Medical and Pediatric Oncology 22:119–124 (1994)

Treatment of Relapsed or Refractory Acute Leukemia in Childhood With Bisantrene Combined With High Dose Aracytine

Thierry Leblanc, MD, François Deméocq, MD, Guy Leverger, MD, André Baruchel, MD, Sophie Lemerle, MD, Jean Pierre Vannier, MD, Brigitte Nelken, MD, Thierry Guillot, MD, and Gérard Schaison, MD

Bisantrene is an anthracene derivative which has demonstrated activity in acute myeloblastic leukemia (AML) and in lymphoma. The present study was designed to assess the reinduction rate and toxicity of bisantrene (250 mg/m^2/d × 5) associated with aracytine (1000 mg/m^2 twice a day × 5) in refractory and relapsed acute childhood leukemia. Patients who relapsed after bone marrow transplantation were eligible. Twenty-six children were included. Diagnoses were as follows: 13 AML, 9 acute lymphoblastic leukemia (ALL), and 4 undifferentiated leukemia (AUL). All patients had been very highly pretreated, especially with anthracyclines, and most of them were of poor prognosis. The overall response rate was 46% with a 95% confidence interval ranging from 27–65%. According to diagnosis, complete remission (CR) rates are: AML: 5/13, ALL: 5/9, and AUL: 2/4. Four children died, three from infection and one from acute lysis syndrome. The major toxicity was infection with grade 3 and 4 episodes occurring in 42% of patients. No significant cardiac toxicity was noted. Hepatic and renal toxicity were limited and transient. Bisantrene in association with aracytine is effective in both AML and ALL of childhood. Bisantrene should be evaluated with a five-day schedule in other pediatric malignancies. In children with acute leukemia previously treated with high dose aracytine, new combination regimen is warranted.

Key words: acute leukemia, children, bisantrene, clinical trial

INTRODUCTION

New drugs or combinations of drugs are needed in acute leukemia to reinduce relapsed patients and to treat refractory leukemias. One such drug is 9,10 anthracenedicarboxaldehyde-bis [(4,5-di-hydro-1H-imidazol-2-yl)hydrazone] dihydrochloride:bisantrene. Bisantrene is a new anthracene derivative which is thought to act as a nonspecific intercalator [1]. It has shown promising activity in experimental tumor systems against a number of tumors including L1210 and P388 leukemias [1]. Experimental studies with human tumor cloning assay have demonstrated large antitumor activity [2] and lack of total cross resistance with adriamycin and mitoxantrone associated with potentially higher cytotoxicity [3]. The lack of cardiac toxicity demonstrated in animal studies indicates that bisantrene has a potential clinical advantage over anthracyclines [1,4]. Preliminary studies in acute non-lymphoblastic leukemias (ANLL) were encouraging and warranted use of bisantrene in association in order to improve the response rate. This study was designed to assess the response rate and toxicity of the combination bisantrene with high dose cytosine arabinoside (HD Ara-C) in heavily pretreated pediatric patients with recurrent or refractory acute myeloblastic leukemia (AML) or acute lymphoblastic leukemia (ALL). This is the first report of the use of bisantrene associated with another drug.

MATERIALS AND METHODS

Patient Eligibility

Inclusion criteria were: patients between 0 and 20 years old, acute leukemia (AL) in first or subsequent relapse or refractory to first line therapy, and recovery from the reversible side effects of prior therapy with normal renal function (creatinin < 1.5N) and liver func-

From the Hôpital Saint-Louis (T.L., A.B., G.S.), and Hôpital Trousseau (G.L.), Paris, Hôtel-Dieu, Clermont Ferrand (F.D.), Hôpital Intercommunal, Créteil (S.L.), Hôpital Charles Nicolle, Rouen (J.P.V.), Hôpital Claude Huriez, Lille (B.N.), and Laboratoires Lederle, Rungis (T.G.), France.

