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Treatment of newly diagnosed patients with acute promyelocytic leukemia with modified spanish treatment protocol

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The results of treatment of acute promyelocytic leukemia, when combination ATRA + chemotherapy is used in induction and maintainance therapy and risk adapted strategy applied in consolidation, improved at present time. Enhanced supportive therapy also contribute to improved outcome of APL patients. 3 - year relapse free, overall survival and clinical and biological presenting features of APL patients were evaluated. Since january 2001 till march 2009 32 patients treated with modified spanish treatment scheme were assesed. After june 2003 risk adapted strategy in protocol therapy according to spanish treatment group with ATRA and anthracyclines in consolidation therapy in high and intermediate risk patients was used. Cytoreduction therapy in patients with initially high leukocyte count was the modification of spanish treatment scheme. 29 (90,6 %) patients achieved complete hematologic remission, 2 (6,3 %) molecular relapses were observed, death was observed in 4 patients (12,5 %). The estimated 3-year OS was 90,6 %; 95 % CI (80,5 % - 100,0 %), and estimated 3- year RFS was 95,5 %; 95 % CI (86,8 % - 100,0 %). Survival results correspond with other published clinical studies. The number of relapses was slightly lower and the incidence of ATRA syndrome (50 %) was higher when compare with the results of other study groups. Current recommendations for treatment with risk-adapted strategy for patients with newly diagnosed acute promyelocytic leukemia resulted in our patients group to comparable outcome and good compliance like in other published studies.

Key words: leukemia, APL, ATRA, therapy, protocol, survival

Acute promyelocytic leukemia (APL) is an infrequent type of leukemia with incidence rate of 0,7 per milion persons per year and form about 5 % – 10 % of adult acute myeloblastic leukemias (AML) [1]. Current treatment strategy has significantly improved prognosis of this type of leukemia. In induction treatment of APL the combination of ATRA (all-trans retinoic acid) with anthracycline is recomended. The use of ATO based regimens should be restricted to patients in whom chemotherapy is contraindicated or for those included in clinical trials. In consolidation at least two cycles of anthracycline ± ATRA are recomended, whereby the doses of anthracycline and the addition of ATRA depends on the stratification of the patient according to risk group (Sanz et al.) [2]. In the maintenance treatment two years of ATRA with low dose chemotherapy is recomended, whereby the discussion about necessity and benefits of maintenance therapy in low risk patients and those, who achieved complete molecular remission at the end of consolidation therapy, is in progress [3]. Spanish treatment group PETHEMA achieved excellent results in the studies LPA96 and LPA99 in the treatment of APL with minimal toxicity [2, 4]. We decided to analyze and compare achieved results of the treatment in our group of patients with the results of published clinical studies. The aim of present analysis was evaluation of 3 - year relapse free survival (RFS) and overall survival (OS) in patients with acute promyelocytic leukemia in two treatment centers treated with modified protocol of spanish leukemic group PETHEMA and description of clinical and biological presenting features of APL patients.

Abbreviations: CR-complete response, ICH – intracranial hemorrhage

Patients and methods

Regarding the published treatment results of the new diagnosed patients with APL, both centers started to treat patients with mentioned diagnoses according to treatment protocol of spanish leukemic group PETHEMA, which was modified [2, 4]. Modified treatment scheme of spanish leukemic group mLPA96 (m = modified) was used since january 2001 and mLPA99 was used since july 2003. Cytoreduction therapy in patients with initially high leukocyte count was the modification of protocol therapy.

Between January 2001 and March 2009 we enrolled 33 patients with de novo acute promyelocytic leukemia. Together we evaluated 32 patients with new diagnosed APL. One patient was excluded from assesment because of death before starting therapy (he died in first 24 hours being in hospital from intracranial hemorrhage).

Patients were enrolled to evaluation when they have confirmation of molecular rearrangement of *PML/RARα* (or variant forms of APL) or cytogenetic confirmation of t(15;17) together with positivity of *PML/RARα* by FISH technique (in the case of failure of molecular confirmation), age over 18 years, no contraindications to anthracycline therapy, performance status WHO 1 and 2.

The risk of relapse was defined by predicting model [4] at the time of confirmation of APL diagnosis according to initial counts of leukocytes and thrombocytes. Low-risk patients has initial counts of leukocytes Leu ≤ 10 x 10^9/l and thrombocytes Tr > 40 x 10^9/l, intermediate risk patients Leu < 10 x 10^9/l a Tr < 40 x 10^9/l and high-risk patients Leu ≥ 10 x 10^9/l a Tr < 40 x 10^9/l [4].

The diagnosis of ATRA syndrome was made according to presence at least two and more signs and symptoms described by Frankel et al. [5].

