

Early onset of chemotherapy can reduce the incidence of ATRA syndrome in newly diagnosed acute promyelocytic leukemia (APL) with low white blood cell counts: results from APL 93 trial

S de Botton, S Chevret, V Coiteux, H Dombret, M Sanz, J San Miguel, D Caillot, A Vekhoff, M Gardembas, A Stamatoulas, E Conde, A Guerci, C Gardin, M Fey, D Cony Makhoul, O Reman, J de la Serna, F Lefrere, C Chomienne, L Degos and P Fenau for the European APL group

Treatment combining ATRA and chemotherapy (CT) has improved the outcome of APL patients, by comparison with CT alone. ATRA syndrome is a life-threatening complication of ATRA treatment whose prophylaxis remains somewhat controversial. In APL93 trial, newly diagnosed APL patients ≤ 65 years and with initial WBC counts below $5000/\text{mm}^3$ were randomized between ATRA until CR achievement followed by CT (ATRA \rightarrow CT) and ATRA with early addition of CT, on day 3 of ATRA treatment (ATRA + CT). The incidence of ATRA syndrome in the ATRA \rightarrow CT arm was 18% (22/122) as compared to 9.2% (17/184) in the ATRA + CT arm ($P = 0.035$). In the ATRA \rightarrow CT arm, three (2.5%) patients died from ATRA syndrome, as compared to one (0.5%) in the ATRA + CT group. Early addition of chemotherapy to ATRA in newly diagnosed APL with low WBC counts significantly reduced the incidence of ATRA syndrome.

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Introduction

Treatment combining ATRA and anthracycline (AraC) chemotherapy has improved the prognosis of APL.^{1–7} ATRA syndrome, a life-threatening complication of ATRA treatment of uncertain pathogenesis,^{8–13} can be observed in 5 to 25% of APL cases.^{7,14–19} It is characterized, generally in a context of increasing WBC counts, by fever, weight gain, respiratory distress with lung infiltrates, pleural and sometimes pericardial effusion, and possible renal failure.²⁰ Mortality of ATRA syndrome ranges from 5% to 30%,^{7,14–19} although it has improved recently due to earlier recognition and better treatment.

Its prophylaxis remains somewhat controversial, consisting of early addition of chemotherapy to ATRA in case of increasing WBC counts for some groups,^{2,18} whereas other groups prefer the addition of high-dose steroids only in this situation.¹⁹ In a randomized trial, we found that early addition of chemotherapy to ATRA in newly diagnosed APL significantly reduced the incidence of ATRA syndrome.

Patients and methods

APL 93 trial

Between 1993 and 1998, patients with newly diagnosed APL were eligible based on the following criteria: (1) diagnosis of APL, based on morphological criteria; (2) age 75 years or less; and (3) informed consent. Diagnosis had to be subsequently

confirmed by the presence of t(15;17) or PML-RAR gene rearrangement. Induction treatment was stratified on age and initial WBC counts. Patients aged 65 or less years with WBC less than $5000/\mu\text{l}$ were randomized between ATRA followed by CT (ATRA \rightarrow CT group) and ATRA + CT (ATRA + CT). In the ATRA \rightarrow CT group, patients received ATRA 45 mg/m²/day orally until CR or for a maximum of 90 days. After CR achievement, they received a course of daunorubicin (DNR) 60 mg/m²/day for 3 days and Ara-C 200 mg/m²/day for 7 days (course I). However, course I was added to ATRA if WBC rose above $6000/\mu\text{l}$, $10\,000/\mu\text{l}$, or $15\,000/\mu\text{l}$ by days 5, 10 and 15 of ATRA treatment, respectively, as from our experience, patients were at higher risk of ATRA syndrome above those thresholds. CT was also to be immediately added if clinical signs of ATRA syndrome developed, irrespective of the WBC count.