Received August 17, 1992; accepted November 10, 1992.

Address reprint request to Dr. T. Leblanc, Service d'Hématologie Pédiatrique, Hôpital Saint-Louis 75010 Paris, France.

tion tests (bilirubin < 1.5N, serum glutamic oxaloacetic transaminase [SGOT], and serum glutamic pyruvic transaminase [SGPT] < 2.5N). There was no limit to prior exposure to anthracyclines but patients had to present clinical and echocardiographic evidence of normal cardiac function. Patients who had relapsed after bone marrow transplantation were eligible.

Evaluation of Therapy

Bone marrow specimens were considered M1 when they presented less than 5% of blasts, M2 between 6% and 25%, M3 between 25 and 50%, and M4 more than 50%. Complete remission (CR) was defined as bone marrow aspiration graded M1 with adequate cellularity associated with normal blood counts and a normal physical examination. Severity of treatment-related toxicity was graded according to the WHO criteria [5], and an echocardiographic evaluation was performed after the induction course.

Treatment Protocol

Induction therapy consisted of bisantrene, 250 mg/m^2/d, infused in 1 hour without any pretreatment by a central venous line from day 1 to day 5 with HD Ara-C, 1000 mg/m^2, infused in 2 hours twice a day from day 1 to day 5. Patients were monitored in conventional isolation rooms. All patients received hyperhydration in an attempt to prevent lysis tumor syndrome. In case of high fever during aracytine infusion, cutaneous toxicity or severe conjunctivitis related to aracytine, use of steroids was allowed. All patients were given gastrointestinal decontamination. Broad spectrum empirical antibiotherapy was initiated as soon as the patient became febrile. Amphotericin B was added in case of persistent fever of unknown origin 48 hours after initiation of antibiotics. A bone marrow aspiration was performed on day 14–18. If bone marrow was M1, aspiration was performed weekly until recovery of aplasia. If bone marrow was M2 or M3, patients received a second course of chemotherapy with 2 days of bisantrene and 3 days of aracytine at the same doses. If bone marrow was M4, patients were classified as failures and other treatment was considered. No hematopoietic growth factor was used in this study. Postinduction chemotherapy for patients who reached CR was not scheduled. Prior to entry in study, informed consent from all patients or their guardians was obtained in accordance with individual and institutional policies.

RESULTS

Patient Population

From October 1989 to October 1991, 26 children (median age 7.5 years, range 1–16) with AL were included. Diagnoses, stage of disease, prior therapy, and result of bisantrene combined with HD Ara-C are listed in Table I. There were 13 cases of AML, 9 of ALL, and 4 of undifferentiated acute leukemia (AUL), 2 of which presented an AML FAB M5 phenotype at the time of relapse (patients 3 and 17). All relapsed patients (pts) had isolated bone marrow relapse. Most patients had been highly pretreated. All patients had previously received one (17 pts), two (6 pts), or three (3 pts) different anthracyclines. Fourteen patients had received daunorubicin with a mean cumulative dose of 245 mg/m^2 (160 to 400), 12 had received zorubicine, 860 mg/m^2 (380 to 1300), 8 had received mitoxantrone, 58 mg/m^2 (30 to 70), and 1 (pt 17) had received doxorubicin, 120 mg/m^2. Four patients (pts 1, 11, 15, 22) had been treated with amsacrin, 410 mg/m^2 (300 to 450). Twenty-three had received aracytine with a mean cumulative dose of 9860 mg/m^2. Aracytine had been used in various schedules: standard dose (100 to 200 mg/m^2/d in continuous infusion) in 16 pts, low dose (25 to 30 mg/m^2 twice a day subcutaneously) in 13 patients, and HD Ara-C (1 to 2 mg/m^2 twice a day) in 6 patients. Relapse occurred in 6 patients after bone marrow transplantation, 2 after autologous bone marrow transplantation (ABMT) and 4 after allogenic bone marrow transplantation (BMT). Four of them were AML grafted in CR1 and 2 were ALL, 1 with translocation (4–11) grafted in CR1 and 1 grafted in CR3. Fifteen patients were in first relapse, six in second, one in third, and four refractory. For five patients in relapse bisantrene-aracytine regimen was used in second- (4 pts) or third- (1 pt) line therapy.

