The results of treatment with idarubicin in childhood acute nonlymphoblastic leukemia

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SUMMARY: Şaşmaz İ, Tanyeli A, Bayram İ, Antmen B, Yılmaz L, Küçükosmanoğlu O, Kılınç Y. The results of treatment with idarubicin in childhood acute nonlymphoblastic leukemia. Turk J Pediatr 2004; 46: 32-37.

Anthracycline and cytosine arabinoside are used in combination as the standard therapy for remission induction of acute nonlymphoblastic leukemia. Idarubicin, a synthetic daunorubicin analogue, shows an improved spectrum activity and diminishes acute or chronic toxicity when compared with the other anthracyclines. This study has been carried out in our clinic in order to evaluate the efficiency of the acute nonlymphoblastic leukemia protocol which includes idarubicin.

Thirty-eight patients admitted to our Department between 1992-1999 and diagnosed as acute nonlymphoblastic leukemia (ANLL) were included in the study. Their median age was 7 years 6 months (range, 8 months to 14 years). Induction therapy consisted of idarubicin plus cytosine arabinoside and etoposide. Consolidation therapy consisted of two courses, followed by maintenance therapy with thioguanine, cytosine arabinoside, vincristine and cyclophoshamide.

The complete remission rate was found to be 71%. The overall survival estimate was found to be 40% for one year and 23% for three years.

We established that the protocol with idarubicin reached a higher remission ratio when compared with the other protocols with anthracycline. However, the degree of the hematologic toxicity ratios related to the therapy increased the complication ratios, which affected the long-term life analyses directly. Therefore this protocol may be revised according to socioeconomical conditions, especially in the developing countries.

Key words: acute nonlymphoblastic leukemia, idarubicin, childhood.

Acute nonlymphoblastic leukemia (ANLL) accounts for 15-20% of all childhood leukemia. Since the classical treatment methods used for ANLL have not produced the required results, experiments for new medicines are still in process[1]. The administration of intensive induction, consolidation, intensification and maintenance therapy, and performance of allogeneic or autologous bone marrow transplantation, together with appropriate supportive care, have resulted in a significant decline in the mortality rate, and the event-free survival has lengthened. However, the present treatments provide a remission of 70-80% and event-free survival of 70-80%[2-5].

Anthracycline and cytosine arabinoside are used in combination for remission induction of ANLL as the standard therapy. The most frequently used drugs in the treatment are daunorubicin, doxorubicin, epirubicin and idarubicin. Idarubicin, a synthetic daunorubicin analogue, shows an improved spectrum activity and diminishes acute or chronic toxicity better when compared with the other anthracyclines[3,6,7]. Idarubicin has a greater influence on cultured human cancer cells in cytotoxicity than the other anthracyclines[8]. It is also less cardiotoxic than daunorubicin and doxorubicin[9]. Idarubicin, which was initially used for refractory or relapse

ANLL or acute lymphoblastic leukemia, has recently begun to be used successfully as the standard therapy, especially for ANLL[7,8].

There are only a limited number of studies in the literature concerning the use of idarubicin for childhood leukemia. This study has been carried out in our clinic retrospectively in order to evaluate the efficiency of the ANLL protocol, which has included idarubicin since 1992.

Material and Methods

Thirty-eight patients (19 females and 19 males) who were admitted to the Department of Pediatric Hematology of Çukurova University Faculty of Medicine were diagnosed as de novo ANLL between March 1992 and September 1999. Their median age was 7 years 6 months (age range: 8 months to 14 years). The bone marrow smears of all the patients were evaluated morphologically according to FAB classification using Giemsa, peroxidase, Sudan Black, periodic acid-schiff and esterase stains[10]. Immunological markers were also assessed in most of those patients[11].

The therapy schedule is shown in Table I, and includes two inductions, two consolidations, and maintenance therapy or bone marrow transplantation. After completing the second consolidation therapy we began the maintenance therapy for the complete remission situations. The maintenance therapy period was one year. Bone marrow transplantation was performed in three patients.

Statistical analyses were made using SPSS v 11.0 package. Methodically, the evaluation was calculated by multivariate analyses and the life duration analyses according to Kaplan-Meier. Event-free survival and overall survival were defined for our patient group as follows: event-free survival for relapse meant the length of time to relapse as end point from the time of diagnosis; overall survival means the total follow-up time of patients from the time of diagnosis.