Treatment. The treatment schedule included an induction therapy with ATRA (all-transretinoic acid) 45 mg/m^2/day, divided into two daily doses, since first day till achievement of complete remission, but not longer than 90 days, together with idarubicine 12 mg/m^2/day, d. 2, 4, 6, 8, (intravenously for 30 minutes). Patients who achieved complete remission in mLPA96 protocol continue by consolidation three cycles: (1) Idarubicine 5 mg/m^2/day, d. 1 - 4; (2) Mitoxantron 10 mg/m^2/day, d. 1 - 5; (3) Idarubicine 12 mg/m^2/day, d.1. Intermediate and high-risk patients in mLPA99 protocol were treated in consolidation by ATRA at dose 45 mg/m^2/day, d. 1 - 15 in combination with increased doses of antracyclines. Idarubicine dose in first consolidation was 7 mg/m^2/day and in third consolidation it was given for two days instead of one. Time interval between cycles was 4 - 5 weeks and for setting of next cycle the hematological parameters had to achieve rates for Tr over 100 x 10^9/l and Neu over 1,5 x 10^9/l. Setting of cytoreduction therapy in high-risk patients (Leu > 10 x 10^9/l) was the modification of protocols mLPA96 and mLPA99. ARA-C was given as a cytoreduction therapy (1 - 2 g/m^2 á 12 hours, 4 succesive doses), eventually hydroxyurea (HU) 2 g/day for 2 - 3 days. Four weeks after finishing of consolidation therapy patients started maintenance therapy for two years: ATRA 45 mg/m^2 d. 1 - 15 every 3 month, 6-mercaptopurin 50 mg/m^2/day and methotrexate 15 mg/m^2 (at DHTUH 10 mg/m^2) weekly. The dose of 6-mercaptopurine and methotrexate could be reduced when hematological parameters were decreased. The dose of mercaptopurine and methotrexate was reduced for 50 % when Leu < 3,5 x 10^9/l, Tr < 100 x 10^9/l. Therapy could be temporary discontinued when Leu < 2,5 x 10^9/l, Neu < 0,5 x 10^9/l and Tr < 80 x 10^9/l.

Supportive therapy. Platelet transfusion treatment started when Tr < 30 x 10^9/l at NCI and Tr < 50 x 10^9/l at DHTUH treatment center. Coagulopathy was solved by treatment with fresh frozen plasma and fibrinogen. At the first signs of ATRA syndrome DXM 10 mg á 12 hours intravenously was instituted. After continual deterioration of vital functions during ATRA syndrome ATRA was temporary discontinuated. Infection was managed by standard antibiotical policy within both centers.

Definition and study endpoints. Complete hematologic remission was defined as cytomorphological finding of normocellular bone marrow with < 5 % of blasts, normal coagulation parameters, neutrophil rates > 1,5 x 10^9/l and thrombocytes > 100 x 10^9/l. Resistant disease was defined as persistance of > 5 % of blasts in bone marrow after 40 days since starting treatment. Complete molecular remission was defined as negativity of *PML/RARα* transcript by PCR technique.

Patients, who died before beginnig of therapy were excluded from the assesment. As early induction death was defined the death in firts 7 days of treatment induction, as late induction death was defined the death after 7 days of treatment induction.

Relapse-free survival (RFS) was the time from setting the diagnosis till event (relapse or death of any cause). Overall survival (OS) was the time from setting the diagnosis till the death from any cause or till the date of last follow-up. Patients lost from follow-up were considered as censored events on the date of last follow-up. Molecular relapse was the reappearance of *PML/RARα* positivity by PCR technique in two succesive bone marrow samples whenever after finishing consolidation therapy. RT-PCR assay technique with a sensitivity level of 10^{-5} was used.

Observation. At DHTUH center bone marrow morphology, cytogenetics, FISH, molecular PCR monitoring, blood count and basic biochemical parameters with clinical examination were performed every 3 month in first year, in second year every 6 month and once a year from third to fifth year. At NCI was follow-up performed every 3 month for the first two years, subsequently every 6 month for next three years and then once a year without bone marrow examination.

Statistical analysis. For continuus variables, data are given as medians (ranges), for some continuus variables also confidence interval CI 95 % is given. For nominal variables data

are reported as number and percentage. The Kaplan-Meier method was use to estimate the probability of OS and RFS. Results were processing by Statistical & Power Analysis Software NCSS 2007, www.ncss.com.