Treatment Effectively Received

All patients except 1 received the full dose of both agents. The exception concerned a patient with acquired G6PD deficiency who developed acute hemolytic anemia and acute renal failure (ARF) on day 4 (pt 4). In four cases, a second course was performed on days 15–20 because of persisting blastic cells. However, in five other cases with persisting blastic cells, the second course was not performed either because of the patient's clinical status (2 pts) or because of obvious failure of treatment (3 pts). One patient who achieved partial remission (M2 bone marrow) after a second course performed on day 20 received a third course of the same regimen.

Efficacy of Induction

The response is evaluable in 22 patients: 12 achieved CR (46% with a 95% confidence interval ranging from 27–65%), 8 of them after the first course, 3 after a second course, and 1 after a third course. Achievement of CR was effective on day 28 (range 21 to 40) after one course and on day 40 (range 37 to 50) after 2 courses. Ten patients were classified as failures. The remaining 4 patients died after the first course of chemotherapy, one on day 6 from tumor lysis syndrome and three on days 6, 15, and 29 from infection (e.g., *Staphylococcus epidermidis*

TABLE 1. Patients' Characteristics and Results of Bisantrene + HD Ara-C*

	Patients		Prior Therapy								Result
				Aracytine		Anthracyclines			BMT or		
No.	(a)	(b)	(c)	(d)	(e)	D (f)	Z (g)	M (h)	ABMT	(i)	(j)
1	AML2	1st R	8m	11,200	+	160	–	60	–	–	F
2	AML5	2nd R	72m	37,000	–	–	800	–	–	–	CR
3	AUL	1st R	6m	2,500	–	320	–	–	–	–	CR
4	AML2	ref	–	1,400	–	–	1,200	–	–	–	F
5	ALL	2nd R	21m	800	–	400	–	–	–	–	F
6	AML5	ref	–	3,000	–	160	–	60	–	–	F
7	AUL	1st R	18m	3,200	–	–	1,000	–	–	–	TD
8	AML4	1st R	11m	14,100	+	–	1,000	–	ABMT	Bu+M	F
9	AML5	1st R	10m	730	–	100	–	70	BMT	Bu+C	CR
10	AML4	1st R	23m	1,880	–	–	800	–	BMT	Bu+C	TD
11	AML7	2nd R	22m	38,940	–	–	1,300	60	–	–	F
12	ALL	1st R	30m	–	–	240	–	–	–	–	F
13	AML2	1st R	17m	9,680	–	–	1,200	–	–	–	CR
14	AML5	1st R	54m	10,040	–	–	800	–	–	–	TD
15	AML5	1st R	18m	9,800	+	160	–	60	–	–	F
16	ALL	1st R	7m	480	–	–	380	–	BMT	Bu+C+V	TD
17	AUL	1st R	14m	34,000	–	290	–	30	–	–	CR
18	ALL	3rd R	37m	17,500	+	360	–	–	ABMT	T+A+M	CR
19	ALL	2nd R	6m	2,300	–	360	–	–	–	–	CR
20	ALL	2nd R	47m	800	–	320	–	–	–	–	CR
21	AUL	2nd R	5m	9,800	+	160	–	60	–	–	F
22	AML4	1st R	13m	5,800	+	160	–	60	BMT	Bu+C	CR
23	ALL	ref	–	–	–	240	–	–	–	–	CR
24	T-ALL	ref	–	–	–	–	480	–	–	–	CR
25	T-ALL	1st R	4m	1,800	–	–	560	–	–	–	F
26	AML2	1st R	38m	10,040	–	–	800	–	–	–	CR