Patients randomized to the ATRA + CT group received the same combination of ATRA and CT, but CT course I was started on day 3 of ATRA treatment. Patients with WBC $> 5000/\mu\text{l}$ at presentation or aged 66 to 75 years and with WBC less than $5000/\mu\text{l}$ were not randomized and received ATRA + CT course I from day 1 (high WBC group) and the same treatment as in the ATRA \rightarrow CT group (elderly group), respectively.

Patients who achieved CR received two consolidation CT courses, and were offered a second randomization testing both intermittent ATRA and continuous CT with 6-mercaptopurine and methotrexate, both scheduled for 2 years, using a (2 \times 2) design.

Diagnosis and treatment of ATRA syndrome

Diagnosis of ATRA syndrome was made on clinical grounds by the association of at least three of the following signs, in the absence of other causes: fever, weight gain, respiratory distress, lung infiltrates, pleural or pericardial effusion, hypotension, and renal failure.^{15,20}

When ATRA syndrome was suspected, the recommended approach was to (1) start treatment with dexamethasone (DXM) (10 mg/12 h intravenously) for at least 3 days; (2) add the first course of CT (if CT had not already been started); (3) discontinue ATRA if the patient had received at least 20 days of ATRA or if ATRA syndrome was life-threatening and did not rapidly improve with CT and DXM.

Statistical methods

Rank sum test of Wilcoxon and Fisher's exact test were used for comparisons. Relapse, EFS and survival curves were estimated by the Kaplan–Meier method and compared by the log rank test. Cox models were used to estimate the effect of ATRA

Correspondence: P. Fenau, Service d'Hématologie Clinique, Hôpital Avicenne, 125 route de Stalingrad, 93009 Bobigny, France; Fax: 33 (0)1 48 95 54 50/99

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on censored end points, adjusting for base line WBC.^{21,23} For quantitative variables, data are given as medians (with the 25th to 75th percentiles in parentheses), while for qualitative variables, data are given as number of patients (percentages).

Results and discussion

Between April 1993 and October 1998, 576 patients from 93 centers were included in APL93 trial. Following the first interim analysis performed in August 1997 at the reference date of 1 January 1997 in patients randomized prior to that date, the ATRA followed by CT group and maintenance groups without CT were closed. Thus, after August 1997: (1) patients aged 65 or less with WBC below 5000/ μ l were not randomized but enrolled in the ATRA + CT arm; (2) for maintenance, all patients in CR were offered randomization between continuous CT alone, and continuous combined or intermittent ATRA. Overall, until October 1998, 122, 184, 215, and 55 patients were assigned to the ATRA \rightarrow CT, ATRA + CT, high WBC and elderly patient groups, respectively. Among the 122 patients assigned to the ATRA \rightarrow CT, 61 (50%) received CT after a median of 8 days (5–12) of ATRA treatment, because of increasing WBC counts in 55 cases and occurrence of ATRA syndrome in six cases. Overall, 533 patients (92.5%) achieved CR, one had leukemic resistance and 42 (7%) had early death (ED).

ATRA syndrome was observed in 80 of the 576 patients (14%) including 13% in the randomized groups, 17% in the high WBC group and 9% in the elderly group ($P = 0.23$). WBC count at diagnosis was not different in the patients who developed ATRA syndrome than in those who did not (median, 3200/ μ l vs 2600/ μ l, respectively, $P = 0.82$). Patients who experienced the syndrome had a significantly lower CR rate (86%) than patients who had no ATRA syndrome (94%) ($P = 0.007$). The 5-year incidence of relapse was significantly higher in patients who experienced ATRA syndrome (43%) than in patients who had no ATRA syndrome (25%) ($P = 0.01$), whereas 5-year event-free survival and 5-year survival were significantly lower (53% vs 66%, $P = 0.001$ and 66% vs 76%, $P = 0.04$), respectively, confirming our previous results.⁸ When adjusting for base line WBC count, estimated effects were slightly attenuated in terms of survival ($P = 0.07$), but remained unchanged in terms of relapse ($P = 0.023$) and EFS ($P = 0.0052$).