Results

Between January 2001 and March 2009 32 patients with de novo APL at DHTUH and NCI centers were assesed. 14 of them were treated according to mLPA96 and 18 patients according to mLPA99. In patient file were 22 women (68,8 %) and 10 men (31,2 %). Cytoreduction therapy with ARA-C or HU due to leukocytosis received together 8 patients (25,0 %), 3 (21,4 %) patients in mLPA96 protocol and 5 (27,8 %) patients in mLPA99 protocol. Alterations of the treatment scheme were performed in 5 patients (15,6 %) for these reasons: in one patient ATRA was definitely excluded after 30 days of ATRA therapy because of recurrent ATRA syndrome, ATRA was given in maintenance therapy in this patient. Second patient started treatment with standard treatment protocol of AML (ARA-C + mitoxantrone), because the first diagnostic results doesn´t indicate the diagnosis of APL. After obtainig the results of conventional and molecular cytogenetics ATRA was included to the therapy and the treatment followed due to treatment protocol. To the third patient was ATRA excluded because of acute vascular brain stroke and ATRA was later added in the maintenance therapy. To the fourth patient was after 11 month of maintenance therapy given only ATRA due to hepatopathy. Reinduction therapy (daunorubicine + ARA-C) after standard induction therapy was given to the last patient because of resistant disease.

Median age was 36 years, (range 21 - 62), in the age cathegory 18 - 40 years was 18 patients (56,3 %), in the cathegory 41 - 60 years were 13 patients (40,7 %), in the cathegory 60 - 70 years was 1 patient (3,1 %) and in the age cathegory above 70 years there wasn´t any patient. Hemorrhagic diathesis on the skin was observed in 26 patients (81,3 %), on the mucosa in 10 (31,2 %) patients, combined and other hemorrhagic manifestations (gastrointestinal bleeding, pulmonal bleeding, metrorrhage, retinal bleeding) were observed in 19 (59,4 %) patients. The basic characteristics of the follow-up patients file presents the Table 1 and Table 2 separately and together according to the type of treatment protocol. According to initial counts of leukocytes and thrombocytes (predicting model of relapse, [4]) were 6 (18,75 %) patients in low risk group, 20 (62,5 %) in intermediate risk and 6 (18,75 %) in high-risk group.(Table 3)**.** In 16 (50 %) patients was made the diagnoses of ATRA syndrome according to the presence of signs and symptoms described by Frankel et al. [5]. It was managed with standard therapy (dexametasone) and none of patients died of it.(Table 4)

Typical translocation t(15;17) by conventional cytogenetics technique we found in 13 (40,6 %) patients, 8 (25,0 %) patients had also additional chromosomal abnormalities except for t(15;17) and in 11 (34,4 %) patients was conventional cytogenetics unsuccesful. Positivity of *PML/RARα* by FISH technique was achieved in 31 (96,8 %) patients, in one patient (3,2 %) was achieved negativity of *PML/RARα* by FISH technique. Molecular rearrangement of *PML/RARα* by PCR technique was achieved in 24 (75 %) patients, in 8 (25 %) was this method unsuccesful due to technical reasons. Variant type (microgranular) of APL was observed in one patient (3,1 %). Graphic description of basic characteristics of patients file represents Figure 1.

Median of the initial count of leukocytes was 2,1 x 10^9/l, (range 0,46 – 122,6 x 10^9/l), median of the initial count of thrombocytes was 21,5 x 10^9/l, (range (5 – 128 x 10^9/l).

Median follow-up of the whole file in both protocols was 32 month (0,24 – 85 month). 5 (15,6 %) patients dropped from follow-up. Four of them moved for the next follow-up to the regional hematology specialist after finishing of treatment protocol. One patient moved to Czech Republic (Prague) during maintenance therapy where he continued in the treatment and was monitored by czech hematologists.

In our study 29 (90,6 %) patients achieved complete hematologic remission, the same number of patients achieved complete molecular remisssion. We observed 2 (6,3 %) hematologic and molecular relapses (both patients were treated according to mLPA96 protocol). Table 5 represents molecular relapses according to risk group. One patient relapsed after 4 years and 10 month and was treated by mLPA99 protocol as second line therapy. At the time of last follow-up he was treated by maintenance therapy, achieved second complete remission which persists for 18 month. Second patient had relaps after 22 month of follow-up. He died of metabolic disruption in the late phase of induction therapy of relapse.

Complete molecular and hematologic remission achieved overall 11 (78,6 %) patients in the mLPA96 protocol and 18 (100 %) patients in the mLPA99 protocol, from that according to age cathegories 18 – 40 years, 40 – 60 years, 60 – 70 years in the protocol mLPA96 as follows: 6 (85,7 %), 4 (66,7 %), 1 (100 %) and in the protocol mLPA99 11 (100 %), 7 (100 %), in the last cathegory there wasn´t any case. Complete molecular and hematologic remisssion we observed in 20 (90,0 %) women and 9 (90,0 %) men. 11 (84,6 %) patients in complete remission had only translocation t(15;17) and 8 (100 %) patients in complete remission had both t(15;17) and additional chromosomal abnormalities. The rates of complete remissions and rates of relapses are presented in the Table 1 and Table 2 in relation with age, sex, leukocytes, thrombocytes, subtype o APL and genetic abnormalities.