* (a) diagnosis; (b) status: R: relapse, ref: refractory; (c) duration of CR1 in months; (d) cumulative dose of aracytine in mg/m^2; (e) prior HD Ara-C therapy; (f)/(g)/(h) cumulative doses of D: daunorubicin, Z: zorubicine, and M: mitoxantrone in mg/m^2; (i) conditioning regimen: Bu: busulfan, 16 mg/kg, M: melphalan, 140 mg/m^2, C: cyclosphophamide, 120 to 200 mg/kg, V: VP16, 30 mg/kg, A: aracytine, 12 g/m^2, and T: total body irradiation; (j) result: CR: complete remission, F: failure, TD: toxic death.

septicemia, septic shock with interstitial pneumonitis and pulmonary aspergillosis). The two later died with an aplastic bone marrow and no persistence of blast cells. According to diagnosis CR rate is: AML: 5/13, ALL: 5/9, and AUL 2/4.

Follow-Up of Patients in CR

Mean duration of CR is 4 months (range 1 to 24). None of the 12 patients in CR had a match-related or unrelated donor. Six patients underwent ABMT: 4 died (1 from veno-occlusive disease [VOD] and 3 from infection), 2 are alive and disease-free after interleukin-2 post-graft treatment (m17+, m24+). One child underwent mismatched BMT and relapsed (m4). Two AML patients, allografted in first CR, without graft rejection in second CR, received interleukin-2 followed by maintenance chemotherapy: 1 relapsed (m14) and 1 is alive and disease-free (m9+). Two patients relapsed early (m1, m2). The last child was treated by chemotherapy alone and is alive and disease free (m7+).

Toxicity

Toxicity was evaluated in all 26 patients but hematological toxicity of induction was evaluated only in those patients who received CR after 1 course.

Hematological toxicity. Toxicity included neutropenia (ANC $< 500/mm^3$) and severe thrombocytopenia (platelets $< 50{,}000/mm^3$) in all patients. Recovery from neutropenia (absolute neutrophil count [ANC] $> 500/mm^3$) was effective on day 25 (range 19 to 40) and from thrombocytopenia (platelets $> 100{,}000/mm^3$) on day 27 (range 21 to 40). For the four patients who received 2 courses hematological toxicity was accentuated with recovery from neutropenia on day 34 to 43 and recovery from thrombocytopenia on day 34 to 50.

Cardiotoxicity. No cardiac failure occurred. One patient not in CR (pt 25) had abnormal left ventricular function evaluated by echocardiography after treatment (shortening fraction decreased from 36% to 29%; normal range of 30% to 40%). One transient and reversible sinusal bradycardia was noted in another patient (pt 3).

Hepatotoxicity. Ten patients exhibited transient elevation of transaminases (grade 2 in 6 patients and grade 3 in 4) and 2 transient elevation of bilirubin (grade 1 and 2). No sign of liver failure and no VOD was noted.

Renal toxicity. Three children exhibited grade 2 renal toxicity with ARF documented by a serum and creatinine increase without urinary flow reduction: one showed evidence of tumor lysis syndrome, one had G6PD deficiency and presented acute hemolytic crisis on day 4, and the other had recieved a second course of treatment. Acute renal failure appeared on days 6 and 4 in the two former and after a second induction course in the third patient. In the two latter patients it was of limited duration with return to normal function within 15 to 20 days. No proteinuria or hematuria were noted.

Infection. Major toxicity with grade 3 and 4 infectious episodes occurred in 11 patients. There were 5 septicemias, *Staphylococcus epidermidis* (2 pts), *Escherichia coli* (1 pt), *Listeria monocytogenes* (1 pt), and *Candida tropicalis* (1 pt), and 6 pneumonitis, 4 of which were identified as aspergillosis.

Other toxicities. Mucositis was severe (grade 3) in 3 cases. Alopecia was constant. No case of neurological toxicity was observed. No hypotension or anaphylactoid reaction was noted.

