Intermediate-dose Cytarabine Treatment Delivered at Moderate Infusion Rates for *De Novo* Acute Myeloid Leukemia-Results of a phase I-II Study

LUISA MANTOVANI[a]*, DIRK HASENCLEVER[b], RAINER KRAHL[c], WOLFRAM PÖNISCH[c], MICHAEL HEROLD[d], RITA PASOLD[e], FRIEDRICH FIEDLER[f], GOTTFRIED DÖLKEN[g], DIETRICH KÄMPFE[h], HANS JOACHIM SCHMOLL[i], RITA SÚBERT[j], MARTIN KUBEL[c], DIETGER NIEDERWIESER†[c] and WERNER HELBIG†[c]for the East German Hematology and Oncology Group (OSHO)

[a]*Division of Medical Oncology and Hematology, Department of Internal Medicine I, St. Georg's Hospital, Delitzscher str. 141, Leipzig 04129, Germany;* [b]*Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany;* [c]*Division of Hematology and Oncology, Department of Internal Medicine II, University of Leipzig, Leipzig, Germany;* [d]*Division of Hematology and Oncology, Klinikum Erfurt, Germany;* [e]*Division of Hematology and Oncology, Klinikum"Ernst von Bergmann", Potsdam, Germany;* [f]*Department of Internal Medicine III, Hospital Küchwald, Chemnitz, Germany;* [g]*Division of Hematology and Oncology, University of Greifswald, Greifswald, Germany;* [h]*Division of Hematology and Oncology, Hospital of Lüdenscheid, Lüdenscheid, Germany;* [i]*Division of Hematology and Oncology, University of Halle/Saale, Halle/Saale, Germany;* [j]*Division of Hematology and Oncology, Klinikum Schwerin, Germany*

Published randomized trials on different cytarabine doses for the treatment of acute myeloid leukemia (AML) provide evidence of a dose–response effect. However, high-dose cytarabine (HIDAC) regimens correlate with increased morbidity and toxicity related mortality. Typical HIDAC regimens deliver $6 \, g/m^2/d$ in infusion rates of $500–3000 \, mg/m^2/h$. However, pharmacokinetic measurements indicate that intracellular Ara-CTP formation is saturated at lower infusion rates than used in HIDAC schedules, probably causing cytarabine accumulation in the plasma and increased toxicity. It was our objective to investigate in a prospective non-randomized phase I-II study feasibility and efficacy of intermediate doses of cytarabine delivered at the presumptive saturating moderate infusion rate (mir-IDAC), as induction therapy in order to optimize intensified treatment for acute myeloid leukemia.

Forty previously untreated patients younger than 60 years of age with *de novo* AML received intermediate doses of cytarabine ($2–4 \, g/m^2/d$) at moderate infusion rates ($250–667 \, mg/m^2/h$) over 6 or 8 h. Cytarabine was applied on alternate days (day 1, 3, 5, 7) in combination with an anthracycline as induction and consolidation therapy. Thirty-two of the 40 patients (80%, 95%CI:64–91%) achieved CR after induction treatment. Treatment-related mortality during induction chemotherapy was 2.5%. No cerebellar toxicity was observed. After two to four mir-IDAC courses stem cell harvesting was successful in 71% of the patients eligible for high-dose chemotherapy. After three years 56% (95%CI:40–72%) of all patients are alive and 59% (95%CI:42–76%) of the patients who entered CR are free of leukemia. In conclusion, favorable long-term outcomes and moderate acute toxicities were observed in patients with *de novo* AML treated with IDAC schedules delivered at moderate infusion rates (mir-IDAC) starting as induction treatment. The data suggest that a randomized trial should now be undertaken to examine whether mir-IDAC has clinical advantages over HIDAC.

Keywords: Acute myeloid leukemia; Cytarabine; Moderate infusion rate; *De novo*

Abbreviations: IDAC, intermediate dose cytarabine; HIDAC, high dose cytarabine; Ara-C, l-beta-arabinofuranosylcytosine; Ara-CTP, 1-beta-arabinofuranosylcytosine 5'-triphosphate; AML, acute myeloid leukemia

*Corresponding author. Tel.: +49-341-9092350. Fax: +49-341-9092352. E-mail: onkologie@sanktgeorg.de
†W.H. was principal investigator of the study until 1998 thereafter followed by D.N.
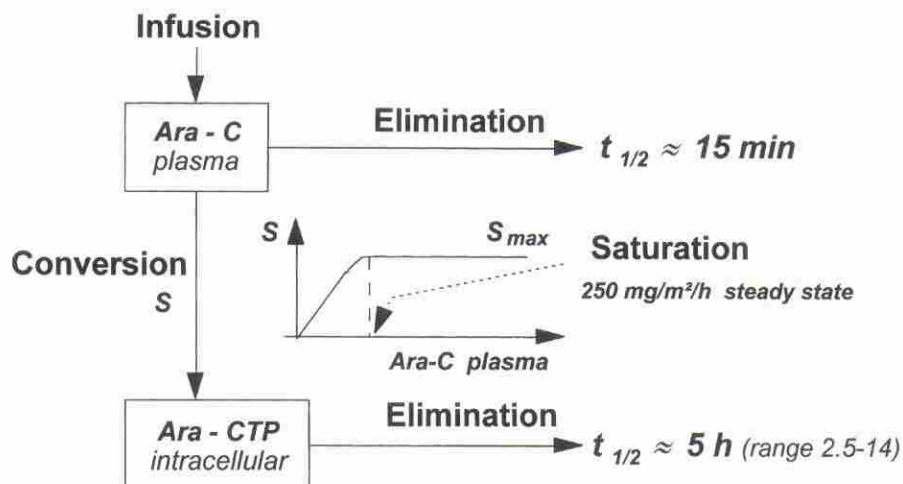
FIGURE 1 Pharmacokinetic model of Ara-C metabolism. Circulating Ara-C can either be eliminated from the plasma or taken up into cells for conversion to Ara-CTP. This step is rate-limited at high Ara-C plasma levels. The model was used to calculate intracellular Ara-CTP peak levels and AUCs for different Ara-C infusion schedules.

