The association of topotecan and cytarabine in the treatment of secondary or relapsed acute myeloid leukemia

A topotecan/cytarabine combination has been reported to be effective in patients with myelodysplastic syndromes. We report our experience with this regimen in 12 patients with relapsed or secondary acute myeloid leukemia. Extra-hematologic toxicity was low, but the response to the treatment was very poor. In our opinion, this association is not a treatment option for these patients, but the addition of other agents could improve this results.

In the present study we analyzed the results of a combination treatment including topotecan and cytarabine (Ara-C) in a group of patients with secondary acute leukemia (sAML) or with AML relapsed following a previous treatment in order to assess the response rate, the treatment tolerability, remission duration and overall survival.

Treatment consisted of induction with topotecan (1.25 mg/m^2/d, by continuous intravenous infusion, days 1 to 5), and cytarabine (1 g/m^2/d by infusion for 3 hours, days 1 to 5). Patients achieving complete remission (CR) or partial remission (PR) received a second course of treatment using the same drugs, at the same dosage. Patients unresponsive to the treatment were excluded from the study.

Patients persistently in CR underwent two cycles of consolidation treatment with oral idarubicin (20 mg/m^2/d, days 1,3,5) associated with oral etoposide (100 mg/m^2/d, days 1 to 3), and subcutaneous cytarabine (100 mg/m^2/d, days 1 to 5). Alternatively, allogeneic peripheral blood stem cell transplantation was considered for patients with a compatible donor.

Twelve patients with AML were enrolled in this study, over an 18-month period. The patients' characteristics are reported in Table 1. Seven of the patients had sAML (5 secondary to RAEB-T, 1 to CMML, and 1 to Hodgkin's disease) and 5 had AML in relapse (3 in first and 2 in second relapse). All patients had received chemotherapy for the previous disease, except for 2 patients who had a previous RAEB-T. All patients were evaluable for response. Two patients achieved complete remission (CR, 17%) (1 sAML and 1 relapsed AML) after the first course of chemotherapy and received a second cycle, followed by consolidation treatment. One patient achieved partial remission (PR, 9%) after the first cycle and underwent allogeneic BMT, without performing consolidation treatment. He achieved CR after transplantation. All the remaining patients were resistant to treatment.

We did not observe any death in induction. Drug-related extra-hematologic toxicity, in particular gastro-intestinal toxicity and mucositis, was very low. Fever of unidentified origin needing antibiotic treatment was observed in all patients, while pneumonia was diagnosed in 3 patients only. One patient had cardiac toxicity (atrial fibrillation). All patients but one experienced prolonged neutropenia (median duration of neutrophil count <0.5×10^9/L, 23 days, range 0-26) and thrombocytopenia (median duration of platelet count <20×10^9/L, 14.5 days, range 4-35). Only the patient with sAML following HD never reached a neutrophil count lower than 0.5×10^9/L.

CR duration in patients who received chemotherapy was 26+ and 34+ weeks, while in the transplanted patient it was 54+ weeks. The overall survival was 20 weeks (range 7-66+). Four patients (3 responsive and 1 unresponsive) are at present alive, while the remaining 8 patients died of AML progression.

Some studies have recently pointed out the usefulness of topotecan in the treatment of acute myeloid leukemia.[1,2] In these phase 1 studies the dose-limiting toxicity of topotecan was established, however its use as monochemotherapy during induction had little success (10%-15%). The efficacy and toler-

Table 1. Patients' characteristics and treatment results.

Median age (years)	61 (44-72)
Male/female ratio	10/2
Performance status (W.H.O.):	
0	3
1	8
2	1
Cytogenetic study	
Normal	5
7 q-	2
5 q-	2
8 trisomy	1
Hyperdiploid	1
Aneuploid	1
Toxicity (W.H.O.):	
Vomiting	3
Diarrhea	1
Infection	3
Hemorrhage	12
Cardiac	1
Outcome	
Complete remission (%)	2 (17)
Partial remission (%)	1 (8)
Resistant (%)	9 (75)
Overall survival (weeks)	20 (7-55+)

Table 2. Literature data on topotecan-based regimens.

Author	*Type of malignancy*	*No. of patients*	*Regimen*	*CR/PR*	*Death in induction*	*Resistant*
Kantarjian *et al.* (1)	Rel./refr. AML/ALL/CML BP	27	Topotecan	6 (22%)	4 (15%)	17 (63%)
Rowinsky *et al.* (2)	Rel./refr. AML/ALL/CML BP	17	Topotecan	2 (12%)	-	15 (88%)
Seiter K *et al.* (3)	Rel./refr. AML/ALL/CML BP	53	Topotecan/Cytarabine	8 (15%)	3 (6%)	42 (79%)
Beran M *et al.* (4)	Sec./*de novo* MDS	86	Topotecan/Cytarabine	48 (56%)	6 (7%)	32 (37%)
Cortes J *et al.* (5)	Rel./refr. AML/CML BP	63	Cyclophosphamide/Topotecan/Cytarabine	13 (20%)	5 (8%)	45 (72%)
Crump M *et al.* (6)	Rel./refr. AML/CML BP	11	Topotecan/Etoposide	1 (9%)	1 (9%)	9 (82%)
Leoni F *et al.* (7)	Sec./*de novo* elderly AML	20	Fludarabine/Topotecan/Cytarabine	12 (60%)	1 (5%)	7 (35%)

Legend: Rel: relapsed; Refr: refractory; Sec: secondary; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML BP: chronic myeloid leukemia in blastic phase; CR: complete remission; PR: partial remission.

ability of topotecan and Ara-C were studied in refractory AML and MDS.[3,4] A high CR rate was observed in patients with MDS (56% in 48 patients), while the results were very poor in refractory AML[3] (Table 2). We used this treatment combination in a trial including patients with AML, preceded by MDS or by another malignancy, and with AML in relapse. Our results are not encouraging. In fact, although no major extra-hematologic toxicity or deaths in induction were observed, the remission rate was very low (25% of overall response), inducing the interruption of the trial.

Synergistic activity has been shown between alkylating agents, topoisomerase-II inhibitors and topotecan, but unfortunately the addition of these drugs to topotecan-based regimens did not increase the remission rate.[5,6] More effective seems to be the association of topotecan/Ara-C and fludarabine in elderly AML patients.[7] This regimen, based on the synergic action of fludarabine and Ara-C, showed encouraging results when considering CR rate and overall survival.

In conclusion, our results, although on a small group of patients, suggest that topotecan/Ara-C has low efficacy in the treatment of sAML. The combination with other chemotherapy agents deserves to be studied, in particular in this poor prognosis group of patients.

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