Ann Hematol (2015) 94:1357–1361
DOI 10.1007/s00277-015-2372-5

ORIGINAL ARTICLE

# Maternal and fetal outcomes in pregnant women with acute promyelocytic leukemia

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Received: 22 October 2014 / Accepted: 27 March 2015 / Published online: 25 April 2015


**Abstract** The management of pregnant women with acute promyelocytic leukemia (APL) is a challenge with limited evidence-based information available. We are reporting a series of 14 consecutive pregnant women with APL who were registered in the PETHEMA Data Centre between 1996 and 2012. APL was diagnosed during early pregnancy in five women, late pregnancy in seven, and two additional patients after delivery in an extremely poor clinical condition (pulmonary and cerebral hemorrhage). Eleven of the 12 patients eligible for induction therapy with all-trans retinoic acid and idarubicin achieved complete remission (CR 92 %) and are still in the first CR. All early pregnancies ended in abortion (four induced and one spontaneous), with four of them achieving CR. Eight of nine women in late pregnancy delivered a healthy infant (six cesarean section and two vaginal delivery). All eight babies developed normally. Our results confirm a high cure rate for pregnant women with APL who received all-trans retinoic acid and idarubicin for induction therapy, and an excellent outcome for babies when the disease is diagnosed during late pregnancy.

**Keywords** Acute promyelocytic leukemia · All-trans retinoic acid · Anthracycline · Pregnancy

## Introduction

The diagnosis of acute promyelocytic leukemia (APL) during pregnancy is a particularly challenging situation. Decision-making in this uncommon clinical scenario is extremely complex according to gestational age, choice of the most suitable therapeutic approach, and attitude of the patient towards the increased maternal and fetal risk, sometimes including ethical/moral considerations.

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The information available on maternal and fetal outcomes in pregnant women with APL is limited to approximately 40 cases published in roughly 35 articles [1] during the past four decades. Due to the limited number of patients reported (some in the pre-ATRA era), specific recommendations for current management of these cases cannot, therefore, be evidence-based. We are now reporting a case series of 14 pregnant women with APL, who received the same induction therapy with all-*trans* retinoic acid (ATRA) plus idarubicin (AIDA regimen) between 1996 and 2012 [2–4]. The analysis of these cases may allow for an improvement in the management of pregnant women with APL, at least in the context of ATRA plus anthracycline-based treatment.

## Patients and methods

### Patients

All patients diagnosed of APL in each participating institution of the PETHEMA group were registered in the PETHEMA data center, regardless of being or not eligible for inclusion in four subsequent PETHEMA trials.

### Treatment

Induction therapy consisted of oral ATRA (45 mg/m$^2$/day) divided into two daily doses, which was maintained until complete remission (CR) and idarubicin (12 mg/m$^2$/day) by intravenous bolus on days 2, 4, 6, and 8. For patients less than 20 years of age, the ATRA was adjusted to 25 mg/m$^2$/day. Patients in CR received three monthly consolidation cycles followed by 2-year maintenance therapy. Details of the post-remission therapy have been described elsewhere [2–4].

### Supportive measures

Details of the management of coagulopathy, transfusion policy, and other supportive measures in the PETHEMA/HOVON trials have been described elsewhere [5]. Patients with active coagulopathy were treated with platelet transfusions to maintain a platelet count of more than $30\times10^9$/L, fresh frozen plasma, cryoprecipitate, or fibrinogen to maintain a fibrinogen level higher than 1.5 g/L.

Treatment of differentiation syndrome (DS) consisted of intravenous dexamethasone at a dose of 10 mg twice daily that was started promptly at the very earliest symptom or sign of DS [6].

When dealing with therapeutic abortion in early pregnancies and cesarean section or vaginal delivery in late pregnancies, decision-making in every case was always discretionary and agreed by both physician and patient.

### Definitions

Remission induction response was assessed according to the recently revised criteria by Cheson et al [7]. Diagnosis of the DS was made according to the presence of at least two of the following signs or symptoms described by Frankel et al [8]: unexplained fever, dyspnoea, pleural and/or pericardial effusion, pulmonary infiltrates, renal failure, hypotension, and unexplained weight gain greater than 5 kg. Patients with alternative explanations for the clinical complex were considered not to have DS. Relapse-risk groups were defined as reported elsewhere [9] as follows: low-risk patients had a WBC count below or equal to $10\times10^9$/L and a platelet count more than $40\times10^9$/L, intermediate-risk patients had a WBC and a platelet counts below or equal to $10\times10^9$/L and $40\times10^9$/L, respectively; and high-risk patients had a WBC count greater than $10\times10^9$/L. Coagulopathy was defined as a prolonged prothrombin time and/or activated partial thromboplastin time in addition to hypofibrinogenemia and/or increased levels of fibrin degradation products or D-dimers.