INTRODUCTION

The long-term survival rate for adults with *de novo* AML is not yet satisfactory. Standard-dose cytarabine (SDAC) based induction regimens lead to a complete remission rate of about 65%, but less than 25% of the patients remain in continuous complete remission [1–5]. Several randomized trials provide evidence that dose escalation with high-dose cytarabine (HIDAC) may significantly prolong remission duration, irrespective of whether this regimen is given as induction or consolidation therapy or both [6–9]. Typical HIDAC regimens use doses of $3-6 \, g/m^2/d$ with high infusion rates above $500 \, mg/m^2/h$ (range $500-3000 \, mg/m^2/h$) over 1–3 h twice daily. However, toxicity also increases with doses of cytarabine (Ara-C) exceeding $1 \, g/m^2/d$ [10], resulting in frequent treatment interruptions and high treatment-related mortality. We speculate that very high infusion rates of cytarabine may impede treatment delivery and mask its potential benefits.

Measurements of intracellular levels of Ara-CTP, the most relevant cytotoxic metabolite, show a saturation of its formation in circulating leukemic cells with infusion rates above $250 \, mg/m^2/h$ [11–13]. This finding suggests that prolonged cytarabine infusion at a moderate rate of $250 \, mg/m^2/h$ might be better suited to increase both area under the curve (AUC) and peak levels of intracellular Ara-CTP than are HIDAC therapies as currently administered. On the other hand, moderate infusion rates might help decrease peak dose-related morbidity and mortality. Based on these considerations, it was our objective to investigate feasibility, toxicity and efficacy of intermediate-dose cytarabine schedules delivered at moderate infusion rate over prolonged infusion time used both in induction and consolidation therapy for *de novo* AML. A non-randomized prospective phase I-II study was initiated to evaluate alternative dose schedule variants so far not investigated. The choice of dosing and scheduling was based on a simple two-compartment pharmacokinetic model of Ara-C metabolism described below.

METHODS AND PATIENTS

Pharmacokinetic Model

To support selection of novel scheduling possibilities we constructed a simple two-compartment pharmacokinetic model consisting of an extracellular Ara-C and an intracellular Ara-CTP compartment (Fig. 1). For both compartments a first-order elimination kinetic was assumed with specific elimination half lives of 15 min and 5 h, as reported in the literature [12,14,15]. The conversion rate of extracellular Ara-C to intracellular Ara-CTP was assumed to increase linearly at low concentration of cytarabine and to reach saturation at $250 \, mg/m^2/h$ [12]. The model was designed to reproduce the Ara-CTP measurements of Plunkett [12,13]. Differential equations were used to calculate area under the curve concentrations (AUCs) and peak concentrations of Ara-CTP for different Ara-C infusion rates and schedules (i.e. infusion duration, infusion intervals, frequency of administrations per day). Figure 2 gives a selection of these calculations. According to the pharmacokinetic model, moderate cytarabine infusion rates (i.e. $333 \, mg/m^2/h$) by standard 3-h infusion every 12 h (twice daily) should yield intracellular Ara-CTP AUCs and peak levels comparable with those achieved in the HIDAC schemes delivered at higher infusion rates (Fig. 2) [8,9,16–25]. Furthermore, the model predicts that prolonged infusions of cytarabine over 8 h at the presumed saturating infusion rate of $250 \, mg/m^2/h$ should lead to higher Ara-CTP peak concentrations (2.2-fold) and higher Ara-CTP-AUCs (1.5-fold) than HIDAC schedules despite a lower total daily cytarabine dose. These considerations encouraged us to examine
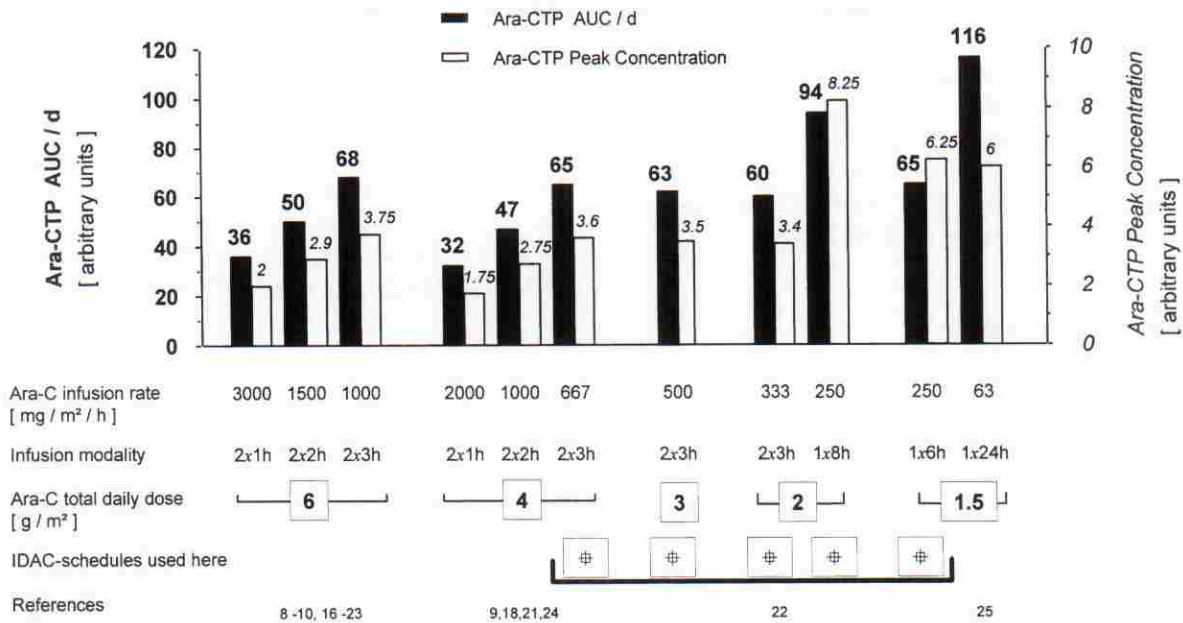
FIGURE 2 Model predicting intracellular Ara-C peak concentrations and Ara-C AUCs according to different cytarabine infusion rates.

intermediate dose Ara-C regimens with moderate infusion rates (mir-IDAC) given over 6–8 h.

Patient Selection

Between January 1996 and January 1997, 40 consecutive previously untreated patients from eight participating centers were entered in this study; all were younger than 60 years and had a morphologically proven diagnosis of *de novo* AML. All patients were evaluable for response and toxicity. Patients with previous myelodysplastic disorder or myeloproliferative disease were excluded. The median age was 41 years (range 17–60). Patient characteristics are listed in Table I.

Evaluation

AML was diagnosed and classified according to the French–American–British (FAB) Group criteria. Cytogenetic analysis was obtained at diagnosis. Complete remission (CR) was defined as restoration of normal hematopoiesis and less than 5% myeloblasts in the marrow (CALGB).