Five patients in CR received a new course of bisantrene (2 days) and aracytine (3 days) as consolidation; resolution of neutropenia and thrombopenia was effective on days 18 and 20 and no extra hematological toxicity was noted.

DISCUSSION

In children with AML, long-term disease-free survival is still achieved in only 20–49% of cases [6]. Most patients relapse and treatment of relapse remains a major unsolved problem in AML therapy. The same difficulties are encountered in treatment of refractory ALL or in ALL with recurrent relapses. In this regard, numerous trials have been carried out to investigate single-agent or combination regimens. These studies were performed because of the need for better salvage therapy but also to search for new drugs with antileukemic activity. Bisantrene, a new anthracene derivative, is one of these new drugs and it has been largely evaluated in adult patients. In phase I studies, limiting toxicity was hematologic [7,8] and five-day schedule was recommended [9]. The Children's Cancer Study Group (CCSG) had evaluated bisantrene in children in a phase I/II study using a one-day schedule with doses ranging from 190 to 430 mg/m^2 every 3 weeks [10]. Nineteen leukemic children were included and the maximum tolerated dose was found to be 360 mg/m^2 with limiting hepatic toxicity. Antileukemic activity was limited to only 1 child who reached CR. In adult patients with relapsed AML, phase I study with bisantrene alone showed a 35% response rate with CR obtained for cumulative doses over 1000 mg/m^2 [10]. Phase II studies with bisantrene alone (250 mg/m^2/d $\times$ 7) in adult patients with refractory or relapsed AML [11, 12, 13, 14, 15, 16] demonstrated CR rates of 26–46%. The lack of cardiac toxicity indicated by animal studies and confirmed by these clinical trials suggests that bisantrene is potentially of higher interest in this respect than anthracyclines.

HD Ara-C is one of the most studied and active agents in the treatment of refractory leukemias. It has been associated with various other agents the majority of which are anthracyclines [17]. Nevertheless, cardiotoxicity of these drugs limit their use for reinduction in refractory or relapsed leukemias especially in patients who are candidates for BMT. A combination of bisantrene plus HD Ara-C was therefore investigated in the present study.

Most of the children included were of very poor prognosis. In this setting, the overall CR rate of 46% is encouraging and compares favorably with other studies [17,18]. It is noteworthy that CR rates obtained in ALL patients indicating that bisantrene is of potential interest in this leukemia subtype. We think that the one-day schedule used in the CCSG study is not adequate for treatment of leukemia because of insufficient myelosuppression. We and others have used a five-day or a seven-day schedule with better results and lower extra-hematologic toxicity.

The toxicity and complications are acceptable for a group of patients with such dismal prognosis. The major toxicity was infection which is not surprising in such patients. Despite intensive prior therapy and exposure to high cumulative doses of anthracyclines, no clinical cardiac event occurred in this trial. Only one child out of 22 evaluated patients exhibited a limited decrease of left ventricular shortening fraction. No secondary cardiac toxicity was noted especially in patients who underwent ABMT. Lack of cardiac toxicity of bisantrene has been recently demonstrated in a randomized trial (doxorubicin versus mitoxantrone versus bisantrene) in women with advanced breast cancer [19].

Hepatic toxicity was moderate. No significant cholestasis as reported with bisantrene in adult patients [11] was noted in this trial. Only one child out of the 6 grafted developed VOD after conditioning regimen for ABMT which included total body irradiation, high-dose VP 16, and cyclophosphamide. This child was in second relapse and had not been grafted in first relapse because of his liver status, e.g., post-hepatitis fibrosis. It is possible that hepatic toxicity noted in the CCSG study was due to repeated administrations of bisantrene for a long period [20].