Results

The clinical and hematological characteristics of patients at diagnosis were as follows: hepatomegaly in 22 patients (57%), splenomegaly in 20 patients (52%), lymphadenopathy in 27 patients (71), central nervous system involvement in 7 patients (18%), and chloroma in 1 patient (2%). The mean WBC count was 39,428 mm^3 (minimum 800 mm^3-maximum 153,800 mm^3) and mean platelet count was 51,131 mm^3 (minimum 11,000 mm^3-maximum 342,000 mm^3).

The results of the protocol with idarubicin are shown in Table II. After the induction therapy, the complete remission rate was found to be 71% (27/38). The consolidation therapy was

Table I. Treatment of Acute Nonlymphoblastic Leukemia

INDUCTION PHASE (two courses every 3 weeks)	
Cytosine arabinoside	: 100 mg/m^2 every 12 hr for 30 minutes, 14 doses
Idarubicin	: 12 mg/m^2/day, 0-2 days, 3 doses
VP-16	: 100 mg/m^2/day for 60 minutes, 3-5 days, 3 doses
Cystosine arabinoside (Intrathecal)	: Day 0
CONSOLIDATION PHASE I:	
Cytosine arabinoside	: 3 gr/m^2 every 12 hr for 4 hours, 0-1 days, 4 doses
L-Asparaginase	: 6000 U/m^2 IM at 42nd hour
Methotrexate (intrathecal)	: Day 0
CONSOLIDATION PHASE II:	
Idarubicin	: 12 mg/m^2/day, 0-1 days, 2 doses
Cytosine arabinoside	: 200 mg/m^2/dose for continuous infusion, 1-5 days, 5 doses
VP-16	: 100 mg/m^2/day for 60 minutes, 1-5 days, 5 doses
Methotrexate (intrathecal)	: Day 0
If the patient has a suitably matched donor, transplantation is recommended after the consolidation therapy.	
MAINTENANCE THERAPY (to be repeated every 30 days, given for 12 cycles):	
6-Thioguanine	: 75 mg/m^2/day p.o., 0-27 days
Vincristine	: 1.5 mg/m^2 iv, day 0
Cytosine arabinoside	: 75 mg/m^2/day iv, 0-3 days
Cyclophosphamide	: 75 mg/m^2/day iv, 0-3 days

Table II. The Results of Treatment of ANLL Patients

Phase of treatment	Number of patients	Complete remission		No response and death		Relapse		Death in CR	
		n	%	n	%	n	%	n	%
Induction	38	27	71	11	29			6	15.7
CP I	21					1*	2.6	1	2.6
CP II	19					1*	2.6	3	7.8
Maintenance	15					5*	13	1	2.6
After completion of all therapy	9					1*	2.6		

CP I: Consolidation phase I.
CP II: Consolidation phase II.
CR: Complete remission.
*: These patients died in relapse.
ANLL: Acute nonlymphoblastic leukemia.

performed on 21 patients. We began maintenance therapy on 15 patients. Nine patients were taken into follow-up without medicine after the completion of therapy.

Nausea, vomiting, alopecia and mucositis developed in all patients. Hepatotoxicity was seen in eight patients (21%). Elevation in serum glutamic-oxaloacetic transaminase was seen in six patients. Hyperbilirubinemia occurred in two patients as an isolated abnormality, with normal serum glutamic-oxaloacetic transaminase. Renal toxicity and hepatotoxicity were seen in two patients and renal toxicity in one patient.

Echocardiographic examination was done on 30 patients. An initial pericardial involvement was seen in two patients. There was an atrioventricular septal defect in one patient and situs inversus totalis in one patient. Left ventricular dysfunction developed in only one patient during the treatment. This patient died due to neutropenic sepsis.

After the induction phase I therapy, 33/38 patients developed severe neutropenia (mean 10 days, minimum 2 days, maximum 30 days), and 36/38 patients developed severe thrombocytopenia (mean 12, minimum 1 day, maximum 28 days). Induction phase II therapy was performed on 25 patients. After the induction phase II therapy, in 16/25 patients severe neutropenia (mean 7 days, minimum 2 days, maximum 16 days) and in 13/25 patients severe thrombocytopenia occurred (mean 10 days, minimum 2 days, maximum 16 days). The hematologic and nonhematologic toxicities of our patient group are given in Table III.