Induction Chemotherapy

Induction chemotherapy consisted of intermediate-dose cytarabine. Three variants of consecutive increasing infusion durations were investigated. In one schedule nine patients received $333–667\,mg/m^2/h$ cytarabine by standard 3-h infusion every 12 h, twice daily (total daily dose $2–4\,g/m^2$). Prolonged infusion over 6 h, once daily with $250\,mg/m^2/h$ cytarabine was administered in a group of seven patients (daily dose $1.5\,g/m^2$). Because no serious toxicity was observed, cytarabine infusion was increased to 8 h at the same infusion rate of $250\,mg/m^2/h$ in further 24 patients to reach the total daily dose of $2\,g/m^2$.

In all three groups of patients cytarabine was given on days 1, 3, 5, 7. Idarubicin $12\,mg/m^2/d$ on days 1–3 was additionally given. G-CSF was scheduled at a dose of $5\,\mu g/kg/d$ s.c., from day 8 until neutrophil recovery $(ANC > 1\times10^9/l)$. Bone marrow aspirates were scheduled

TABLE I Patient characteristics

Characteristics	N
Number of enrolled/evaluable patients	40/40
Age median, years (range)	41 (17–60)
Sex: male/female	20/20
AML FAB	
M0/M1/M2/M3/M4/M5/M6/M7	0/14/13/1/3/8/1/0
WBC at diagnosis median (range) [×10⁹/l]	24 (1–278)
Karyotype	
Normal	22
Abnormal, favourable t(8;21), t(15;17), inv(16)	4
Abnormal, unfavourable $-5/5q-$, $-7/7q-$, 11q23, multiaberrant	3
Abnormal, other	8
Inadequate cytogenetics	3

for day 21 and at the time of peripheral blood count recovery (absolute neutrophil count > 1.500/µl and platelet count > 100,000/µl). Patients in complete remission after the first induction course were assigned to receive consolidation therapy. Patients who did not achieve CR after the first cycle received one more induction course consisting of mir-IDAC and mitoxantrone at a dose of 10 mg/m² on days 1–3.

Post-remission Treatments

Patients in CR after induction were scheduled to receive one or two consolidation courses with mir-IDAC infused at 333 mg/m²/h over 3 h every 12 h (on days 1, 3, 5, 7 in the first course and on days 1, 3, 5 in the second course). Mitoxantrone (10 mg/m² on days 1–3) was additionally administered.

All patients less than 50 years of age with an HLA-compatible related donor in CR after induction and at least one mir-IDAC-consolidation treatment were assigned to receive allogeneic peripheral blood stem cell transplantation (PBSCT). Likewise, high-dose chemotherapy (HDCT) and autologous PBSCT were scheduled for patients who could not undergo allogeneic PBSCT. One more consolidation course with mir-IDAC was given to patients not eligible for HDCT. Peripheral blood stem cells (PBSC) were harvested after the first or second consolidation course and cryopreserved according to standard techniques. Consecutive leukaphereses were performed after the 1st or 2nd consolidation course in patients in CR during G-CSF administration (5 µg/kg/sc/BID) when the total WBC count was rapidly increasing and CD34+ cells were present in the peripheral blood (>5×10⁶/l). A minimum of 2×10⁶/kg CD34+ cells was considered sufficient for transplantation with PBSC alone. No purging procedure was used.

Statistical Methods

Kaplan Meier Estimates were Obtained for the Following Endpoints:

Overall survival (OS) includes all deaths; failure-free survival (FFS) counts failure to achieve CR, relapses or deaths as events, whichever comes first. Time of diagnosis was recorded as starting date. Leukemia-free survival (LFS) counts relapses or deaths for those patients who entered CR after induction treatment. To separate the effects of mir-IDAC from those of HDCT procedures all survival analyses were repeated censoring at the date the patients received HDCT.

RESULTS

Figure 3 gives a flow sheet of the trial conduct and details of the treatment outcomes.

Induction Treatment: Outcome

Of the 40 evaluable patients 80% (95% CI:64–91%) achieved CR after induction treatment, 27 patients (67.5 %; 95% CI:51–81%) needed a single course, five patients entered CR after a second induction course. Resistant AML occurred in seven patients (2 PR, 5 NR). One patient died in PR during the 2nd induction course. Similar outcome measures were observed in the patients treated with the three schedule variants (Table II).

Induction Treatment: Toxicity

In the 32 patients who entered CR the median duration of neutropenia (absolute neutrophil count < 1×10⁹/l) was 21 days (range 15–29) and the median duration of thrombocytopenia (unsupported platelet count < 50×10⁹/l) was 23 days (range 18–41) for the first induction course. Hematological toxicity according to Ara-C schedules is shown in Table III. The incidence of microbiologically or clinically proven infections was similar in the three treatment groups and consisted of fever of unknown origin, pneumonia and septicemia. The median number of febrile days were 3 (0–20) and 5 (0–14) in induction 1 and 2, respectively (Table IV). Non-hematological toxicity consisted mainly of nausea (WHO grade 1–2). Eye toxicity (WHO grade 2) was observed in one patient. Serious CNS toxicity of grade 3 or more was not reported (Table III). No early deaths occurred within the first six weeks. One patient with persistent AML died of fungal pneumonia while being neutropenic after the second induction course (see above). Hence, treatment-related mortality of the induction therapy was 1/40 (i.e. 2.5%).

Post-remission Treatments

After mir-IDAC induction treatment first consolidation chemotherapy was feasible in 31 of 32 patients in CR (Fig. 3). Twenty-one of 23 patients assigned to a second consolidation course were able to receive it. Furthermore, three patients could not receive a third consolidation course. Total six patients were taken off consolidation treatment because of toxicity (one case peripheral neuropathy, one case fungal pneumonia and four cases delayed hematological reconstitution). Four of them are still in CCR. Hence the mir-IDAC schedules allow 75% (=31/32 × 26/28 × 15/18 × 100%) of the responding patients to receive the full scheduled treatment. The occurrence of infectious complications during mir-IDAC courses are listed in Table IV.