At median follow-up of all patients 32 month (range 0,24 – 85 month) the estimated 3-year OS by Kaplan-Meier was 90,6 %; 95 % CI (80,5 % - 100,0 %), and estimated 3- year RFS was 86,5 %; 95 % CI (74,1 % - 99,0 %). Figure 2**.** In follow-up file the death was observed in 4 patients (12,5 %), from that 3 (9,4 %) patients of fatal intracranial hemorrhage on the days 7, 8 and 11 of induction therapy. One patient (3,1 %) was early and

Table 1: Basic characteristics of APL patients and results of protocol therapy at DHTUH and NCI, mLPA96/mLPA99 (both treatment centers together, separately according to treatment scheme)

basic characteristics	DHTUH + NCI mLPA96 / DHTUH + NCI mLPA99				
	median (range) mLPA96 / mLPA99	patients N (%) mLPA96 / mLPA99	CMR (%) mLPA96 / mLPA99	relapse mLPA96 / mLPA99	OS (%) mLPA96 / mLPA99
total counts		14 (100,0) / 18 (100,0)	11 (78,6) / 18 (100,0)	2 (14,3) / 0	10 (71,4) / 18 (100,0)
age	41 (23 - 62) / 36 (21 - 58)				
18 – 40		7 (50,0) / 11 (61,1)	6 (85,7) / 11 (100,0)	1 (14,3) / 0	6 (85,7) / 11 (100,0)
41 – 60		6 (42,8) / 7 (38,9)	4 (66,7) / 7 (100,0)	1 (16,7) / 0	3 (50,0) / 7 (100,0)
61 – 70		1 (7,1) / 0	1 (100,0) / 0	0 / 0	1 (100,0) / 0
> 70		–		–	
sex					
male		7 (50,0) / 15 (83,3)	5 (71,4) / 15 (100,0)	0 / 0	5 (71,4) / 15 (100,0)
female		7 (50,0) / 3 (16,7)	6 (85,7) / 3 (100,0)	2 (28,6) / 0	5 (71,4) / 3 (100,0)
hemorrhage					
skin mucous		11 (78,6) / 15 (83,3) 4 (28,6) / 6 (33,3)	–	–	
other + combinated		6 (21,3) / 13 (72,2)	–	–	
FAB subtype					
typical		14 (100,0) / 17 (94,4)	11 (78,6) / 17 (100,0)	2 (14,3) / 0	10 (71,4) / 17 (100,0)
variant		0 / 1 (5,56)	0 / 1 (100,0)	0 / 0	0 / 1 (100,0)
WBC x 10^9/l	2,0 (0,8 - 122,6) / 2,1 (0,46 - 55,2)				
≤ 3,5		10 (71,4) / 13 (72,2)	9 (90,0) / 13 (100,0)	2 (20,0) / 0	8 (80,0) / 13 (100,0)
3,5 – 10		2 (14,3) / 1 (5,56)	2 (100,0) / 1 (100,0)	0 / 0	2 (100,0) / 1 (100,0)
11 – 50		0 / 3 (16,7)	0 /3 (100,0)	0 / 0	0 / 3 (100,0)
> 50		2 (14,3) / 1 (5,56)	0 / 1 (100,0)	0 / 0	0 / 1 (100,0)
Tr x 10^9/l	16,5 (5 - 76) / 24 (8 - 128)				
≤ 10		4 (28,6) / 2 (11,1)	4 (100,0) / 2 (100),0	2 (25,0) / 0	3 (75,0) / 2 (100,0)
11 – 40		7 (50,0) / 12 (66,7)	4 (57,1) / 12 (100,0)	0 / 0	4 (57,1) / 12 (100,0)
> 40		3 (21,4) / 4 (22,2)	3 (100,0) / 4 (100,0)	0 / 0	3 (100,0) / 4 (100,0)

N – number of patients**, CMR** – complete molecular remission, **OS** – overall survival

two patients (6,5 %) were late induction death of intracranial hemorrhage (Table 4).

At mentioned median follow-up, 29 (90,6 %) patients are alive without evidence of disease. This means, that all patients who achieved complete hematologic and molecular remission didn`t experience fatal intracranial hemorrhage FICH and/or relapse during induction therapy (Figure 3).

In the observed group of patients 10 of surviving patients weren´t in follow-up for 3 years on the date of last follow up March 2009. The results of complete remissions rates, relapse rates and OS in relation to risk groups [4] presents the Table 3 and Table 5.

