Impact of international collaboration on the prognosis of childhood acute promyelocytic leukemia in Iraq

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The promotion of an operational network between hospitals and medical schools in Iraq and in Western countries is a primary humanitarian objective of international collaboration. As a consequence of a collaborative project between the Al Mansour Hospital for Pediatrics in Baghdad and the Pediatric Unit of Hematology of "La Sapienza" University, in Rome, in October 2003 a specific all-trans-retinoic acid-based protocol was designed in order to offer a modern therapeutic program for the management of Iraqi children with acute promyelocytic leukemia, adapted to the severe local difficulties. The preliminary encouraging results represent a substantial improvement over the earlier experience in childhood acute promyelocytic leukemia in Iraq.

Key words: acute promyelocytic leukemia, children, all-trans retinoic acid, developing countries.

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In a Report of March 2004, published in Lancet Oncology,[1] Salma Al-Hadad, head of the Pediatric Oncology Unit at the Al-Mansour Teaching Hospital in Baghdad (Figure 1), Iraqi oncologists and hematologists very lucidly expressed the desperate need for support from their colleagues throughout the world. Dr. Al-Hadad also reported an increase in the number of patients suffering from different types of childhood cancer (brain tumors, subtypes of leukemia and lymphoma). In August 2003, as a consequence of a collaborative project between the Al-Mansour Pediatric Hospital and the Pediatric Hematology Unit of our Institute at *La Sapienza* University of Rome, supported by the Italian non-governmental organization INTERSOS, one of us (AMT) had the opportunity of visiting the Al-Mansour Teaching hospital in Baghdad. The war-related conditions have dramatically worsened the Iraqi health system, reducing the technological resources available, as well as drugs and medical supplies of primary importance. The medical staff, who have never stopped their daily activities, have been seeking for improvements in medical education and training, and attempts have been made to re-establish international channels of communication. During the visit, particular attention was given to childhood acute promyelocytic leukemia (APL). This is a rare disease in children and is generally considered to account for 3-9% of pediatric acute myeloid leukemias.[2] At the Pediatric Oncology Unit, in Baghdad, during the period January 2002 and January 2003, a total of 11 children (age <15 years) out of 32 having acute myeloid leukemia were diagnosed as having APL on morphological grounds (no immunophenotypic, cytogenetic or molecular analyses could be carried out). This represents an overall very high incidence (34%) of childhood APL referred to a single institution, the Al-Mansour Teaching hospital, which represents a referral center for childhood cancer in Iraq. At that time, no specific protocol for APL could be employed. All-trans-retinoic acid (ATRA) was not available and the prognosis of these children was very poor with less than 10% becoming long-term survivors. Most children received standard induction therapy for acute myeloid leukemia with the combination of cytarabine and anthracycline. This treatment exacerbated and prolonged the typical disease coagulopathy requiring intensive supportive measures such as platelet and red cell concentrates. The latter were frequently not available or insufficient, resulting in more than 50% early deaths, mainly due to hemorrhagic events. It should be recalled that with ATRA-based regimens, 96% of children with APL achieve a hematologic remission and 78% are disease-free more than 10 years after diagnosis.[3]

Design and Methods

Through the collaboration between our two institutions, a specific protocol was designed according to the modern strategies for the management of Iraqi children with APL and adapted to the severe local difficulties. ATRA was included in the induction treatment. The treatment plan (Figure 2) consisted of induction treatment with ATRA (25 mg/m^2/day, administered orally in two equally divided doses) for 30 days associated

Figure 1. A patient with leukemia at the Pediatric Oncology Unit of the Al-Mansour Hospital