Fourteen patients were assigned to receive HDCT with autologous PBSC. In 10 of these patients (71%) sufficient PBSC were harvested during consolidation courses after a median number of four leukaphereses (range 2–5). One patient relapsed before and one patient refused this procedure. Eight patients were finally autografted. Further six patients received HDCT with allogeneic PBSCT.
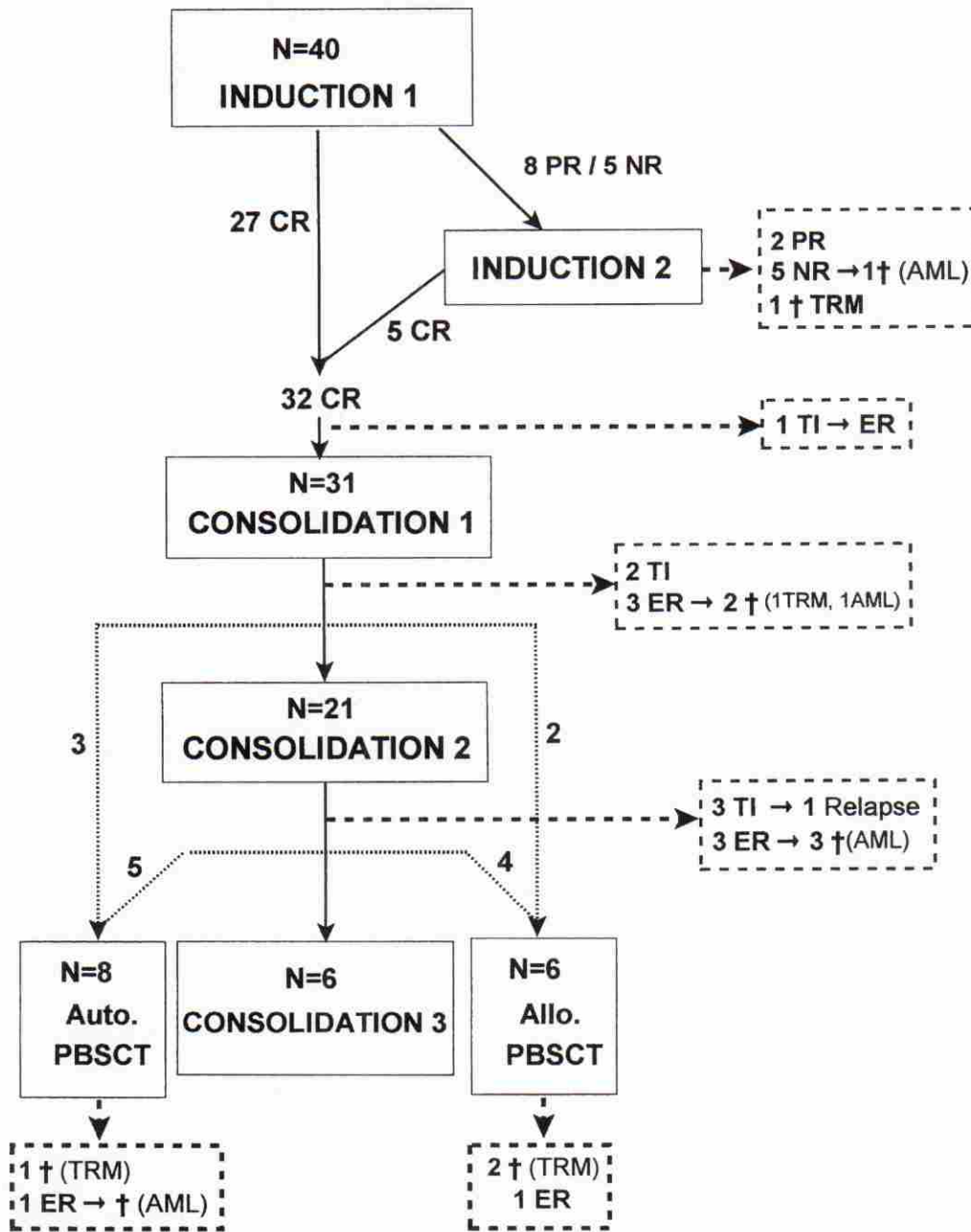
FIGURE 3   Flow diagram of treatment with events: complete remission (CR), partial remission (PR), non-responder (NR), early relapse (ER), treatment interruption (TI), treatment-related mortality (TRM) and death (+).

Three patients died in CR during post-remission treatment: one case after autologous PBSCT (at day+9 due to cardiotoxicity) and two cases after allogeneic PBSCT (VOD at day +40, cGvHD at day +120). No treatment-related mortality occurred during mir-IDAC consolidation courses.

Overall Outcome

Figure 4 gives the Kaplan Meier estimates for OS and FFS for all patients as well as LFS for patients who entered CR.

The median times of observations exceeds 3.5 years. At three years the estimated OS rate is 56% (95%CI: 40–72%) and 47% (95%CI: 32–63%) of all patients are free

of treatment failure. Ten (31%) of the 32 patients who entered CR have relapsed to date. Leukemia-free survival shows that an estimated 59% (95%CI: 42–76%) of the patients who achieved CR are free of leukemia after two years. Censoring for high-dose chemotherapy treatments with PBSCT does not change this overall picture (dashed curves).

DISCUSSION

The aim of this non-randomized phase I-II trial presented here was to investigate feasibility, toxicity and efficacy of intermediate doses of cytarabine delivered at prolonged

TABLE II Results of induction chemotherapy

Ara-C infusion rate (mg/m²/h)	Infusion modality	Number of patients	CR after first course	CR after second course	CR overall	PR	NR	Early death
333–667*	2×3 h	9	6 (67%)	1	7 (77%)	1	1	
250	1×6 h	7	4 (57%)	2	6 (86%)			
250	1×8 h	24	17 (71%)	2	19 (79%)	1	4	1
Overall (%)		**40**	**27 (67.5%)**	**5 (12.5%)**	**32 (80%)**	**2(5%)**	**(12.5%)**	**(2.5%)**

* Three patients received 333, 4 pts 500 and 2 pts 667 mg/m²/h Ara-C infusion rate.

moderate infusion rates (mir-IDAC) as intensified treatment for patients with *de novo* AML. To our knowledge such scheduling variants have not been investigated before. Previous intracellular pharmacological studies suggested that conversion from Ara-C to Ara-CTP is a rate-limiting step with a saturation characteristic. This stimulated us to ask the question whether mir-IDAC regimens may be as effective as the currently used high-dose, high-infusion rate HIDAC regimens [13] but sparing of toxicity, through more efficient use of the drug.