Renal toxicity of bisantrene has not been encountered in clinical trials in solid tumors with one-day schedule [7,8,9]. In refractory adult leukemias, reversible renal failure has been noted in 30% of courses in a phase I

study and was dose-related in patients treated with bisantrene 1,250–1,750 mg/m^2 [10]. Renal toxicity was not encountered in subsequent phase II studies [12–16]. Renal toxicity seems to be related mostly to tubular damage [11]. It appears early and is of limited severity and of short duration. Nevertheless, we feel that all other potentially renal-toxic medications should be excluded and that during therapy there should be a careful monitoring of renal function, especially in the event of repeated administration.

Mucositis is uncommon and more frequent with doxorubicin at equimyelotoxic doses [19]. None of the anaphylactoid reactions or hypotension noted in adult patients [7,21] were encountered in this trial leading us to conclude that bisantrene infusion is well tolerated in children. Phlebitis was prevented by the use of a central venous line.

Overall toxicity and complications are acceptable in view of the fact that the children were highly pretreated.

CONCLUSION

We conclude that a five-day schedule of bisantrene and HD Ara-C is effective and well-tolerated as a treatment for children with refractory and relapsed leukemias. Antileukemic activity is demonstrated in both AML and ALL. Lack of immediate cardiac toxicity is a definite advantage over anthracyclines in heavily pretreated patients. Long-term cardiac toxicity in children treated with chemotherapy is a major problem in pediatric hematology [22] and warrants use and evaluation of intercalating agents without cardiotoxicity. Bisantrene should be evaluated in leukemias and other pediatric malignancies with a five-day schedule. However, because HD Ara-C is currently used in frontline therapy, especially in children with AML, new studies using bisantrene in combination with other agents should be undertaken. We are currently testing an association of bisantrene, VP 16, and carboplatin in children with relapsed and refractory acute leukemia.

ACKNOWLEDGMENTS

We thank Laurence Augusto and Marie-Hélène Bourg for their assistance in manuscript preparation.

