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Effective salvage therapy using all-*trans* retinoic acid for relapsed and resistant acute promyelocytic leukemia

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All-trans retinoic acid (ATRA) has been shown to be active against acute promyelocytic leukemia (APL). Six patients with APL, either in relapse or resistant to initial chemotherapy were reinduced with ATRA 100 g/m²/day for 6 weeks. Complete remission was achieved in all six of them. Side effects were seen in two of them. ATRA appears to provide a relatively safe and reliable means to induce a complete remission in patients with refractory or relapsed APL.

Key words: Acute promyelocytic leukaemia, all-*trans* retinoic acid.

Introduction

Although the majority of newly diagnosed patients with acute myeloid leukemia (AML) can be induced into clinical complete remission, many eventually relapse. Various salvage chemotherapy regimens can induce a second remission in 25–50% of patients with refractory or recurrent disease but the remission is often of brief duration. All-*trans* retinoic acid (ATRA) has been shown to be active against acute promyelocytic leukemia (APL). We report here the results of our experience in using this agent to induce clinical complete remission in refractory or relapsed APL.

Patients and methods

Between January and December 1992, six patients with APL, either in relapse or resistant to initial induction chemotherapy containing Ara C 100 mg/m²/day (i.v. infusion) for 7 days, daunorubicin 50 mg/m²/day (i.v.) for 3 days and etoposide 75 mg/m²/day (i.v.) for 7 days were reinduced with oral ATRA 100 mg/m²/day for 6 weeks. After achieving complete remission with ATRA, they received either further consolidation chemotherapy or allogeneic bone marrow transplantation.

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Results

Table 1 shows patient characteristics and clinical outcomes. There were four males and two females. Their age ranged from 18 to 55 years. Patient no. 2 had a 2 cm splenomegaly and the remaining had no significant lymphadenopathy or hepatosplenomegaly at initial presentation. All had the characteristic chromosomal t(15;17) translocation. Two patients (nos. 3 and 4) were refractory to the initial induction chemotherapy and the other four had a first complete remission lasting for 8–15 months before the leukemia relapsed. All six of them responded to reinduction with ATRA and the time to complete remission was 3–5 weeks. The reinduction was complicated by severe mucositis in patient no. 2. Transient swelling of the right upper limb was seen in patient no. 5 during his first week of ATRA therapy and he also developed a subdural haemorrhage while he was still thrombocytopenic during the second week. He subsequently had an operation to evacuate the clot resulting in only partial recovery of his motor power. No significant marrow toxicity was seen in any of the six patients.

Patient no. 6 has received an allogeneic bone marrow transplantation from an HLA-identical sibling. The remaining five were given consolidation chemotherapy as suitable marrow donors were not available.

Discussion

ATRA is a differentiating agent that has been shown to be effective in inducing remission in APL. In the first of the studies reported, a complete remission rate of 100% was observed in 24 patients, including eight who had relapsed or refractory disease.[1] The efficacy of this agent has been supported by other studies with a complete remission rate of more than 60%. One advantage of this therapy is the lack of marrow toxicity. Unlike

Table 1. Patient characteristics and clinical outcome

	Patient no.					
	1	2	3	4	5	6
Sex	F	F	M	M	M	M
Age (years)	55	41	38	18	19	35
Initial white cell count (10^6/l)	0.6	2.0	1.1	1.0	3.4	4.4
Initial platelet (10^6/l)	47	497	31	54	17	23
Disseminated intravascular coagulation	−	+	−	+	+	+
t(15; 17)	+	+	+	+	+	+
Other cytogenetic change	−	−	−	−	+8 del (X)	−
Response to initial chemotherapy	CR (8 months relapse)	CR (9 months relapse)	NR	NR	CR (10 months relapse)	CR (15 months relapse)
Response to ATRA	CR	CR	CR	CR	CR	CR
Complications following ATRA	−	+	−	−	+	−

CR, complete remission; NR, no response.

chemotherapy, disseminated intravascular coagulation, which is often present in these patients, improves rather than deteriorates with the ATRA therapy. Reported side effects of ATRA include dry skin, mucositis, leucocytosis and adult respiratory distress syndrome, increased liver enzymes, hypertriglyceridemia, and thromboembolism.

We are impressed by the efficacy of ATRA in inducing complete remission in our six patients with relapsed or refractory APL. Significant side effects were seen in only two of them. For patient no. 5, it is possible that his arm swelling may be due to venous thrombosis related to the use of ATRA.

ATRA appears to provide a relatively safe and reliable means to induce a complete remission in patients with refractory or relapsed APL. This should be followed by consolidation chemotherapy or an allogeneic bone marrow transplantation if a suitable donor is available.[1–3]

References

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