We selected dosing schedules of cytarabine infusion rates, infusion duration and infusion intervals, using a simple two-compartment pharmacokinetic model. This enabled to calculate Ara-CTP AUCs and Ara-CTP peak levels for various cytarabine schedules (see Figs. 1 and 2). The model suggested that prolonged infusions of cytarabine over 3 h, twice daily at a moderate infusion rate of 333 mg/m²/h should yield Ara-CTP peak levels and AUCs similar to those of HIDAC schedules. Furthermore, an increase in infusion duration to 8 h at the saturating infusion rate of 250 mg/m²/h was predicted to produce a 1.5-fold increase in Ara-CTP AUCs and about 2.2-fold higher Ara-CTP peak levels as compared to conventional 1000 mg/m²/h cytarabine infusion rates given over 3 h twice daily. This encouraged the use of intermediate infusion rates of about 250 mg/m²/h at prolonged infusion intervals.

With this approach we investigated in our phase I-II study three similar mir-IDAC schedules with consecutive increasing infusion durations in *de novo* AML patients younger than 60 years. We started with intermediate doses at conventional twice-daily 3-h infusion durations, changed to one 6-h interval, which was subsequently prolonged to 8 h. The pharmacokinetic model predicted successively increasing AUC and peak values of Ara-CTP for these schedules.

The overall CR rate (80%) and the LFS rate after three years (59%) are in the upper range of values expected for HIDAC regimens. To better understand the effects of induction therapy on subsequent outcome for patients with AML, we used failure-free survival as endpoint. After three years 47% of all patients are alive and free of treatment failure. To highlight the effect in patients to receive only mir-IDAC treatment, we censored all outcome endpoints for any kind of HDCT followed by PBSCT. The resulting curves did not change.

Mir-IDAC treatment was associated with a low mortality and morbidity during 111 administered mir-IDAC courses. Only one patient died of mir-IDAC treatment-related mortality (2.5 %). After induction 97% of the responding patients could receive a consolidation treatment and 75% of the patients in CR could complete the full treatment program. After two to four mir-IDAC schedules harvesting was successfully carried out in ten of 14 available patients indicating no major prolonged bone marrow toxicity after repeated mir-IDAC courses. Non-hematological toxicity was a minor problem. Cerebellum toxicity at these intermediate doses of cytarabine was not

TABLE III   Toxicity of induction chemotherapy

Toxicity	Overall	Ara-C-Schedule*		
		$333-667\,mg/m^2/h\ 2\times3\,h$	$250\,mg/m^2/h\ 1\times6\,h$	$250\,mg/m^2/h\ 1\times8\,h$
WBC recovery $>1\times10^9/l$ d median (range)	21 (15–29)	22 (19–27)	20 (15–25)	21 (15–29)
PLTS recovery $>50\times10^9/l$ d median (range)	23 (18–33)	26 (21–28)	22 (18–22)	24 (21–33)
Nausea, vomiting WHO grade ≥2	2/40	0/9	0/7	2/22
CNS WHO grade ≥2	0/40	0/9	0/7	0/22
Eyes WHO grade ≥2	1/40	0/9	1/7	0/22

* No significant differences were observed between the treatment schedules.

TABLE IV   Infections after induction and consolidation IDAC courses

	Induction 1	Induction 2	Consol. 1	Consol. 2
FUO	17	5	9	5
Pneumonia	5	1	4	2
Septicemia	7	3	6	2
Soft tissue infections	2	1	0	1
None (%)	7 (18%)	2 (17%)	10 (34%)	10 (50%)
Number of days febrile, median (range)	3 (0–20)	5 (0–14)	2 (0–28)	0 (0–6)
Number of days on antibiotics, median (range)	9 (0–46)	12 (0–27)	8 (0–28)	3 (0–30)

observed. Similar toxicities were observed between the three schedule variants used during induction. We conclude that mir-IDAC is a feasible regimen and that our results must be viewed in the light of results obtained with standard- or high-dose cytarabine regimens.

Bishop [2,3] randomized HIDAC ($2\times3\,g/m^2$ daily, infusion rate $>1000\,mg/m^2/h$) vs. SDAC as induction treatment. HIDAC significantly prolonged remission duration (70 vs. 12 months) but was also associated with significantly more side effects, treatment interruptions as well as treatment-related mortality (18 vs. 11%). In our trial two-year LFS was 58% and treatment-related mortality for induction therapy was 2.5%.

Mayer [8] compared standard vs. intermediate- ($400\,mg/m^2/d$, c.i. at infusion rates of about $20\,mg/m^2/h$) vs. high-dose cytarabine given as post-remission therapy. The group receiving HIDAC ($2\times3\,g/m^2$ daily; infusion rate $1500\,mg/m^2/h$) had a significantly better relapse-free survival at four years (39% for HIDAC vs. 25% for IDAC vs. 21% for SDAC), associated with a longer overall survival than did the other two treatment, groups. However, only 56 % of the patients completed the post-remission treatment because of interruptions due to cumulative toxicity (particularly neurotoxicity).

The South West Oncology Group (SWOG) published the results of a trial that compared HIDAC with SDAC used for both induction and consolidation therapy for *de novo* AML [9]. They used cytarabine in a standard dose of $200\,mg/m^2/d$ as continuous infusion (infusion rate of about $10\,mg/m^2/h$) and in a high dose of $2\times2\,g/m^2$ daily (infusion rate $2000\,mg/m^2/h$). Patients who received both HIDAC induction and consolidation had the best post-remission outcomes. For patients aged less than 50 years who entered remission the four-year relapse-free survival was 33% for HIDAC induction and 21% for SDAC induction, but no statistically significant improvement in

CR rate or survival was seen. The proportion of CR patients who did not go on to scheduled consolidation therapy was twofold higher after HIDAC induction than after SDAC because of higher toxicity associated with HIDAC. The treatment-related mortality of HIDAC therapy overall was 14% compared to 5% for SDAC.

Hiddemann [22] in a randomized trial investigated $2\times1\,g/m^2$ daily (infusion rate $1000\,mg/m^2/h$) vs. $2\times3\,g/m^2$ daily (infusion rate $1000\,mg/m^2/h$) for the treatment of relapsed and refractory AML. No major differences in overall response rate were observed (44 vs. 52%). A significant advantage in favor of the $3\,g/m^2$ group was found for patients with refractory AML and early relapse (within six months) compared to late relapses that occurred after six months remission duration. More early deaths were observed in the $3\,g/m^2$ group (37 vs. 15%, $p < 0.05$) and more CNS toxicity (27 vs. 7%, $p < 0.01$) compared to the $1\,g/m^2$ group.