Discussion

In the pre ATRA era the number of cured patients with APL ranged from 20 % to 40 % [4, 6]. After introduction of combined differentiation therapy of ATRA + chemotherapy (according to publicated studies since the 1991) this count increased to about 75 % - 80 % cured patients and the number of complete remissions ranged from 90 % to 95 % [7]. From our assesment we observed 90,6 % CMR and CHR (29 patients), which is comparable with the previously published reports [2, 3, 4,] where LPA96 and LPA99 estimated 3 – year DFS 81 ± 6 % and 90 ± 5 % and estimated 3 – year OS 78 % ± 6 % and 85 %

Table 2: Assesment of whole patients file (both treatment protocols mLPA96 + mLPA99 together, treatment centers together)

basic characteristics	median (range)	patients N (%)	KMR (%)	relapse (%)	OS (%)
total counts		32	29 (90,6)	2 (6,3)	28 (87,5)
follow up month	32 (0,24 - 85)				
age (years)	36 (21 - 62)				
18 – 40		18 (56,3)	17 (94,4)	1 (5,6)	17 (94,4)
41 – 60		13 (40,7)	11 (84,6)	1 (7,7)	10 (76,9)
61 – 70		1 (3,1)	1 (100,0)	0	1 (100,0)
> 70		–	–	–	–
sex					
male		22 (68,8)	20 (90,9)	0	20 (90,9)
female		10 (31,2)	9 (90,0)	2 (20,0)	8 (80,0)
hemorrhage[a]					
skin		26 (81,3)			
mucous		10 (31,2)			
other + combinated		19 (59,4)			
subtype FAB					
M3		31 (96,9)	28 (90,3)	2 (6,5)	27 (87,1)
M3v		1 (3,1)	1 (100,0)	0	1 (100,0)
APL					
t(15;17)		13 (40,6)	11 (84,6)	0 (0)	11 (84,6)
t(15;17) + additional chromosomal changes		8 (25,0)	8 (100,0)	1 (12,5)	8 (100,0)
Leu	2,1 (0,46 - 122,6) x 10^9/l				
≤ 3,5		23 (71,8)	22 (95,7)	2 (8,7)	21 (91,3)
3,5 – 10		3 (9,4)	3 (100,0)	0	3 (100,0)
11 – 50		3 (9,4)	3 (100,0)	0	3 (100,0)
> 50		3 (9,4)	1 (33,3)	0	1 (33,3)
Tr	21,5 (5 - 128) x 10^9/l				
≤ 10		6 (18,8)	6 (100,0)	2 (33,3)	5 (83,3)
11 – 40		19 (59,3)	16 (84,2)	0	16 (84,2)
> 40		7 (21,9)	7 (100,0)	0	7 (100,0)

a – some patients have several types of hemorrhage at the same time, types of hemorrgahe are combinated

Table 3 : Risk groups, DHTUH and NCI together

risk group	DHTUH a NCI mLPA96 / 99				
	patients N (%)	CR (%)	relapses (%)	OS (%)	induction death (%)
low	3 (50,0) /3 (50,0)	3 (100,0) / 3 (100,0)	0 (0) / 0 (0)	3 (100,0) / 3 (100,0)	0 (0) / 0 (0)
intermediate	9 (45,0) / 11 (55,0)	8 (88,9) / 11 (100,0)	2 (22,2) / 0 (0)	7 (77,8) / 11 (100,0)	1 (11,1) / 0 (0)
high	2 (33,3) / 4 (66,7)	0 / 4 (100,0)	0 (0) / 0 (0)	1 (50,0) / 4 (100,0)	2 (100,0) / 0 (0)

N – number of patients, **CR**- complete remission, **OS** – overall survival

± 5 % in the APL patients. In our patients group the estimated 3 – year OS is 90,6 % which correlates with mentioned values. We cannot exactly compare results of our RFS with this study because of different deffinition of DFS and RFS, but our results (RFS 86,5 %) corresponds with the reported results of clinical outcome (Table 6). Our treatment protocol is the same (with the exception of modification) as that used by spanish leukemic group [7]. It is proven that maintenance therapy significantly improves survival and decreases the number of relapses [8]. In our observation we achieved 2 (6,3 %) relapses, which is slightly lower when compared with results in literature [2, 4]. The incidence of early (3,1 %) death during induction therapy is similar to that described in other studies (2,9 % – 12 %) [7, 9]. The main cause of death so in our patients group as in