No significant differences in pre-treatment parameters were seen between patients assigned to ATRA \rightarrow CT and the ATRA + CT (Table 1). Twenty-two of 122 patients (18%) and 17 of the 184 patients (9.2%) included in the ATRA \rightarrow CT arm and the ATRA + CT arm, respectively, had ATRA syndrome ($P = 0.035$).

After diagnosis of ATRA syndrome, patients assigned to the ATRA \rightarrow CT, received CT in 17/22 cases (78%), DXM in 20/22 cases (91%), and ATRA was stopped in 8/22 cases (36%), whereas patients assigned to the ATRA + CT received DXM in 16/17 cases (94%), and ATRA was stopped in 12/17 cases (70%). In the patients who experienced ATRA syndrome in the ATRA \rightarrow CT group, 17 achieved CR and five died, from ATRA syndrome (three cases), leukemic resistance (one case) and sepsis (one case). In the ATRA + CT group, 15 achieved CR and two died from ATRA syndrome (one case) and sepsis (one case). Thus, overall, three of the 122 patients (2.5%) included in the ATRA \rightarrow CT group died from ATRA syndrome vs one of the 184 patients (0.5%) included in the ATRA + CT group.

Table 1 Initial characteristics and incidence of ATRA syndrome of patients included in the ATRA \rightarrow CT and ATRA + CT groups (randomization prior to August 1997, and enrollment of all patients in the ATRA + CT group after that date)

	ATRA \rightarrow CT	ATRA + CT	<i>P</i> value
Number of patients	122	184	
M/F	56/66	79/105	0.64
Median age	45.5 (35–54)	45 (33.5–55)	0.82
Median WBC count ($10^9/l$)	1.35 (0.8–2.4)	1.40 (1.0–2.6)	0.21
Microgranular variant (M3v)	6/122 (4.9%)	9/184 (4.9%)	1.00
Incidence of ATRA syndrome	22/122 (18%)	17/184 (9%)	0.035

For quantitative variables, data are given as medians (with the 25th to 75th percentiles in parentheses), while for qualitative variables, data are given as number of patients (percentages).

Table 2 Initial characteristics and outcome of patients included in the ATRA \rightarrow CT and ATRA + CT groups (randomization prior to August 1997, and enrollment of all patients in the ATRA + CT group after that date) who experienced ATRA syndrome

	ATRA \rightarrow CT	ATRA + CT	<i>P</i> value
Number of patients	22	17	
M/F	10/12	10/7	0.52
Age	46.5 (37–51)	45 (31–55)	0.91
WBC count ($10^9/l$)	0.9 (0.7–1.6)	1.5 (1.1–2.4)	0.21
Time to onset of ATRA syndrome (days)	10 (2–35)	10.5 (4–23)	
CR achievement	17/22 (77%)	15/17 (88%)	
Early death	5 (23%)	2 (12%)	
Cause of early death	ATRA syndrome: 3 Sepsis: 1 Leukemic resistance: 1	ATRA syndrome: 1 Sepsis: 1	

For quantitative variables, data are given as medians (with the 25th to 75th percentiles in parentheses), while for qualitative variables, data are given as number of patients (percentages).

In published APL trials where CT was introduced after CR had been reached with ATRA, the incidence of ATRA syndrome ranged from 16 to 27%.^{15,16,19} In recently published APL trials with early addition of CT to ATRA (between day 1 and day 3 of ATRA treatment) the incidence of ATRA syndrome appeared somewhat lower (6 to 15%).^{2,4,7,18} However, this is the first trial demonstrating that early addition of CT significantly reduces the incidence of ATRA syndrome.

