	ADR	DNR
S 180	2	2	1
L 1210	1	2	3
P 388	1	2	3
AKR	1	1	2
Mam C.	1	3	2
Leuco S.	2	1	3

MTD: DNR-DEA-14 DNR 2.5 mg/kg/d/5 days; ADR 1.25 mg/kg/d/5 days

The *antitumoral activity* has been studied experimentally by means of tumor-cell transplants in the mouse, and sarcomas, leukemias (L 1210, AKR, P 388), and diverse carcinomas have been utilized for this purpose. The activity has been estimated according to two parameters, the weight of the tumor or the survival of the animal. The activity of the different anthracycline compounds depends on the nature of the tumor, the route of administration of the medication, and the treatment protocol. For example, using leukemia L 1210 cells administered intraperitoneally (day 0) and treated for a period of 5 days (days 0–4) by IP therapy, the therapeutic indices (LD_{50}/active $dose_{50}$) are, respectively, 10–12 for rubidazone, 6–10 for daunorubicin, and markedly greater than 12 for diethoxyacetoxy-14-daunorubicin (DEA.14.DNR). We have classified daunorubicin, adriamycin, and DEA.14.DNR according to these criteria (Table 1), demonstrating the superiority of this latter agent. (Maral, 1978).

The *immunosuppressive activity* of the anthracyclines varies according to the compound studied and the experimental techniques selected. It would seem, however, that rubidazone and DEA.14.DNR are less immunosuppressive than adriamycin and daunorubicin.

The *metabolism* of the anthracycline compounds has been studied by Bachur et al. (1970) and Asbell et al. (1972), who have demonstrated in vitro that daunorubicin is degraded by two processes occurring simultaneously, a cleavage of the glycosidic radical (to

aglycone) and a reduction of the acetyl group giving daunorubicinol. Bachur has shown that the reduction of daunorubicin to daunorubicinol is catalyzed by the enzyme daunorubicin reductase (aldoketoreductase). Huffman and Bachur (1972) have reported that leukemic myeloblasts have a concentration of this enzyme which is 4–9 times greater than that of normal leukocytes. A relationship between the enzyme concentration and the therapeutic activity has also been documented.

Pharmacokinetic differences may explain the individual pharmacologic properties of these products.

The majority of metabolite excretion occurs into the bile, urinary elimination accounting for only 10%.

The kinetics of the disappearance of the anthracyclines from the plasma have been studied by Benjamin et al. (1976). The distribution of these products occurs according to a two-compartment mathematical model, there being a rapid hepatic clearance (half-life 1.1 h) and a slow excretion (half-life 16.7 h). This delayed and prolonged excretion permits the use of intermittent high-dose therapy. Benjamin has reported that rubidazone disappears less rapidly than daunorubicin, with a relatively diminished excretion of daunorubicinol. The preponderant role of the liver in anthracycline metabolism necessitates tremendous precaution in the face of hepatic dysfunction: the dose should be reduced by 50% if the serum bilirubin exceeds 30%, and by 75% if greater than 100 mg-%. In contrast, renal insufficiency does not necessitate such strict restrictive measures.

The distribution of adriamycin following IV injection in the rat has been studied by Harris and Gross (1975), who have documented the rapid appearance of high concentrations of the drug in all tissues except those of the central nervous system (a finding well known to clinicians). The cytotoxicity of these agents is augmented at a temperature exceeding 42° C, which may explain the favorable results obtained by certain workers using hyperthermia combined with an intermittent, high-dose chemotherapeutic regimen. It should be pointed out that the administration of phenobarbital or its analogs, which induce microsomal activation, augments the cytotoxicity of the anthracyclines.

Toxicity

Although marrow suppression or total aplasia are therapeutic goals in the treatment of acute leukemia, it is precisely this acute toxicity which may limit therapy in the management of solid tumors.