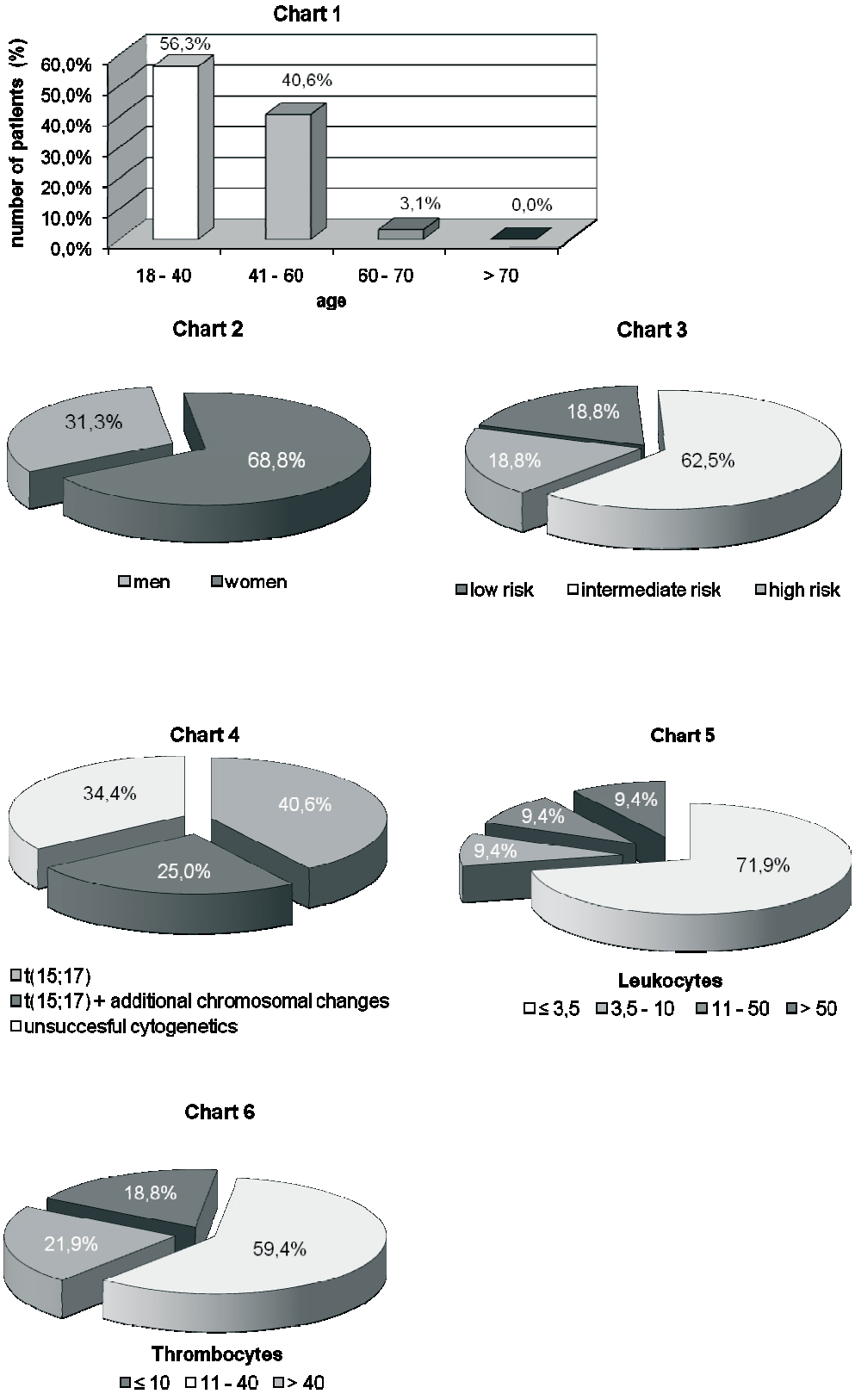

Figure 1: Graphic characteristics of patients file

Table 4: Induction death number and presence of ATRA syndrome in APL patients in relation to age and number of leukocytes

	both centers (%)	DHTUH	NCI	≥ 50 years DHTUH / NCI	< 50 years DHTUH / NCI	Le ≤ 10 x 10^9/l DHTUH / NCI	Le > 10 x 10^9/l DHTUH / NCI
Induction death	3 (9,4)	1	2	1 / 0	0 / 2	0 / 1	1 / 1
early	1 (3,1)	1	0	1 / 0	0 / 0	0 / 0	1 / 0
late	2 (6,3)	0	2	0 / 0	0 / 2	0 / 1	0 / 1
hemorrhage	3	1	2	1 / 0	0 / 2	0 / 1	1 / 1
infection	0	0	0	–	–	–	–
ATRA syndrome	0	0	0	–	–	–	–
other	0	0	0	–	–	–	–
ATRA syndrome	16 (50,0)	10	6	1 / 1	9 / 5	8 / 5	2 / 1

