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ISOLATED OCULAR RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA DURING CONTINUING COMPLETE REMISSION

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ABSTRACT

Leukemic relapse of the eye has sometimes been cured. In this paper we review the cases of leukemic infiltration of the eye tissue with the aim of ascertaining whether an optimal treatment can be suggested. Data from 25 children (16 males, 9 females) with isolated ocular relapse (10 in therapy, 15 off therapy) of acute lymphoblastic leukemia (ALL) in first complete remission are examined. The patients were treated according to different chemotherapy schedules, with (20 pts) or without local radiotherapy (5 pts). Isolated ocular relapse can be successfully treated, especially if it occurs after the withdrawal of therapy; second ocular infiltration was seen only in anterior chamber involvement after low doses of local radiotherapy. While the need for high doses of chemotherapy is not evident, high doses of ocular radiotherapy (> 20 Gy) seem to be mandatory to cure this leukemic relapse.

Key words: acute lymphoblastic leukemia, isolated ocular relapse, childhood leukemia

Leukemic relapse of the eye tissue is rarely reported in the literature. In two previous studies,[1,2] we analyzed patients (pts) with ocular leukemia and reported that, as already noted by other authors,[3-8] leukemic eye infiltration can be eradicated following appropriate treatment. In order to investigate the clinical and therapeutic features associated with the complete eradication of the infiltrate, we performed a review of the literature concerning patients who had isolated ocular relapse during continuing complete remission (CCR),[3-8] thus at a time when a cure was still possible.

Patients and Methods

Patients with isolated eye relapse of acute lymphoblastic leukemia (ALL) in CCR were analyzed: 13 patients from our 2 previous studies,[1,2] eleven reported in the literature,[3-8] and another new patient (Table 1).

Eye relapse was treated according to different schedules, including chemotherapeutic agents (at high doses in 6 cases) and ocular radiotherapy (RT) in 20 patients.

Results

Data concerning the 25 available patients are reported in Table 2. Since chemotherapy schedules were different for each patient, we did not compare the results of the various treatments. Patients were classified in 4 groups according to the different doses of ocular radiotherapy.

Group I: 5 patients (cases #4, 6, 10, 11, 13) were treated with systemic chemotherapy (CT) only at standard doses and all of them achieved ocular remission; bone marrow (BM) relapse occurred in four of them, who died of progressive disease. One (case #6) died from sepsis 30

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Table 1. References for the reported cases of LO in continuing complete remission.

Case N°	*Author*	*Reference*
1	Nitschke	3
2	Dossa	4
3	Boutard	5
4-6	Bunin	6
7-9	Schwartz	7
10-18	Lo Curto	1
19-21	Lo Curto	2
22	Jankovic	11
23-24	Ninane	8
25	Casale	pers. comm.

months after eye relapse.

Group II: 2 patients (cases #12 and 20) were treated with standard doses of chemotherapeutic agents and RT on the eye at doses < 10 Gy (3.9 and 9, respectively) and achieved ocular remission; both of them suffered a second ocular relapse 30 and 9 months, respectively, after eye remission. The first one had a 3rd ocular relapse: enucleation was performed and the patient is disease free in IV CCR 12 years after her last relapse.[9] The other had a subsequent BM and testicular relapse and died of progressive disease 6 months after his 2nd ocular relapse.[10]

Group III: 7 patients (cases #2, 5, 15, 16, 17, 18, 23) were treated with CT (one with high doses of cytosine arabinoside, case #17), and RT at doses from 10 to 20 Gy (12, 10, 13, 12, 15, 10, 20 Gy, respectively); all of them obtained ocular remission. BM relapse occurred in the patient treated with high doses of CT and RT and in other 4 patients (cases #2, 15, 18, 23); 2 children are alive and have been disease free for 54 and 106 months, respectively (cases #5, 16).

Group IV: 11 patients (cases #1, 3, 7, 8, 9, 14, 19, 21, 22, 24, 25) were treated with CT and RT at doses > 20 Gy (23, 25, 33, 34, 30, 34, 25, 24, 30, 24, 38 Gy, respectively); four of these patients were given high-dose CT (cases #19,

Table 2. Characteristics, treatment and outcome of the study patients at diagnosis of ALL and at LO.