Thirty patients were lost: 11 were lost in complete remission in the induction phase, consolidation I and II phases and in the maintenance of protocol (at the end of induction phase: 6 patients, consolidation phase I: 1 patient, consolidation phase II: 3 patients, maintenance therapy: 1 patient). The causes of death were: neutropenic sepsis (4 patients), pneumonia (2 patients), neutropenic sepsis and renal failure (1 patient), neutropenic sepsis together with renal and hepatic failure (1 patient), and complications related to bone marrow transplantation (3 patients). Eleven patients who did not go into remission died in the early period. The causes of death were: neutropenic sepsis (7 patients), neutropenic sepsis together with renal and hepatic failure (1 patient), neutropenic sepsis and renal failure (1 patient), cardiac and nervous system involvement (1 patient), and pneumothorax development during the tracheostomy due to a hemangiomatous lesion on the vocal cord accompanying the neutropenic sepsis (1 patient). Eight patients with relapse died due to ANLL progression. Eight patients are still alive.

Table III. Toxicity Rates of the ANLL Patients

	n	%
Mucositis	38	100
Alopecia	38	100
Myelotoxicitiy	36	94
Infection	35	92
Hepatotoxicity	8	21
Hepatic and renal toxicity	2	5
Bleeding	1	2.5
Renal toxicity	1	2.5
Cardiac dysfunction	1	2.5

ANLL: Acute nonlymphoblastic leukemia.

According to Kaplan-Meier life-table analyses, overall survival estimate was 40% for one year and 23% for three years (Fig. 1). When the influence on the overall survival period of patient age ($p>0.5$), gender, and WBC ($p>0.5$)

count was observed by multivariate analyses, it was found that the female gender was effective ($p<0.001$), and that the female gender was the positive factor for the prognosis (Fig. 2). Event-free survival for relapse was estimated as 32% by Cox regression analysis.

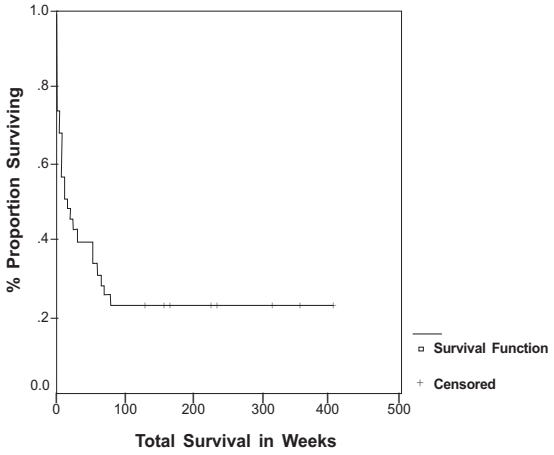

Fig. 1. Estimates of survival by Kaplan-Meier.

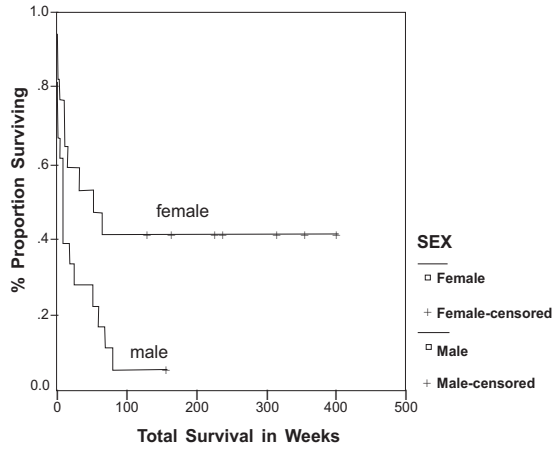

Fig. 2. Survival distribution by gender.

Discussion

Childhood ANLL chemotherapy regimen has failed to reach the required results to date. Thus, new drug treatments and new protocol developments are still being tested. Although the results (especially with bone marrow transplantation) have shown some improvements, they are still not satisfactory[4,5,12,13].

The standard treatment of ANLL is anthracycline and cytosine arabinoside in combination. Remission rate increases with the addition of mitoxantrone etoposide[13,14]. Idarubicin was used initially for adult ANLL treatment. Wiemik et al.[15] found better results for 214 adult ANLL patients who reached remission and proved long-term survival. Complete remission was found to be 70% in the idarubicin group and 59% in the daunorubicin group. Especially when etoposide was added to the therapy, remission rates could reach up to 81%[8].