The term intermediate dose cytarabine has been used in a variety of different meanings and there is no clear definition with regard to dose or to dose rate. Several authors have used intermediate doses of $1.0-1.5\,g/m^2$ daily in the setting of continuous infusion over 4 to 5 days [25–28]. This implies a rather low infusion rate of $42-62\,g/m^2/h$ very much below the presumptive saturation level. Our mir-IDAC uses slightly higher total daily doses but markedly higher infusion rates between 250 and $667\,mg/m^2/h$. Hence the infusion intervals can be reduced to 6–8 h. Other authors [29] report about regimens in which of intermediate doses of 2 times $500\,mg/m^2$, intravenously daily are used.

To clearly distinguish our regimen from the others we used the prefix "mir" (=moderate infusion rate) to the term IDAC.

The published data on HIDAC treatments provide clinical evidence of dose-response effect for cytarabine in
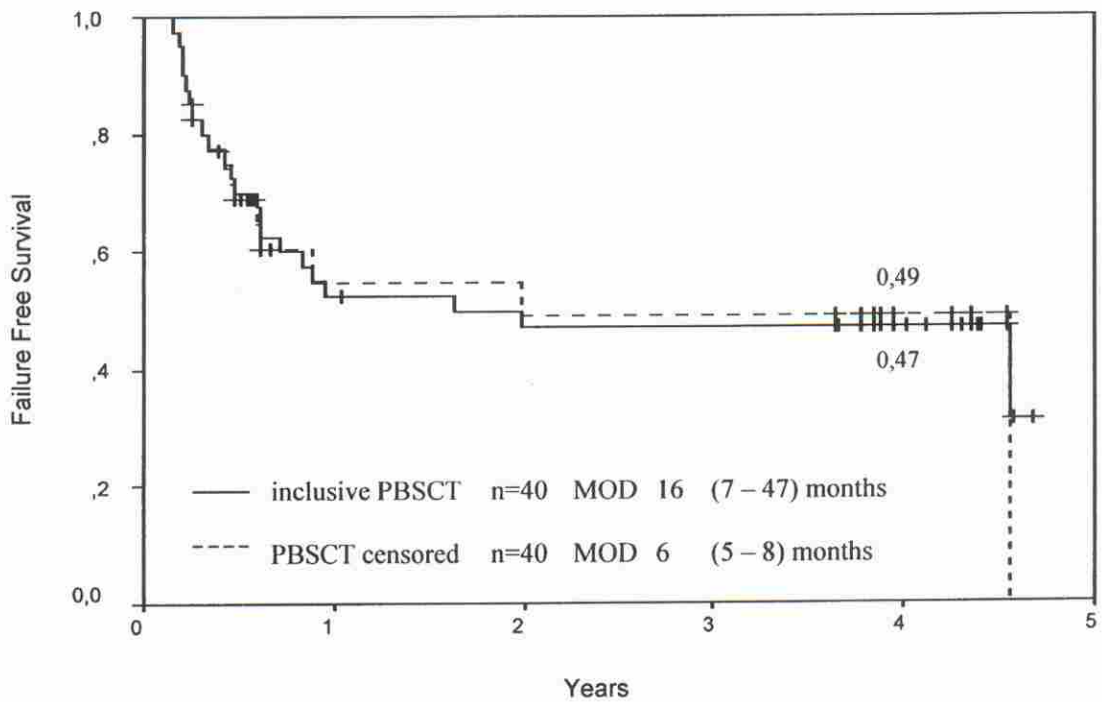
(A)
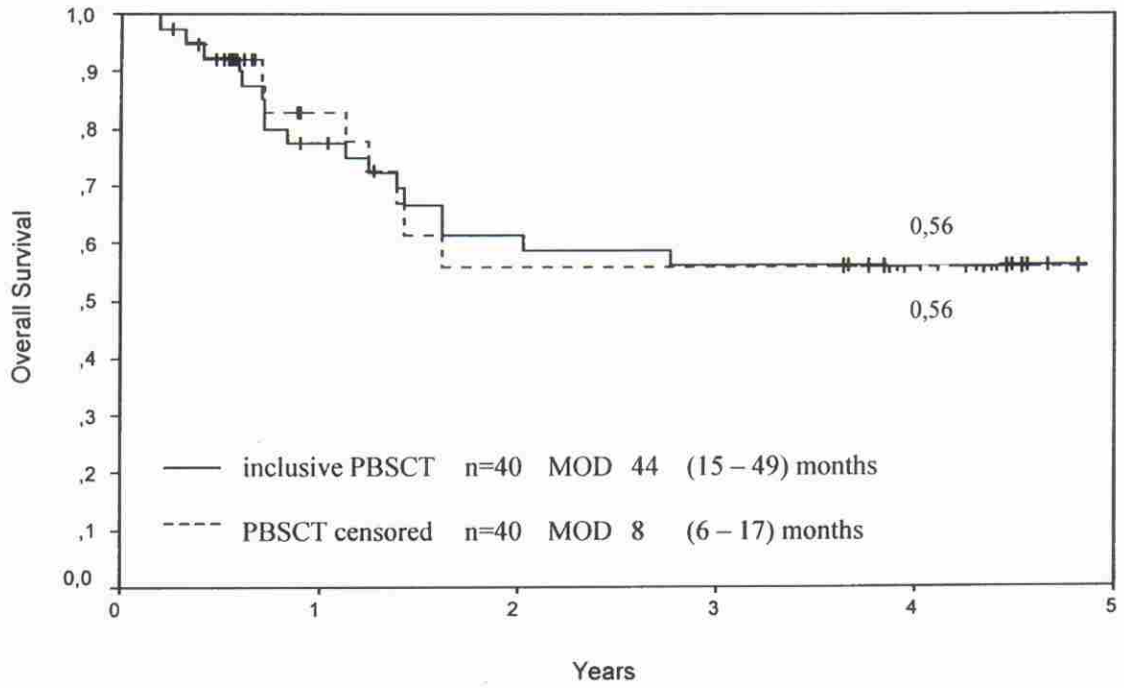
(B)