The long-term toxicity of the anthracyclines is essentially limited to the myocardium. Certain electrocardiographic changes may occur either during or immediately following the single injection of an anthracycline (sinus tachycardia, extrasystoles, ST or T wave changes, or diminished systolic interval). These acute manifestations are generally rapidly reversible; certain ones, however, when persistent, may suggest the development of a cardiomyography (prolongation of QRS interval, microvoltage). The immediate cessation of therapy and the commencement of digitalis, diuretic, and corticosteroid therapy generally control the manifestations of cardiac insufficiency. The frequency of development of cardiac failure is a function of the total administered dose (exceptional below 300 mg/m^2, very rare below 500 mg/m^2, 10% of cases above 800 mg/m^2, 50% of cases above 1200 mg/m^2). It is customary to cease therapy when the respective cumulative doses reach 500 mg/m^2 for adriamycin, 650 mg/m^2 for daunorubicin, and 1800–2000 mg/m^2 for rubidazone.

The mechanism of the cardiotoxicity remains poorly understood. The inhibitory effect on DNA synthesis in the cardiac muscle does not seem to be the primary cause. Iwamoto et al. (1974) has demonstrated that the anthracyclines inhibit the coenzyme Q10-dependent enzymes such as succinoxydase and NADH-oxydase, which are intimately concerned in the energetic metabolism of the heart. Further, Bachur et al. (1977) and Ferrero et al. (1976) have shown the existence, in the rabbit, of a reduction in the oxidative capacity of myocardial mitochondria, a reduction attributed to the capture by the anthracyclines of the electrons transported by the respiratory chain; the semiquinone radical thus formed is capable of generating free radicals, in particular O_2^- which may result in the peroxidation of membrane lipids. This generation of free radicals explains the cytotoxicity in the G0 phase. On this basis, the administration of α-tocopherol (free radical scavenger) or antioxidant agents has been suggested in order to diminish the cardiotoxicity.

Among those anthracyclines studied in the rat and the rabbit, certain ones appear to be less cardiotoxic: in addition to rubidazone, these are N-trifluoro-acetyl-adriamycin-14-valerate (AD 32) and adriamycin octanoate, which have been investigated by Israel et al. (1975) and Pratesi et al. (1978), respectively.

These derivatives appear to be less toxic, but are not water soluble. Similarly, daunorubicin and adriamycin when complexed with DNA are active in the human and less cardiotoxic than the uncomplexed product.

Attempts have been made to prevent cardiotoxicity by the use of other therapeutic protocols, for example, the administration of small doses of the agent at weekly intervals (30 mg/m^2/week) over a prolonged period. We had already noticed in 1966 that, rather than the total dose of drug administered, the important parameter was the cumulative dose (mg/kg)/duration (months) ratio, which should remain less than 1.

A number of authors have proposed the administration of digitalis prior to commencing therapy in order to

prevent cardiotoxicity by a local competitive effect; however, it has been observed that adriamycin binding in the heart is not modified by strophanthine.

Finally, to conclude the problem engendered by anthracycline toxicity, it is important to bear in mind the propensity of these agents to aggravate the sequelae of anterior radiotherapy, particularly when these lesions are localized to the skin or the esophagus. Even when used prior in radiotherapy, the anthracyclines limit the maximal tolerated dose, thus perhaps compromising the combined use of these two forms of therapy in the lymphomas, cancer of the breast, and small-cell cancer of the lung.

Prior to concluding this general review of the biological properties of the anthracyclines, it should be noted that the covalent binding of antibodies to the anthracyclines produces agents with dual activity, both chemotherapeutic and immunologic.

Clinical Use

The initial results were published more than 10 years ago, and in 1967, an international symposium on these agents was convened in Paris (Bernard, 1969; Colloque Int. Rubidomycine, Daunorubicin, Paris 1967; Dubost, 1963; Jacquillat, 1966). Within a few months, due to remarkable teamwork, the complete role of daunorubicin in hematology had practically been established.

Daunorubicin. Outstanding medication for the induction of complete remission in acute myeloblastic leukemia, remission being achieved in more than half the patients (2 mg/kg/day for 5 days). A tremendous amount of patience was required to convey this fact to our American colleagues, but now the combination of cytosine arabinoside and daunorubicin is utilized throughout the world in this situation (Weil et al., 1973).