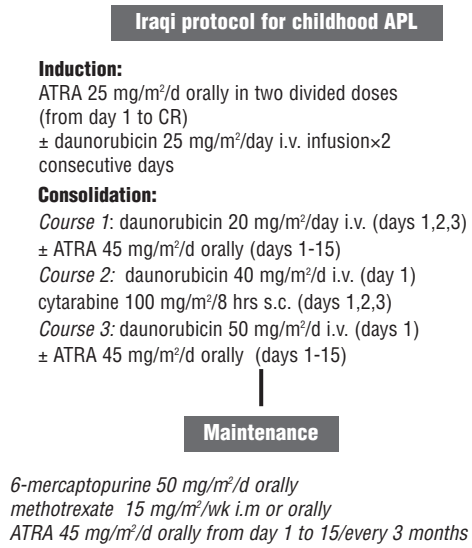

Figure 2. Protocol for childhood APL in Iraq: treatment schedule

with daunorubicin (25 mg/m²/day for two consecutive days) only for high-risk patients. We considered as high-risk all patients with a white cell count >10×10⁹/L at diagnosis and those with an increasing leukocyte count, defined as follows: white cell count >10×10⁹/L at days 5 and 10 and white cell count >15×10⁹/L at day 15 after the start of ATRA induction. Consolidation included three chemotherapy cycles (daunorubicin; daunorubicin + standard dose cytarabine by subcutaneous injection; daunorubicin). Both daunorubicin and cytarabine were available in Baghdad. ATRA was associated with each consolidation cycle only for high-risk patients. Standard 6-mercaptopurine and methotrexate maintenance with 14 days ATRA, every 3 months, was administered to all patients who had obtained a morphological complete remission for 2 years, from the end of consolidation. Intrathecal methotrexate prophylaxis (for a total of three doses) was given during each consolidation course to high-risk patients.

Results

Between October 2003 and August 2004, nine children with APL, out of 26 pediatric cases of acute myeloid leukemia (35%), were diagnosed at the Al-Mansour Pediatric Oncology Unit and enrolled in the protocol. The main clinical characteristics of the patients at disease presentation are shown in Table 1: six were male and three were females; their median age was 11 years (range 1-15); the median hemoglobin level was 6.0 g/dL (range 3.4-7.4 g/dL), the median white cell count 6×10⁹/L (range 1.6-120×10⁹/L) and the median platelet count 7×10⁹/L (range 3-29×10⁹/L). Fever and bleeding were present at the onset of the disease in eight and seven children, respectively; hepatosplenomegaly was observed in one case. The morphological diagnosis was hypergranular M3 APL in seven children and the microgranular variant form (M3v) in two. Eight children were defined as high-risk (four with a white cell count at diagnosis >10×10⁹/L; four with increasing leukocytosis during ATRA induction treatment) and one as low-risk. One child with M3v had a very high white cell count and died the very day of referral due to massive bleeding, while the other eight children achieved a complete remission. All children received prophylactic antibiotics (cotrimoxazole, or clarithromycin or amoxicillin, depending on what antibiotic was available at the time) during induction; five of the eight responders developed fever and were treated with intravenous antibiotics. Blood cultures were not available. One child developed pneumonia and one gastrointestinal infection; both resolved with intravenous antibiotics. Tranexamic acid (100 mg/kg/day) was given by continuous infusion when the platelet count was less than 50×10⁹/L. Prophylactic and therapeutic platelet transfusions were given to all children for a median of 8 days (range 5-11); hemorrhages (WHO grade >2) occurred in two patients. Prednisone

Table 1. Patients' clinical characteristics at diagnosis.

#pt	Sex m/f	Age yrs	WBC ×10⁹/L	Plts ×10⁹/L	Hb g/dL	Bleeding	Hep/ Spl.	Fever	M3c/v
#1	m	7	11.2	7.0	3.6	no	no	yes	c
#2	f	11	120.0	5.0	5.9	yes	yes	yes	v
#3	m	11	10.3	17.0	6.8	no	no	yes	c
#4	f	11	2.0	3.0	6.0	yes	no	yes	c
#5	f	15	1.6	10.0	3.4	yes	no	yes	c
#6	m	14	2.4	7.0	8.7	yes	no	yes	c
#7	m	12	4.0	16.0	4.8	yes	no	yes	c
#8	m	3	68.0	29.0	6.7	yes	no	yes	v
#9	m	1	6.0	7.0	7.4	yes	no	no	c

M3c/v: classical (c) or variant (v) form of APL.

(0.5 mg/Kg/day from day 1 to the end of therapy with ATRA) was employed in all patients to prevent the ATRA syndrome. No child developed an overt ATRA syndrome; ATRA-related *pseudotumor cerebri* was observed in one child and was successfully managed with temporary discontinuation of ATRA and intravenous dexamethasone (10 mg/12 hours) for three consecutive days. Seven of the eight responders continued consolidation and maintenance therapy, as planned. One child, still in continuous complete remission, discontinued treatment due to the parents' decision. With a median follow-up of 10 months (range: 5-15), all eight children are alive, well and in continuous complete remission.