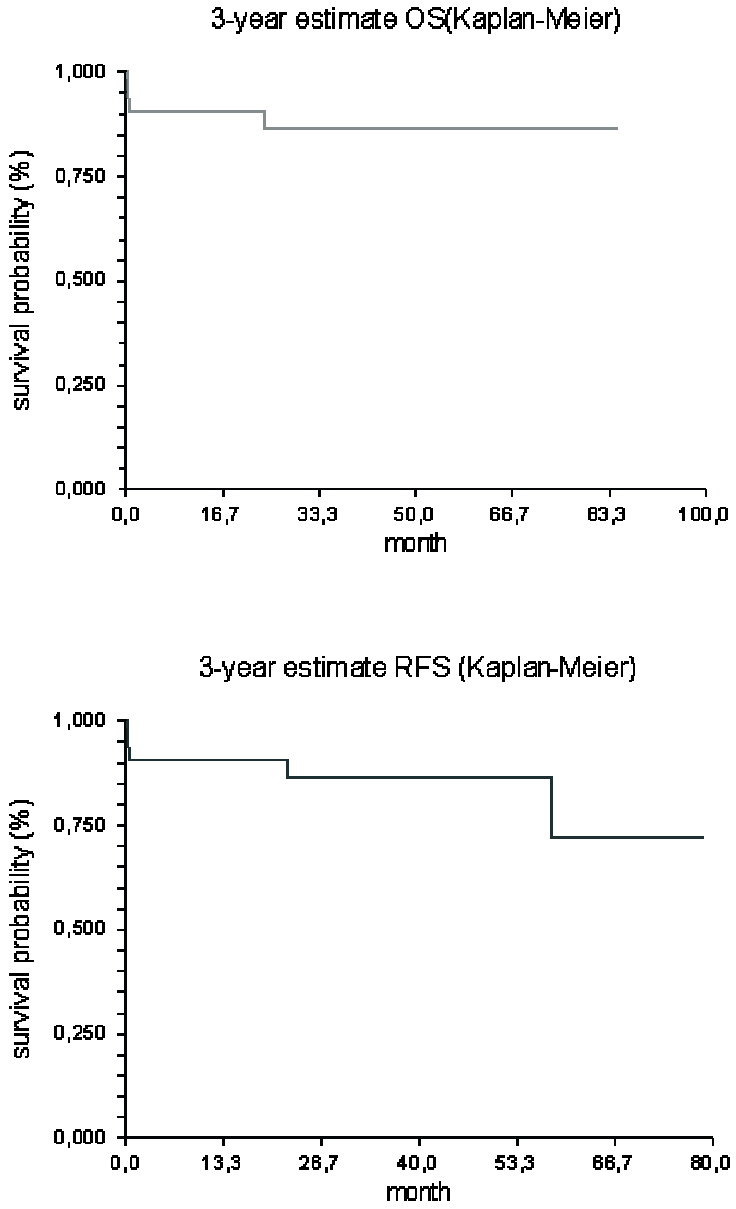

Figure 2: Kaplan –Meier estimate of 3 - year OS and RFS

Table 5: Molecular relaps according to risk group

risk group (Sanz et al.)	Patients N (%)	molecular relaps	
		N	time to relapse, month
low	6 (18,75)	0	–
DHTUH	6	0	–
NCI	0	0	–
intermediate	20 (62,5)	2	-
DHTUH	13	1	58
NCI	7	1	24
high	6 (18,75)	0	–
DHTUH	4	0	–
NCI	2	0	–
together	32	2	–

N – number of patients

other world treatment centers is hemorrhagic event, most frequently intracranial hemorrhage. In our patients file we didn´t observed any other early death event. One patient died of intracranial hemorrhage even before started therapy, whereby leukemic group PETHEMA and US Intergroup present that 3 % to 5 % of patients with new diagnosed APL die of hemorrhage even before starting therapy [10, 11]. The summary of outcomes, number of relapses, frequency of early induction death in several studies is presented in Table 6.

The incidence of ATRA syndrome in our follow-up file was higher (50,0 %) when compare with reports from other centers (10 % and lower when patient is treated with combination ATRA + CHT and 25 % in ATRA treatment only) [12]. This result is probably caused by different criteria used for the diagnosis of ATRA syndrome when compare to published studies. It may also be the result of incidental configuration of