## Results

One thousand seven hundred and forty-four patients consecutively diagnosed of APL in 69 institutions from Spain, Uruguay, and Argentina were registered in the PETHEMA data center, regardless of being eligible or not for inclusion in the PETHEMA trials. One hundred thirty-four and 994 patients were younger than 18 years and older than 41 years, respectively. Among the remaining 616 patients, 323 were women, including 14 patients who were pregnant at the time of diagnosis. The median age of pregnant women with APL was 33 years (range, 23 to 41). The distribution of other presenting features, such as ECOG performance status, white blood cell and platelet counts, relapse-risk score, and PML/RARA isoform, as well as the gestational age and week of delivery is also shown in Table 1.

APL was diagnosed during early pregnancy in five women. The average gestational age at diagnosis of APL in these patients was 9 weeks (range, 3 to 14). The remaining nine pregnant women were diagnosed in late pregnancy or after delivery (cases no. 13 and no. 14), ranging from 25 to 37 weeks of gestational age.

### Maternal outcome

Except for two patients who were admitted in an extremely poor clinical condition due to pulmonary and cerebral hemorrhage (cases no. 13 and no. 14, respectively), and then diagnosed with APL, the remaining 12 pregnant patients were considered eligible for induction therapy (Table 2). All eligible patients were treated with the AIDA regimen as scheduled without delay. Eleven patients achieved CR (92 %). The only induction failure (case no. 2) was attributed to DS as the main cause of death, which occurred 2 weeks after starting

**Table 1** Characteristics of patients with APL presenting during pregnancy

| Case number | PETHEMA protocol | Year at diagnosis | Mother's age | Week of pregnancy at diagnosis | Week of pregnancy at delivery | Performance status (ECOG) | WBC count $\times 10^9$/L | Platelet count $\times 10^9$/L | Risk score | Coagulopathy | PML/RARA isoform |
|---|---|---|---|---|---|---|---|---|---|---|---|
| First trimester | | | | | | | | | | | |
| 1 | LPA2005 | 2011 | 33 | 3 | 5 | 0 | 0.6 | 39 | Intermediate | No | BCR1 |
| 2 | LPA2012 | 2012 | 23 | 14 | 15 | 2 | 2.2 | 1.5 | Intermediate | No | BCR1 |
| 3 | LPA99 | 2000 | 31 | 4 | 6 | 0 | 2.2 | 60 | Low | No | BCR1 |
| 4 | LPA2005 | 2006 | 28 | 9 | 10 | 1 | 1.2 | 13 | Intermediate | No | BCR1-2 |
| 5 | LPA2005 | 2006 | 30 | 13 | 17 | 1 | 1.5 | 9 | Intermediate | Yes | BCR1 |
| Second and third trimester | | | | | | | | | | | |
| 6 | LPA2005 | 2006 | 34 | 25 | 26 | 1 | 118 | 37 | High | Yes | BCR3 |
| 7 | LPA99 | 2001 | 39 | 30 | 36 | 3 | 6.2 | 15 | Intermediate | Yes | BCR1 |
| 8 | LPA2005 | 2008 | 32 | 33 | 33 | 3 | 1.2 | 2 | Intermediate | Yes | BCR1 |
| 9 | LPA96 | 1998 | 31 | 35 | 35 | 1 | 1.8 | 40 | Intermediate | No | BCR3 |
| 10 | LPA99 | 2005 | 41 | 35 | 36 | 1 | 3.7 | 36 | Intermediate | Yes | BCR3 |
| 11 | LPA99 | 2002 | 32 | 37 | 37 | 0 | 1.4 | 46 | Low | No | NA |
| 12 | LPA2005 | 2008 | 33 | 38 | 38 | 2 | 1.3 | 54 | Low | No | BCR1 |
| 13 | LPA96 | 1999 | 35 | After delivery | 38 | 4 | 3.8 | 27 | Intermediate | Yes | NA |
| 14 | LPA99 | 2002 | 38 | After delivery | 32 | 4 | 7.0 | 98 | Low | Yes | BCR1 |

**Table 2** Maternal and fetal outcomes in pregnant women with APL

| Case number | Induction therapy | Induction outcome | Current status | Months of follow-up | Delivery method | Status at birth |
|---|---|---|---|---|---|---|
| First trimester | | | | | | |
| 1 | ATRA + Idarubicin | Complete remission | First complete remission | 15 | Therapeutic abortion | Aborted fetus |
| 2 | ATRA + Idarubicin | Death (DS) | – | – | Therapeutic abortion | Aborted fetus |
| 3 | ATRA + Idarubicin | Complete remission | First complete remission | 149 | Spontaneous abortion | Aborted fetus |
| 4 | ATRA + Idarubicin | Complete remission | First complete remission | 77 | Therapeutic abortion | Aborted fetus |
| 5 | ATRA + Idarubicin | Complete remission | First complete remission | 73 | Therapeutic abortion | Aborted fetus |
| Second and third trimester | | | | | | |
| 6 | ATRA + Idarubicin | Complete remission | First complete remission | 82 | Vaginal | Dead fetus |
| 7 | ATRA + Idarubicin | Complete remission | First complete remission | 39 | Vaginal | Healthy infant |
| 8 | ATRA + Idarubicin | Complete remission | First complete remission | 57 | Cesarean | Healthy infant |
| 9 | ATRA + Idarubicin | Complete remission | First complete remission | 171 | Cesarean | Healthy infant |
| 10 | ATRA + Idarubicin | Complete remission | First complete remission | 86 | Cesarean | Healthy infant |
| 11 | ATRA+Idarubicin | Complete remission | First complete remission | 122 | Cesarean | Healthy infant |
| 12 | ATRA + Idarubicin | Complete remission | First complete remission | 47 | Cesarean | Healthy infant |
| 13 | – | Death (pulmonary hemorrhage) | – | – | Vaginal | Healthy infant |
| 14 | – | Death (CNS hemorrhage) | – | – | Cesarean | Healthy infant |