case	*age (yrs)*	*Sex*	*Immun. phenotype*	*WBC at diagnosis ($X10^9$/L)*	*Interval ALL eye relapse (months)*	*Site of eye relapse (segment)*	*Ocular RT (Gy)*	*CT*	*Outcome (months since ocular remission)*
1	3	M	n.d.	27,4	53	Post.	23	SD	CR +30
2	2	F	n.d.	28	18	Ant.	12	SD	BM Rel (11)
3	8	M	n.d.	n.d.	38	Ant.	25	HD	CR +33
4	1.6	F	n.d.	8,8	37	Ant.	No	SD	BM Rel (39)
5	2	F	n.d.	4,0	32	Ant.	10	SD	CR +54
6	4	M	n.d.	62	17	Ant.	No	SD	Died from sepsis (30)
7	3	M	c-ALL	52	21	Post.	33	SD	CR +63
8	9	F	c-ALL	32,7	14	Post.	34	SD	CR +55
9	2	M	pre-pre B	19,7	8	Post.	30	SD	BM+test Rel (n.d.) II CR +104
10	13	F	n.d.	50	14	Ant.	No	SD	BM Rel (10)
11	3	M	n.d.	30	40	Ant.	No	SD	BM Rel (12)
12	8	F	n.d.	23	48	Ant.	3.9	SD	Eye Rel (24), IV CR +144
13	8	M	n.d.	71	36	Ant.	No	SD	BM Rel (9)
14	6	M	n.d.	30	44	Post.	34	SD	CR +180
15	1	M	n.d.	n.d.	42	Ant.	13	SD	BM Rel (10)
16	4	F	nT/nB	3	27	Ant.	12	SD	CR +106
17	6	M	nT/nB	28,4	22	Post.	15	HD	BM Rel (48)
18	1.2	F	n.d.	3,5	10	Ant./Post.	10	SD	BM Rel (6)
19	4	M	c-ALL	2,9	31	Ant.	25	HD	CR +36
20	4	M	n.d.	31	18	Ant.	9	SD	Eye Rel (9) —>BM+test Rel
21	2	M	preB	69	26	Ant.	24	HD	BM + Contr. eye Rel (18)
22	2	M	c-ALL	41	29	Ant. bil.	30	HD	CR +60
23	3.5	M	n.d.	n.d.	29	Ant.	20	SD	BM Rel (33)
24	2	F	n.d.	22	31	Ant.	24	SD	BM Rel (13)
25	12	M	c-ALL	3,1	15	Ant./Post.	38	HD	BM Rel (6)

Abbreviations: Immun. phen. = immunologic phenotype; WBC = white blood count; ALL = acute lymphoblastic leukemia; RT = radiotherapy; CT = chemotherapy; Post. = posterior; SD = standard doses; CR = complete remission; Ant. = anterior; Rel = relapse; BM = bone marrow; n.d. = not done; HD = high doses; test = testicular; Contr. = controlateral; bil. = bilateral.

21, 22, 25). Autologous bone marrow transplantation was performed in one case (#3). One patient (#21), treated with high-dose CT and 24 Gy on the eye, suffered combined BM and controlateral eye relapse and died of progressive disease; two others (cases #24 and 25) experienced BM relapse 13 and 6 months, respectively, after ocular remission and the former died of disease progression. Another patient (case #9) had a combined BM and testicular relapse: he has been disease free for 104 months since his last relapse following autologous BMT.

Seven patients (cases #1, 3, 7, 8, 14, 19, 22) are alive and have been in second CCR without evident disease for 30, 33, 63, 55, 180, 36, 60 months, respectively, after ocular relapse. Another patient (case #9) is disease free in 3rd CR (+104 months) after autologous BMT (performed for a subsequent combined BM and testicular relapse).

The outcome of patients according to the site of eye infiltration was as follows: a) BM relapse occurred in 2 out of 6 patients with posterior eye segment involvement and in nine out of 17 patients with anterior chamber involvement; one of these (#21) experienced concomitant BM and controlateral eye relapse; b) second eye infiltration was observed in two out of 17 patients with anterior chamber involvement.

Discussion

Analysis of our patients shows that ocular relapse occurred after a median time of 29 months from diagnosis of ALL; the outcome was more favorable in cases of ocular relapse off therapy, as is observed in all relapses. Treatment of the reported cases consisted of systemic chemotherapy and, in most cases, radiotherapy on the affected eye.

Long-term disease-free survival (DFS) after eye relapse was observed only in patients treated with CT and local RT, and second eye relapse occurred only in 2 patients treated with low doses of RT. As we have mentioned in previous reports,[2,9] low doses of RT could be responsible for resistent leukemic cells, as in the patient who underwent enucleation for a third ocular relapse (case #12). Behrendt reported a patient with leukemic ophtalmopathy (LO) in 3rd remission who obtained ocular remission with high-dose CT; however, 16 months later a second iris infiltration appeared that was eradicated following RT at 36 Gy on the affected eye.[11] Jankovic described bilateral involvement of the eyes that was treated successfully with an electron beam in order to decrease the risk of blindness, at a dose of 30 Gy.[12] It is interesting that one patient suffered combined BM and controlateral eye relapse after high doses of CT and high-dose RT on the affected eye (case #21); it must be noted that the controlateral eye had not been irradiated. This case and the one reported by Behrendt show that high-dose CT is not sufficient to cure eye infiltration.

Analysis of the results of our cases shows that eye infiltration was eradicated only in patients who underwent RT, and it has to be emphasized that a higher rate of long-term DFS occurred in patients treated with RT at doses higher than 20 Gy.

On the contrary, as far as high doses of chemotherapeutic agents are concerned, we observed BM relapse in three out of 6 patients treated with high doses and in ten out of 19 treated with standard doses; thus we cannot confirm the need for high-dose CT to treat eye relapse.

Regarding treatment failure, bone marrow relapse occurred equally after infiltration of the anterior or the posterior segment of the eye; a second eye infiltration was observed only after anterior chamber involvement. In some cases a bone marrow relapse occurring a few months after eye infiltration led us to think that LO could be a feature of systemic disease.

In conclusion, isolated eye relapse can be eradicated, mainly if it occurs after the withdrawal of therapy; the outcome seems to be independent of the site of the ocular infiltration. The most important prognostic factor is aggressive local treatment with RT on the affected eye at doses higher than 20 Gy plus systemic CT.

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