The only active medication which is rapidly effective in the treatment of acute promyelocytic leukemia, achieving a 75% incidence of complete remission (Table 2) with a median remission of 4 years (with plateau), survival of 35%, and no recurrence after 3 years of remission (11 patients followed for between 3 and 11 years) (Fig. 2).

Daunorubicin is of debatable value in acute lymphoblastic leukemia, common in childhood, where the combination of prednisone and vincristine induces a complete remission in nearly 90% of cases. On the other hand, in the adult, and in the childhood forms with poor prognostic features (age greater than 15 years, white count greater than 30,000/mm^3, cytologic type 2 or 3, tumor masses, in particular mediastinal), the addition of daunorubicin to this regimen seems to be essential, increasing the incidence of remissions to 80%. In acute lymphoblastic leukemia in relapse, daunorubicin combined with cytosine arabinoside and cyclophosphamide, according to a number of protocols, permits the achievement of a second complete remission in 55% of cases.

Table 2. Results of induction therapy in acute promyelocytic leucemia

	Previous therapy	Daunorubicin	Daunorubicin + heparin
Complete remission	5	13	21
Incomplete remission	–	–	1
Failure	11	–	–
Death during induction	26	16	5
Total patients treated	42	29	26
% Complete remission	12	45	78
	$P < 0.001$	$P < 0.01$	

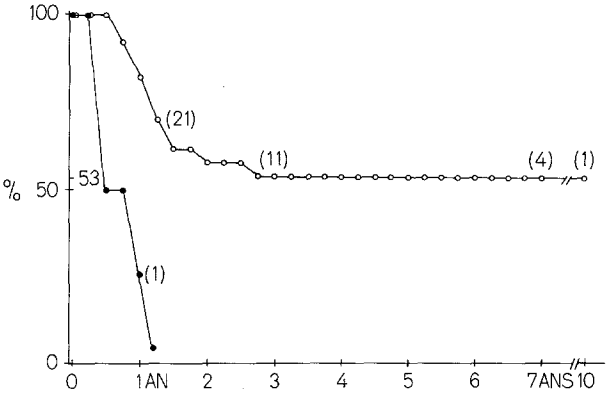

Fig. 2. Actuarial survival curve of patients with acute promyelocytic leukemia treated with daunorubicin. ● = Previous protocols: 42 cases; ○ = daunorubicin ± heparin: 55 cases

Doxorubicin (Adriamycin). This is medication which is active against solid tumors (thyroid, breast, soft tissue sarcomas, osteosarcomas in particular), and also effective against lymphomas, and may be combined with other antimitotic agents in variable polychemotherapeutic protocols. Our experience with adriamycin has concerned particularly the therapy of lymphosarcoma, using the protocol 03 LRS 74 which consists of the combination of cyclophosphamide 600 mg/m^2, day 1; vincristine 2 mg/m^2 IV, day 1; adriamycin 30 mg/m^2 IV, days 1–3; and prednisone 45 mg/m^2 orally, repeated every 10 days. This combination used as induction therapy has resulted in complete remission in 75% of cases in those forms of the disorder with the least favorable prognosis (diffuse and disseminated).

Rubidazone. This agent has been used in this service since 1972, in more than 500 patients (Jacquillat, 1972). The indications for its use we consider to be as follows:

In acute monoblastic leukemia (5% of acute leukemias) in a dose of 4 mg/kg/day for 5 days, repeated around the 20th day in one third of cases, it results in complete remission in two-thirds of cases (Table 3). With regular monthly reinduction therapy and irradiation of the central nervous system, remissions are relatively prolonged, as shown in Fig. 3.

In acute myeloblastic leukemia, used as the sole agent, the same protocol of rubidazone administration results in a 60% complete remission rate (Table 4), and the less rapid action of this agent permits a greater therapeutic margin. The total dose required to induce complete remission varies, in our series, between 20 and 30 mg/kg while with daunorubicin the therapeutic range is 2–25 mg/kg. Rubidazone is thus certainly easier to manipulate than daunorubicin when the therapeutic end point is marrow aplasia.