FIGURE 4 Kaplan Meier estimates for overall survival (A), and failure-free survival (B) for 40 patients from time of diagnosis and leukemia-free survival (C) for all 32 patients who achieved CR after induction treatment. Two curves are presented in each figure: the dashed curves show the KM estimates with patients being censored at the time of high-dose chemotherapy and PBSCT. The full curves do not consider such censoring.
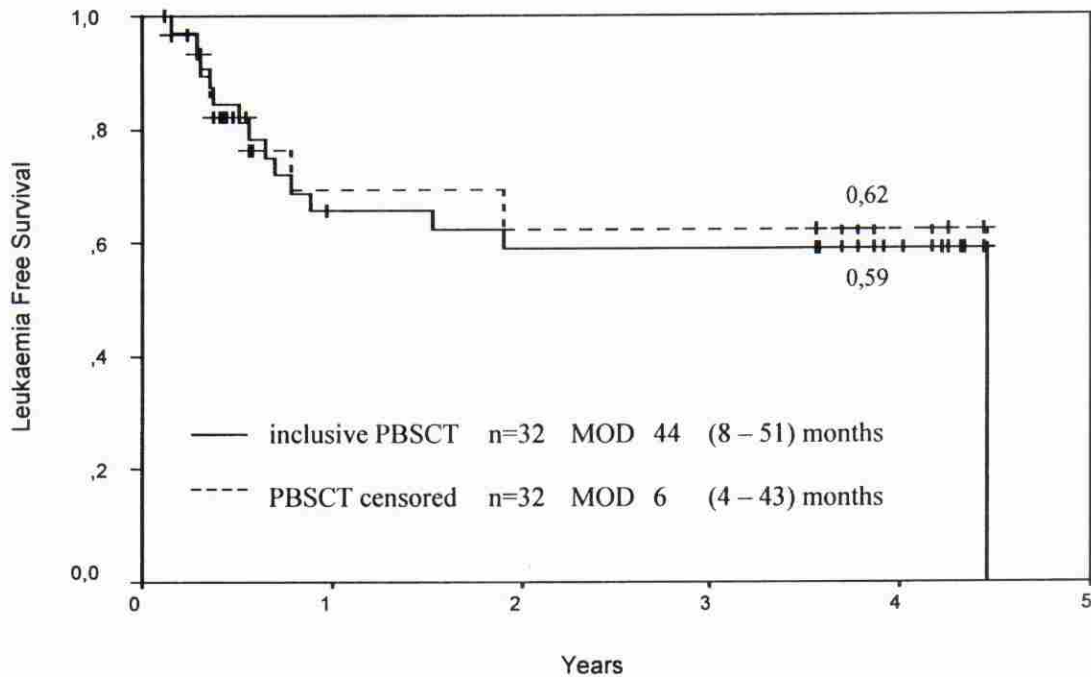
(C)

FIGURE 4 *Continued*

AML. However, this also correlates with higher toxicity in terms of death rate. To optimize intensified treatments more feasible schedules are desirable. Our results suggest that mir-IDAC may be a promising therapeutic option with high efficacy, low treatment-related mortality and low rate of treatment interruptions. Our data on schedules using moderate infusion rates over 6–8 h suggest a favorable potential which should now be investigated in a prospective randomized phase III trial comparing HIDAC with mir-IDAC.

References

[1] Stone, R.M. and Majer, R.J. (1993) "Treatment of the newly diagnosed adult with de novo acute myeloid leukemia", *Hematology/Oncology Clinics of North America* 7, 47.

[2] Weinstein, H.J., Mayer, R.J., Rosenthal, D.S., Coral, F.S., Camitta, B.M. and Gelber, R.D. (1983) "Chemotherapy for acute myelogenous leukemia in children and adults", *Blood* 62, 315.

[3] Mayer, R.J. (1987) "Current chemotherapeutic treatment approaches to the management of previsouly untreated adults with de novo acute myelogenous leukemia", *Seminars in Oncology* 14, 384.

[4] Preisler, H., Davis, R.B., Kishner, J., Dupre, E., Richards, F., Hoagland, H.C., Kopel, S., Levy, R.N., Carey, R., Schulman, P., Gottlieb, A.J. and McIntyre, O.R. (1987) "Comparison of three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: A Cancer and Leukemia Group B study", *Blood* 69, 1441.

[5] Vogler, W.R., Velez-Garcia, E., Weiner, R.S., Flaum, M.A., Bartolucci, A.A., Omura, G.A., Gerber, M.C. and Banks, P.L. (1992) "A Phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: A Southeastern Cancer Study Group study", *Journal of Clinical Oncology* 10, 1103.

[6] Bishop, J.F., Matthews, J.P., Young, G.A., Szer, J., Gillett, A., Joshua, D., Bradstock, K., Enno, A., Wolf, M.M., Fox, R., Cobcroft, R., Herrmann, R., Van.Der Weyden, M., Lowenthal, R.M., Page, F., Garson, O.M. and Huneja, S. (1996) "A randomized study of high-dose cytarabine in induction in acute myeloid leukemia", *Blood* 87, 1710.

[7] Bishop, J.F., Matthews, J.P., Young, G.A., Bradstock, K. and Lowenthal, R.M. (1998) "Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and update results of the Australian Leukemia Study Group", *Leukemia and Lymphoma* 28, 315.

[8] Mayer, R.J., Davis, R.B., Schiffer, C.A., Berg, D.T., Powell, B.L., Schulman, P., Omura, G.A., Moore, J.O., McIntyre, O.R. and Frei, III, E. (1994) "Intensive post-remission chemotherapy in adults with acute myeloid leukemia", *New England Journal of Medicine* 6(14), 331–896.

[9] Weick, J.K., Kopecky, K.J., Appelbaum, F.R., Head, D.R., Kingsbury, L.L., Balcerzak, S.P., Bickers, J.N., Hynes, H.E., Welborn, J.L., Simon, S.R. and Grever, M. (1996) "A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group Study", *Blood* 88, 2841.

[10] Herzig, R.H., Wolff, S.N., Lazarus, H.M., Phillips, G.L., Roessmann, D. and Fishman, J. (1983) "High-dose cytosine arabinoside therapy for refractory leukemia", *Blood* 62, 361.

[11] Riva, C.M., Rustum, Y.M. and Preisler, H.D. (1985) "Pharmacokinetics and cellular determinants of response to 1-beta-arabinofuranosyl-cytosine (Ara-C)", *Seminars in Oncology* 12(Suppl. 3), 1.

[12] Plunkett, W., Liliemark, J.O., Adams, T.M., Nowak, B., Estey, E., Kantarjian, H. and Keating, M.J. (1987) "Saturation of 1-beta-arabinofuranosylcytosine 5'-triphosphate accumulation in leukemia cells during high-dose 1-beta-arabinofuranosylcytosine therapy", *Cancer Research* 47, 3005.

[13] Plunkett, W., Liliemark, J.O., Estey, E. and Keating, M.J. (1987) "Saturation of ara-CTP accumulation during high-dose ara-C therapy: pharmacologic rationale for intermediate-dose ara-c", *Seminars in Oncology* 14, 159.