In the study carried out by Mehta et al.[16], which included 52 patients, the BF 12 protocol containing idarubicin, high-dose cytosine arabinoside and etoposide was given, and the complete remission ratio was found to be 78% and overall survival ratio for three years as 49%. A recent multicenter study in Great Britain by Rassam et al.[17] used a protocol with IDA for newly diagnosed ANLL patients and relapse cases. The remission ratio for the newly diagnosed patients was found to be 57% and for the relapse cases 42%.

Heyli et al.[18] used cytosine arabinoside and idarubicin treatment on 23 ANLL adult patients and attained an 80% complete remission rate, but they could not indicate a difference in long-term survival results.

Sackmann-Muriel et al.[19] reported a 78% complete remission in the 68 ANLL childhood patients on whom they used idarubicin, cytosine arbinoside and etoposide. The four-year event-free survival estimate was 42% and overall survival estimate was 44%. Dinndorf et al.[20] reported an 80% complete remission by using the protocol with idarubicin, cytosine arabinoside and fludarabine on 10 ANLL patients with relapse and refractory. They did not observe many side effects except for hematological toxicity.

In a multicenter study carried out in our country for the first time, protocol with idarubicin was used on newly diagnosed ANLL children by Gedikoğlu et al.[21] Complete remission rate was found to be 88% and the 30-month long life duration 29%. They detected a high relapse rate and toxic effect related to the medicines.

Fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF) and idarubicin (FLAG-IDA) protocol was used in relapsed and poor risk childhood acute leukemia by Yalman et al.[22]. In this study authors reported that FLAG-IDA protocol appeared to be myelotoxic in their patient group and was not cost effective for developing countries.

We began using idarubicin content protocol in 1992 and used the same protocol for all patients until September 1999. The remission rate, which was found to be 71% after the induction therapy, was compatible with the other studies in the literature. When evaluated according to Kaplan-Meier, overall survival estimate was 40% for one year and 23% for three years. The patients in our clinical studies could not attend controls for economic and social-cultural reasons, which affected the mortality ratio negatively.

Gastrointestinal toxic effects (vomiting, mucositis, nausea, diarrhea) and myelosuppressive effect in the ANLL patients treated with idarubicin were no different from that seen in the cases treated with other anthracyclines[7,8]. In our study group we noticed nausea, vomiting and mucositis in all our patients and treatments were given for these complications. There was also 94% myelotoxicity. 21% hepatotoxicity, 2.5% renal toxicity, and 5% renal and hepatotoxicity. This myelotoxicity comes forward as a factor prohibiting the continuation of the chemotherapy schema in a regular phase. The high ratio of myelotoxicity explains the high ratio of the patients with neutropenic sepsis.

The fact that anthracyclines cause dose-dependent cardiomyopathy, decreased left ventricular ejection fraction and congestive heart failure related to these has been proven by animal experiments, radionuclide studies and endomyocardial biopsies. However, idarubicin was tolerated in cardiotoxicity better than the other anthracyclines[7,8]. The decrease in left ventricular ejection fraction was seen less frequently in the patients treated with idarubicin. The drug dependent cardiomyopathy ratio was 5% in a study carried out on an adult patient group[9]. In Sackmann-Muriel's study cardiotoxicity ratio was found to be 1.5%[19].

In our patient group pericardial involvement was found in two patients during the analyses done premedically by echocardiography. In the heart function tests carried out after the consolidation phase II therapy, no defect was observed in these patients. Cardiotoxicity was only seen during the therapy in one patient, which was detected by echocardiography and electrocardiography. Different toxic effects mentioned above occurred in almost all of our patients. We think that the most important factors related to mortality are the long duration of neutropenia and the other toxic effects of idarubicin.

According to the results of our study, no correlation was proven between the WBC count, age and prognosis. Weinstein et al.[23] detected no relation between the WBC count and prognosis. However, sex was found to be effective. It was indicated by the Cox regression analyses that the female gender had a positive effect.

In conclusion, we have observed that the protocol with idarubicin achieves a higher remission ratio when compared with the other protocols with anthracycline. However, the magnitude of the hematological toxicity ratios related to the therapy increases the complication ratios, affecting the long-term life analyses directly. We consider that this protocol is well adjusted to the needs and socioeconomical conditions in the developing countries. This myelotoxic therapy should be taken into consideration by clinicans in view of the high mortality ratio in ANLL. In order to obtain more reliable results, we suggest that the studies should be carried out in a larger patient group and for a longer follow-up period.

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