We had previously shown that early addition of chemotherapy to ATRA in newly diagnosed APL reduced the incidence of relapse² and our prior findings also supported the fact that, in patients with high WBC counts, very early addition of CT reduced the risk of severe ATRA syndrome.²⁴ Our current results also strongly suggest that in patients with low WBC, it reduces the incidence of ATRA syndrome. Thus, we feel that CT should be rapidly added to ATRA in the induction treatment of all APL patients, after 2 to 3 days of ATRA (allowing for improvement of coagulopathy). Elderly patients could however constitute exceptions, as the incidence of ATRA syndrome, for unknown reasons, was low in that age group (9%), although most of them did not receive early CT.

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Appendix

Dr P. Fenaux and Dr L. Degos served as cochairmen, and Dr C Chastang and S Chevret-Chastang (Department of Biostatistics, Hopital St Louis, Paris) as biostatisticians. The following clinical departments participated in APL93 trial.

French APL group

S Castaigne, H Dombret (Paris), R Zittoun (Paris), E Archimbaud (Lyon), P Travade (Clermont Ferrand), C Gardin (Clichy), A Guerci (Nancy), P Fenaux (Lille), AM Stoppa (Marseille), F Dreyfus (Paris), F Stamatoulas (Rouen), F Rigal-Huguet (Toulouse), H Guy (Dijon), JJ Sotto (Grenoble), F Maloisel (Strasbourg), J Reiffers (Pessac), A Gardembas (Angers), D Bordessoule (Limoges), N Fegueux (Montpellier), A Veil (Paris), T Lamy (Rennes), M Hayat (Villejuif), E Deconinck (Besancon), E Guyotat (St Etienne), M Martin (Annecy), E Cony-Makhoul (Bordeaux), JP Abgrall (Brest), O Reman (Caen), B Desablens (Amiens), JL Harousseau (Nantes), Y Bastion (Lyon), JP Pollet

(Valenciennes), J Pulik (Argenteuil), M Lepeu (Avignon), M Renoux (Bayonne), P Morel (Lens), P Henon (Mulhouse), N Gratecos (Nice), P Colombat (Tours), D Machover (Villejuif), A Dor (Antibes), P Casassus (Bobigny), J Donadio (Castelnou), B Salles (Chalon), B Legros (Clermont Ferrand), P Audhuy (Colmar), A Dutel (Compiègne), N Philippe (Lyon), B Benothman (Meaux), C Christian (Metz), C Margueritte (Montpellier), F Witz (Nancy), A Pesce (Nice), A Baruchel (Paris), L Sutton (Paris), C Quetin (Pointe à Pitre), B Pignon (Reims), E Vilmer (Paris), E Bourquard (St Briec), JP Marolleau (Paris), P Robert (Toulouse), B Despax (Toulouse), G Nedellec, P Auzanneau (Paris), M Janvier (St Cloud).

Spanish AML group

O Rayon (Oviedo), M Sanz (Valencia), J San Miguel (Salamanca), J Montagud (Valencia), E Condé (Santander), P Javier de la Serna (Madrid), G Martin (Valencia), M Perez Encinas (Santiago), JP Torres Carrete (Juan Canalejo), J Zuazu (Barcelone), J Odriozola (Madrid), E Gomez-Sanz (Madrid), L Palomera (Zaragoza), L Villegas (Almeria), A Deben (Juan Canalejo), P Besalduch (Palma de Mallorca).

Cooperative AML study group, Germany

H Link (Hannover), A Ganser (Frankfurt), E Wandt (Nurnberg), A Breitenbach (Stuttgart), B Brennscheidt (Freiburg), D Hermann (Ulm), H Soucek (Dresden), H Strobel (Erlangen).

SAKK Swiss AML group

K Geiser (Berne), M Fey (Berne), T Egger (Berne), E Jacky.

Belgian groups

JL Michaux (Bruxelles), A Bosly (Yvoir), E Meeus (Anvers), A Boulet (Mons).

Dutch groups

P Daenen (Groningen), P Muus (Nijmegen).