Conclusions

These preliminary, but highly encouraging results show that relatively simple measures had a substantial impact on the prognosis of childhood APL in the main pediatric center in Iraq. This is of particular relevance as this subgroup of acute myeloid leukemia, for which a specifically designed therapeutic strategy has modified the natural course of the disease, seems to have a very high prevalence in Baghdad: about one third of childhood acute myeloid leukemia diagnosed during the period 2002 and 2003 were, in fact, APL. It is difficult to comment on this apparent high prevalence of childhood APL in Baghdad. In the past years the embargo condition has profoundly affected the Iraqi Health System and no genetic, epidemiological or environmental studies could be carried out; epidemiologists worked heroically to have an Iraqi cancer database through these years but a pediatric cancer registry is not available. However, since 1994, in the Al-Mansour Teaching Hospital, a reference center for childhood cancer in Iraq, all cases of childhood neoplasms (leukemias, lymphomas and solid tumors) have been registered. An increased incidence of some childhood leukemia and lymphoma subtypes was observed; this may reflect a true increase as well as a better awareness or greater referral to this center.

The Iraqi protocol for APL, was an ATRA-based induction therapy that has proved its effectiveness and safety in this condition. The primary advantage is that ATRA does not cause lysis, but rather the differentiation of the leukemic cells; as a consequence, the extent and severity of coagulation abnormalities typical of this disease, are reduced and usually corrected within the first week of treatment.[3] The induction mortality rate, mainly due to hemorrhages, is significantly reduced and the intensive supportive blood concentrate requirement is also decreased.[4,5] ATRA was not available at that time in Iraq and the protocol could only be implemented because ATRA was generously supplied by Roche, Italy. Compared to conventional chemotherapy ATRA has demonstrated superiority, but the most important and potentially fatal side effect is the *ATRA syndrome*, which can occur at any time during the course of ATRA treatment and appears to be more frequent in patients with leukocytosis and especially those who develop leukocytosis during ATRA administration. As demonstrated by the French Group,[6] one approach to prevent the ATRA syndrome is to add chemotherapy in patients with leukocytosis. Consequently, daunorubicin, an anthracycline particularly effective in APL and available in Baghdad, was added to the induction phase for high-risk patients at diagnosis and for those patients with an increasing white cell count during ATRA induction. With this strategy, no child treated in Baghdad had so far developed an overt *ATRA syndrome*.

The results obtained also clearly demonstrate that modern therapeutic strategies, adapted to the local reality, are a primary necessity and can be effectively implemented through international collaborative efforts even in countries with limited resources, as well as severe and prolonged difficulties. The success of the international collaborations between centers of excellence and low-income countries has been demonstrated for childhood acute lymphoblastic leukemia.[7,8] These experiences have shown that expanding efforts to treat acute lymphoblastic leukemia in childhood in such countries not only improves the prognosis of patients, but mobilizes new energies, stimulates imaginative solutions and broadens public awareness. Effective therapies do not necessarily have to be expensive, but depend on effective drugs being available in those countries at reasonable costs at the right time. Nonetheless the contribution of pharmaceutical companies in supporting cooperative protocols designed *ad hoc* for developing countries could allow the employment of more expensive drugs, essential for specific diseases. In our experience, ATRA was generously supplied for the first year by Roche, Italy. This drug, which demonstrated its efficacy with a reduced requirement for supportive therapy – a major problem in the specific scenario - and consequently reduced treatment costs, is now available in Baghdad, from Jordan at a reasonable cost. The protocol remains open and accrual of patients continues. The Italian company Telbios (a tele-communications company) and the European Space Agency are supporting a teleconsultation and distance learning project between our Institution and Iraq.

All authors contributed equally to the writing and conception of the manuscript. The authors declare that they have no potential conflict of interest.

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Members of TelBios (Società Italiana di Telecomunicazioni) and ESA (Agenzia Spaziale Europea) are contributing to continue the project with telemedicine connections from the University "La Sapienza" of Rome and the Teaching Hospital of Baghdad.

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