treatment. All patients who achieved CR proceeded to consolidation and then to maintenance therapy. All of them are still alive and well in complete continuous remission for a median time of 83 months (range, 15 to 172).

### Fetal outcome

All early pregnancies terminated in abortion (four induced and ones spontaneous) and four of these patients achieved CR (Table 2). The spontaneous abortion (case no. 3) occurred after 2 weeks of starting AIDA with no additional complication.

Eight of nine APL patients who were diagnosed in late pregnancy delivered a healthy infant, six by cesarean section and two by vaginal delivery. All these babies developed normally. The remaining patient (case no. 6) delivered a dead fetus at 26 weeks' gestation after 1 week of ATRA treatment, even though fetal monitoring had been normal on admission.

## Discussion

In this study, we report the maternal and fetal outcomes in a series of 14 consecutive pregnant women with APL undergoing a state-of-the-art treatment based on ATRA and idarubicin for induction and consolidation therapy. We confirm a high cure rate and an excellent outcome for babies when APL diagnosis is made during late pregnancy.

In order to minimize selection bias, the policy of the PETHEMA group is that once the first APL patient from each individual institution is registered, every participating institution is committed to register all subsequent APL patients, regardless of whether or not they are eligible for treatment. We can infer that the incidence reported here represents a realistic approach to the incidence and treatment outcome of APL during pregnancy using state-of-the-art treatment. Regarding the average maternity age observed in the present series, this is very similar to that reported by the National Statistics Institute [10] for the Spanish population during the last decade.

The distribution of significant presenting features in pregnant women with APL, such as ECOG performance status, white-blood cell and platelet counts, relapse-risk score, and PML/RARA isoform, was similar to that reported in non-pregnant APL patients with a comparable age. In addition, our results show for the first time in a relatively large case series that maternal outcomes in pregnant women with APL are comparable to those reported in non-pregnant patients treated with similar therapeutic approaches [2–4].

As far as we know, five out of the nine cases reported in the literature in which APL was diagnosed in early pregnancy ended in abortion (four induced and one spontaneous). The remaining four pregnant women with APL delivered two healthy infants [11, 12], one with transient dilated cardiomyopathy [13] and one with low weight, jaundice, and respiratory distress syndrome at birth [14]. All early pregnancies in our series, however, terminated in abortion (four induced and one spontaneous), with four of these patients achieving CR. As for the spontaneous abortion (case no. 3), we can speculate on a potential role of antileukemic treatment, particularly of

ATRA, in fetal death, since it occurred after 2 weeks of starting ATRA plus idarubicin. It should be noted that an additional dead fetus (case no. 6) was delivered at 26 weeks' gestation after 1 week of ATRA treatment, even though fetal monitoring had been normal on admission. The remaining eight of nine APL patients who were diagnosed in late pregnancy delivered a healthy infant who developed normally, including two babies from mothers with fatal outcomes who were admitted in extremely poor condition.

In conclusion, taking into account that the APL cases reported during pregnancy were limited to a few publications that included only two [15–17] or three cases [18, 19] maximum, with most being single case reports [1]. Our case series of 14 consecutive pregnant women with APL, of which 12 of them were treated with a similar state-of-the-art approach allowed a much better assessment of maternal and fetal outcomes in this particularly challenging situation. Based on our results, we can confirm a high cure rate in pregnant women with APL who received ATRA and idarubicin for induction therapy, as well as an excellent outcome for babies when the maternal disease is diagnosed during late pregnancy. Decision-making from a multidisciplinary perspective, involving the patient, hematologist, obstetrician, and neonatologist, is needed to increase the possibilities of a successful outcome for mother and baby.

**Acknowledgments** The authors thank all participating institutions and clinicians in the PETHEMA studies. This work was supported in part by Cooperative Research Thematic Network Grant RD12/0036/014 (Instituto de Salud Carlos III and European Regional Development Fund).

**Author contribution** M.A.S. conceived the study and analyzed and interpreted the data; M.A.S., P.M., A.P., and A.P. wrote the paper; M.F.C, J.D-M., S.J., I.F., P.F., J.G-C., J.D.G., P.H., E.L., T.O., R.R., O.S., and M.J.S. included data of patients treated in their institutions, reviewed the manuscript, and contributed to the final draft.

**Conflicts of interest** The authors declare no competing financial interests.

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