[14] Hiddemann, W., Schleyer, E., Unterhalt, M., Zühlsdorf, M., Rolf, K., Reuter, C., Kewer, U., Uhrmeister, C., Wörmann, B. and Büchner, T. (1992) "Differences in the intracellular pharmacoki-

netics of cytosine arabinoside (ara-C) between circulating leukemic blasts and normal mononuclear blood cells", *Leukemia* **6**, 1273.

[15] Braess, J., Berkovioc, D., Feuring-Buske, M., Fleer, E., Pfoertner, J., Wegendt, C., Keve, S., Riggert, J., Kern, W., Unterhalt, M., Hiddemann, W. and Schleyer, E. (1998) "Ara-C metabolism in fresh leukemic blasts/normal bone marrow/hematopoetic stem cells and its impact on the lipid composition of leukemic cells (HL60)", In: Hiddemann, W., Büchner, T., Wörmann, B., Ritter, J., Creutzig, U., Keating, M. and Plunkett, W., eds, Acute Leukemias VII—Experimental Approaches and Novel Therapies (Springer, Berlin/-Heidelberg), p 596.

[16] Phillips, G.L., Reece, D.E., Shepherd, J.D., Barnett, M.J., Brown, R.A., Frei-Lahr, D.A., Klingemann, H.G., Bolwell, B.J., Spinelli, J.J., Herzig, R.H. and Herzig, G.P. (1991) "High-dose cytarabine and daunorubicin induction and post remission chemotherapy for the treatment of acute myelogenous leukemia in adults", *Blood* **77**, 1429.

[17] Wolff, S.N., Marion, J., Stein, R.S., Flexner, J.M., Lazarus, H.M., Spitzer, T.R., Phillips, G.L., Herzig, R.H. and Herzig, G.P. (1985) "High-dose cytosine arabinoside and daunorubicin as consolidation therapy for acute nonlymphocytic leukemia in first remission: a pilot study", *Blood* **65**, 1407.

[18] Schiller, G.J., Nimer, S.D., Territo, M.C., Ho, W.G., Champlin, R.E. and Gajewski, J.L. (1992) "Bone marrow transplantation versus high-dose cytarabine-based consolidation chemotherapy for acute myelogenous leukemia in first remission", *Journal of Clinical Oncology* **10**, 41.

[19] Baer, M.R., Christiansen, N.P., Frankel, S.R., Brunetto, L., Mròzek, K., Bloomfield, C.D. and Herzig, G.P. (1993) "High-dose cytarabine, idarubicin, and granulocyte colony-stimulating factor remission induction therapy for previously untreated de novo and secondary adult acute myeloid leukemia", *Seminars in Oncology* **20**, 6.

[20] Kantarjian, H.M., Estey, E.H., Plunkett, Keating, M.J., Walters, R.S., Iacoboni, S., McCredie, K.B. and Freireich, E.J. (1986) "Phase I-II clinical and pharmacologic studies of high-dose cytosine arabinoside in refractory leukemia", *American Journal of Medicine* **81**, 387.

[21] Schiller, G., Gajewski, J., Territo, M., Nimer, S., Lee, M., Belin, T. and Champlin, R. (1992) "Long-term outcome of high-dose cytarabine-based consolidation chemotherapy for adults with acute myelogenous leukemia", *Blood* **80**, 2977.

[22] Hiddemann, W., Aul, C., Maschmeyer, G., Schonrock-Nabulsi, R., Ludwig, W.D., Bartholomaus, A., Bettelheim, P., Becker, K., Balleisen, L., Lathan, B., Koeppler, H., Grueneisen, T., Donhuijsen-Ant, R., Reichle, A., Heinecke, A., Sauerland, C. and Büchner, T.H. (1993) "High-dose versus intermediate-dose cytosine arabinoside combined with mitoxantrone for the treatment of relapsed and refractory acute myeloid leukemia: results of an age adjusted randomized comparison", *Leukemia and Lymphoma* **10**, 133.

[23] Büchner, T., Hiddemann, W., Wörmann, B., Loeffler, H., Maschmeyer, G., Hossfeld, D., Ludwig, W.D., Nowrousian, M., Aul, C., Schaefer, U.W., Sauerland, C. and Heinecke, A. (1992) "Longterm effects of prolonged maintenance and of very early intensification chemotherapy in AML: data from AMLCG", *Leukemia* **6**(Suppl. 2), 68.

[24] Rohatiner, A., Slevin, M.L., Dhaliwal, H.S., Malpas, J.S. and Lister Tal (1984) "High-dose cytosine arabinoside: response to therapy in acute leukaemia and non-Hodgkin's lymphoma", *Cancer Chemotherapy and Pharmacology* **12**, 90.

[25] Estey, E., Keating, M.J., Plunkett, W., McCredie, K.B. and Freireich, E.L. (1987) "Continuous-infusion high-dose cytosine arabinoside without anthracyclines as induction and intensification therapy in adults under age 50 with newly diagnosed acute myelogenous leukemia", *Seminars in Oncology* **14I**(Suppl. 1), 58.

[26] Ghaddar, H.M., Plunkett, W., Kantarjian, H.M., Pierce, S., Freireich, E.J., Keating, M.J. and Estey, E.H. (1994) "Long-term results following treatment of newly-diagnosed acute myelogenous leukemia with continuous-infusion high-dose cytosine arabinoside", *Leukemia* **8**, 1269.

[27] Lee, J.H., Lee, K.H., Kim, S., Seol, M., Kim, S.H., Kim, W.K. and Lee, J.S. (2001) "Combination chemotherapy of intermediate-dose cytarabine, idarubicin, plus etoposide and subsequent mobilized donor leukocyte infusion for relapsed acute leukemia after allogenic bone marrow transplantation", *Leukemia Research* **4**, 305.

[28] Bahng, H., Lee, J.H., Ahn, J.H., Lee, J.H., Lee, J.S., Kim, S.H., Kim, W.K. and Lee, K.H. (2001) "Combination chemotherapy utilizing continuous infusion of intermediate-dose cytarabine for refractory or recurrent acute myeloid leukemia", *Leukemia Research* **3**, 213.

[29] Sternberg, D.W., Aird, W., Neuberg, D., Thompson, L., MacNeill, K., Amrein, P. and Shulman, L.N. (2000) "Treatment of patients with recurrent and primary refractory acute myelogenous leukemia using mitoxantrone and intermediate-dose cytarabine: a pharamacologically based regimen", *Cancer* **9**, 2037.