REFERENCES

1. Citarella RV, Wallace RE, Murdock KC, Angier RB, Durr FE, Forbes M: Activity of a novel anthracenyl bishydrazone, 9, 10-anthracene-dicarboxaldehyde bis ([4,5-dihydro-1H,imidazol-2.yl]hydrazone) dihydrochloride, against experimental tumors in mice. Cancer Res 42:444, 1982.
2. Von Hoff DD, Coltman CA, Forseth B: Activity of 9-10 anthracenedicarboxaldehyde bis ([4,5-dihydro-1H-imidazol-2-yl]-hydrazone) dihydrochloride (CL216, 942) in a human tumor cloning system: Leads for phase II trials in man. Cancer Chemother Pharmacol 6:141–144, 1981.
3. Cowan JD, Von Hoff DD, Clark GM: Comparative cytotoxicity of Adriamycin, mitoxantrone and bisantrene as measured by a human tumor cloning system. Invest New Drugs 1:139–144, 1983.
4. James V, Chiccarelli F, Dougherty W, Hall C, Henderson B, Iatropoulos M, et al.: Preclinical toxicology studies on mitoxantrone and bisantrene. In Rozenberg M, et al. (eds): "New anticancer drugs: Mitoxantrone and bisantrene." New York: Raven Press, 1983, pp. 47–69.
5. World Health Organization: "Handbook for Reporting Results of Cancer Treatment." Geneva: World Health Organization, 1979.
6. Stevens RF: Acute leukemias. In Hann IM, Gibson BES (eds): "Pediatric Haematology. Bailliere's Clinical Haematology," Vol. 4. London: Baillière Tindall, 1991, pp. 429–458.
7. Alberts DS, Mackel C, Pocelinko R, Salmon SE: Phase I clinical investigation of 9,10-anthracene dicarboxaldehyde bis ([4,5-dihydro-1H-imidazol-2-yl]hydrazone) dihydrochloride with correlative in vitro human tumor clonogenic assay. Cancer Res 42:1170–1175, 1982.
8. Von Hoff DD, Myers JW, Kuhn J, Sandbach JF, Pocelinko R, Clark G, Coltman CA: Phase I clinical investigation of 9,10-anthracene dicarboxaldehyde bis ([4,5-dihydro-1H-imidazol-2-yl-]hydrazone) dihydrochloride (CL216, 942). Cancer Res 41:3118–3121, 1981.
9. Spiegel RJ, Blum RH, Lewin M, Pinto CA, Wernz JC, Speyer JL, Hoffman KS, Muggia FM: Phase I clinical trial of 9,10-anthracene dicarboxaldehyde (Bisantrene) administered in a five-day schedule. Cancer Res 42:354–358, 1982.
10. Movassaghi N, Krivit WA, Krailo MD, Hammond GD: Phase I/II study of bisantrene in childhood cancer: A report from the Children Cancer Study Group. Med Ped Onc 16:333–336, 1988.
11. Marty M, Ferme C, Gisselbrech TC, Guy H, Clark MJ, Bancillon A, Boiron M: Phase I study of bisantrene in acute non-lymphoblastic leukemia. Cancer Treat Rep 69:703–705, 1985.
12. Marty M, Guy H, Calvo F, Gisselbrecht C, Schaison G, Castaigne S, Nguyen-Dinh C, Boiron M: A phase II study of bisantrene in ANLL. Proc ASCO 3:194, 1984.
13. Marty M, Clark MJ, Collado S, Calvo F, Gisselbrecht C, Schaison G, Laport JP, Nguyen-Dinh C, Boiron M: A phase II study of bisantrene in ANLL. Therapie 41:521–524, 1986.
14. Bezwoda WR, Seymour L: Bisantrene in the treatment of relapsed acute non-lyphocytic leukemia (ANLL). Bone Marrow Transplant 4(Supp. 3):65, 1989.
15. Tosi P, Visani G, Colombini R, Verlicchi F, Benfati D, Cenacchi A, Russo D, Luffa E, Papadopulu P, Tura S: Phase II study of bisantrene in relapsed/refractory acute non-lymphoid leukemias (ANLL). Haematologica 74:555–558, 1989.
16. Arlin ZA, Bezwoda WR, Gisselbrech TC, Hammershaimb L, Barr N, et al.: A phase II study of bisantrene in relapsed/refractory acute non-lymphocytic leukemia. Proc ASCO 9:213, 1990.
17. Hiddemann W, Buchner T: Treatment strategies in acute myeloid leukemia B: Second line treatment. Blut 60:163–171, 1990.
18. Miller LP, Pyesmany AF, Wolff LI, Rogers PC, Siegel SE, Wells RJ, Buckley JP, Hammond GD: Successful reinduction therapy with amsacrine and cyclocytidine in acute non-lymphoblastic leukemia in children: A report from the Children's Cancer Study Group. Cancer 67:2235–2240, 1991.
19. Cowan JD, Neidhart J, McCluse S, Coltman CA, Gumbart C, Martino S, Hutchins LF, Stephens RL, Vaughan CB, Osborne CR: Randomized trial of doxorubicin, bisantrene and mithoxantrone in advanced breast cancer: A Southwest Oncology Group Study. J Natl Cancer Inst 83:1077–1084, 1991.

20. Lu K, Savaraj N, Yap BS, Feun LG, Umsawasdi T, Loo TL: Clinical pharmacokinetic of 9,10-anthracenedicarboxaldehyde-bis ([4,5-dihydro-1H-imidazol-2yl]hydrazone) dihydrochloride. Cancer Chemother Pharmacol 16:156–159, 1986.
21. Myers JW, Von Hoff DD, Kuhn JG, Obsborne CK, Sandbach JF, Pocelinko R: Anaphylactoid reaction associated with bisantrene infusions. Invest New Drugs 1:85–88, 1983.
22. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP: Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in children. N Engl J Med 324:808–815, 1991.