In the lymphomas, lymphosarcomas, and Hodgkin's disease, rubidazone may induce remission in patients resistant to standard protocols, but our experience in this field remains limited.

Randomized studies are underway both in France and in the United States (Southwest Oncology Group) to compare the respective advantages of these three compounds, daunorubicin, adriamycin, and rubidazone, in the management of solid tumors, lymphomas, and leukemia. An interesting combination, rubidazone 200 mg/m^2, day 1, vincristine 1.4 mg/m^2, day 1, prednisone 100 mg/m^2, days 1–7, cytosine arabinoside 70 mg/m^2, days 1–7, results in a greater than 70% incidence of complete remission in acute myeloblastic leukemia in the adult (Benjamin et al., 1976).

Duborimycin (Daunorubicinol). This is the first metabolite isolated in an animal following daunorubicin injection, but, while presenting certain interesting experimental characteristics, it has not lived up to expectations. The group headed by Chauvergne et al. (1976) at Bordeaux has terminated the study on this agent; it had demonstrated several interesting subjective effects in cancer of the breast with painful bony metastases and objective effects in metastatic melanoma.

Aclacinomycin A. Recently, Oki et al. (1975) has demonstrated the possibilities of the aclacinomycines, anthracyclines containing three sugars: daunosamine, deoxyfucose, and deoxycinerulose. Experimentally, these compounds would not appear to be cardiotoxic, but as of the present we have no experience with them.

Dietoxy-Acetoxy-Daunorubicin (DEA-DNR). A few months ago, we obtained a new semisynthetic anthracycline 33 921 RP, which appears extremely interesting (Fig. 1). The experimental antitumoral activity of this compound has been compared with that of the other products in this group (Maral, 1978). The classification

Table 3. Results of induction therapy in acute monoblastic leukemia (99 cases)

	Previous protocols	DNR 2 mg/kg/ 5 days	RBD 4 mg/kg/ 5 days
Complete remission	10	7	22
Incomplete remission	2	1	1
Failure	23	1	2
Death during induction	17	5	8
Total	52	14	33
% Complete remission	19	50	67
		$P < 0.0001$	

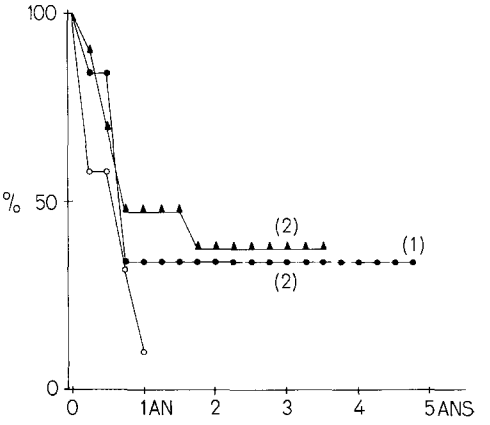

Fig. 3. Duration of complete remission in patients with acute monoblastic leukemia treated with rubidazone or daunorubicin. ○ = Previous protocols: 10 cases; ● = daunorubicin: 7 cases; ▲ = rubidazone: 22 cases

Table 4. Results of induction therapy in 287 patients with acute myeloblastic leucemia

	DNR	DNR + Ara-C	RBD	Total
Complete remission	48	55	38	141
Incomplete remission	10	6	3	19
Failure	33	23	13	69
Death	31	13	14	58
Total	122	97	68	287
% Complete remission	39	57	56	
		$P < 0.02$		
			$P < 0.04$	

presented in Table 1 demonstrates that DEA-DNR is often superior to doxorubicin, occasionally equivalent but very rarely inferior. The maximum tolerated dose is 2.5 mg/kg/day both for DEA-DNR and for daunorubicin and 1.25 mg/kg/day for doxorubicin. Although the cardiotoxicity of the two products is of the same order, as determined by the tests of Zbinden (Zbinden and Brandle, 1975) and Jaenke (1974), a careful follow-up of cardiac function in clinical practice has revealed no complications up to the present time with the use of doses less than 20 mg/kg (the period of retrospect, however, being rather short).