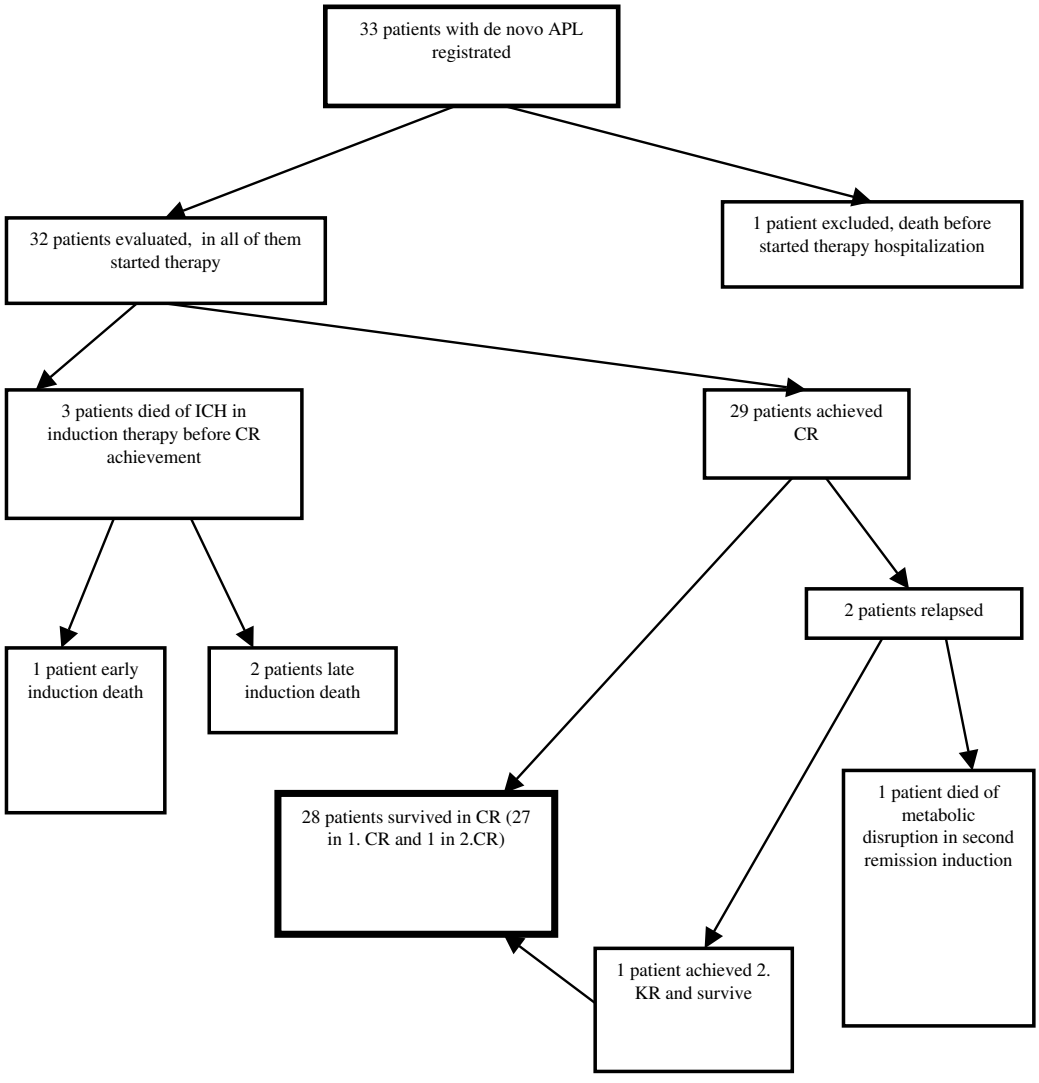

Figure 3: Study diagram.

Table 6: Summary of clinical studies in patients with de novo APL, results of outcome with all-trans retinoic acid regimens, ED and relapses

	patients N	CR (%)	DFS/EFS/RFS 2-3 years (%)	OS (%)	ED (%)	relapse (%)
PETHEMA LPA 96 [2]	175	90	81 ± 6	78 ± 6	8,5	17,2 (median FU[b] 48 month)
PETHEMA LPA 99 [2]	251	90	90 ± 5	85 ± 5	9,6	7,5 (median FU 21 month)
GIMEMA LAP 0493 [13, 14]	807	94,3	90[a]	87	–	–
European APL Group APL 91 [15]	54[d]	97	79	–	9	–
European APL Group APL 93 [16]	99[e]	94	86	–	7	9
European APL Group APL 2000 [17]	101[h]	94	77,2	89,6	4 patients	22 patients (median FU 35 month)
Medical Research Council [18]	120	87	78	71[f]	12	–
North American Intergroup[c] [10]	94	72	74[g]	–	11	32

N – number of patients, **CR** – complete remission, **DFS** – disease free survival, **RFS** – relapse free survival, **EFS** – event-free survival, **OS** – overall survival, **ED** – early death

a – arm with ATRA + IDA + maintenance, **b** – follow-up, **c** – arm where in induction and maintenance therapy was ATRA only, **d** – only patients in arm ATRA + CHT in induction, **e** – arm with ATRA + CHT in induction (simultaneously) and maitenance, **f** - at 4 years, **g** – at 5 years, **h** - only arm with no ARA-C in induction

patients with ATRA syndrome in globally small file of patients or by subjective assesment of physician. The total number of patients with ATRA syndrome may be also influenced by differences in induction therapy and supportive measures in various clinical studies.

In our patients file analysis we achieved comparable results with other studies in respect of RFS, OS, number of complete remissions and early death. The most frequent cause of early death (intracranial hemorrhage) is the same as in published studies. The number of relapses is slightly lower and the incidence of ATRA syndrome is higher when compare with the results of other study groups. From the results of this analysis it cannot be concluded that the modification of the spanish treatment protocol leads to better survival parameters. It is necessary to be mentioned that the results of analysis of our patients file are affected by small number of patients. With respect to small number of patients in the group, the conclusions of this analysis couldn´t be generalized, but the results may be the asset in the metaanalysis of similar patients files with small number of patients.

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