The doses which we are currently using in man are: 2 mg/kg, with 4–6 consecutive administrations in acute leukemia, 120 mg/m^2 as a single dose every 3 weeks in solid tumors, 2 mg/kg for two consecutive administrations every 15 days in malignant lymphomas, and 1 mg/kg per week in generalized hematodermia.

Table 5. Patients treated with DEA.14.DNR

	Cases
Acute lymphoblastic leukemia	31
Acute myeloblastic leukemia	14
Acute promyelocytic leukemia	1
Lymphosarcoma	7
Hodgkin's disease	5
Chronic myeloid leukemia	4
Soft tissue sarcoma	3
Epithelial carcinoma	7
Adenocarcinoma	6
Others	5
Total	83

The patients we have treated up to the present time are reported in Table 5. With continuous treatment, and a total dose of 10–14 mg/kg, immediate cardiac tolerance is good, but digestive disorders are more marked than with daunorubicin. The appearance of severe buccal and gastrointestinal ulcerations occurring in coincidence with marrow aplasia at the tenth day has necessitated the discontinuation of this protocol, which was otherwise remarkably effective as evidenced by the remission rate in acute lymphoblastic leukemia. We have similarily obtained a remarkable remission in generalized rhabdomyosarcoma with marrow, hepatic, muscular, and soft tissue metastases. This complete clinical, laboratory, and scintigraphic remission lasted for 6 months prior to the development of a localized recurrence partially sensitive to cyclophosphamide and actinomycin D.

Intermittent therapy, using the MTD given once or twice every 15–20 days, has achieved remarkable results in cases of lymphosarcoma (2 mg/kg/day × 2). All cases so treated (Table 6) were advanced forms resistant to the standard therapeutic protocols comprising cyclophosphamide, prednisone, adriamycin, vincristine, and VM 26.

Three of these cases were complicated by severe cutaneous involvement and extranodal, mesenteric, and mediastinal spread. We have observed only one total treatment failure in leukemia therapy, and nine short, but definite, remissions. These results appear outstanding and merit a large-scale study of this agent in this situation.

In four cases of mycosis fungoides (Sezary syndrome), we have observed rapid improvement in the cutaneous lesions, and a delayed and incomplete effect on the lymphadenopathy. The total dose used was low, and no toxicity was observed.

Table 6. Sarcomas treated with DEA.14.DNR

	Histology	No. relapse	Toxicity: buccal and GIT	Result	Remarks
1. Cas., L. 9 M	RHBDS	1	+++	CR	Nodules
2. Ler., S. 5 M	LBS	2	++	CR	2nd month meningeal recurrence 6th month hematologic relapse
3. Ber., C. 69 F	LBS	2	+	IR	–
4. Pau., J. 28 M	IMM.S	1 (O3LRS74 failure)	0	IR	Cutaneous lesions Nodes
5. Gro., R. 69 M	LBS	2	++	Failure	No effect
6. Jar., A. 76 M	RS	3	0	IR	Cutaneous lesions Nodes
7. Pre., R. 42 F	LBS	1	0	IR	Pleural effusion Mediastinal involvement

Conclusion

It would seem that, rather than pursuing a perfect chemical compound with minimal toxicity, future research should be directed toward the elucidation of derivatives having a selective action on a specific tumor type; daunorubicin in promyelocytic leukemia, rubidazone in acute myeloblastic and monoblastic leukemias, and DEA-DNR in the lymphomas.

Collaboration among chemists, devising specific molecular modifications dependent upon the proposed target organ, biochemists, explaining the mechanism of therapeutic action of the agents, clinical pharmacologists, documenting their metabolism, and oncologists, assessing their clinical results, should facilitate new developments in this chemical series of such remarkable potential.

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