Central nervous system relapse in acute promyelocytic leukaemia

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Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia, characterized by the presence of the specific t(15;17) translocation, leading to a formation of the PML/RARA fusion gene, that play a crucial pathogenetic rule in the leukemia development. The introduction of ATRA has changed the natural course of the disease inducing the differentiation of the APL blasts. However, treatment failure occurs in approximately 30% of patients, because of early death during induction or, more frequently, for relapse.[1,2] The relapses involved more frequently bone marrow, even if recent study reported an increased incidence of extra medullar relapse.[5-12] Extra medullar localizations are developed in a sizable proportion of acute myeloid leukemia (3-8%), mainly in patients with myelomonocytic and monocytic FAB subtypes. Primary CNS localization in APL is rare. Conversely, extramedullary (EM) relapse has been increasingly reported in APL after the introduction of ATRA as standard treatment, with incidence of 1 to 5%.[3,4] The sites of EM relapse included skin, mediastinum, gingival, testis, ear and mainly CNS. The possible causes of the increased frequency of EM relapse in APL include the improved patient survival or and upregulation of adhesion molecules induced by ATRA. It has been suggested that risk factors for CNS relapse may be high WBC at presentation, ATRA syndrome with leukocytosis and capillary leakage, M3v morphology and bcr3 isoform.[4-7] Recently, a study conducted on three large multicenter trials (APL91, APL 93 and PETHEMA 96) demonstrated that in univariate analysis age < 45 years, bcr3 isoform and WBC count ≥ 10000/mcL are risk factors for extra medullar relapse, but in multivariate analysis only high WBC count remained significant.[8] Here we describe three unusual cases of CNS relapses out of 60 APL treated with ATRA plus idarubicin (AIDA 2000 protocol) in our Division from 1993.[9] The main characteristics of these patients at presentation are outlined in Table 1. All 3 patients had a WBC at presentation lower than 10000/mcL, that is usually the main factor associated with CNS disease in APL: in fact two patients were classified as intermediate risk APL according to GIMEMA-PETHEMA scoring system, one as low risk APL [5].Considering the other factors that some authors are found associated to CNS localization, in our patients only one had a micro granular morphology, two showed increased expression of CD56 on blast cells while no one had increased level of CD11c, two patients had ATRA toxicity, one had PML/RARA bcr3 type, while all showed ITD-FLT3 detected by RT-PCR. Moreover, in all patients, CNS localization underwent after hematological (2 cases) or molecular (1 case) relapse. The first patient developed asymptomatic CNS localization at the time of second hematological CR; he received intrathecal methotrexate and cranial radiotherapy, but he developed a further medullar relapse and died for resistant APL. The second patient had CNS disease in third CR, before starting conditioning chemotherapy for allogeneic bone marrow transplantation, and despite urgent chemotherapy with high-dose cytarabine, he died for infectious complication. The third patient had a diagnosis of CNS relapse in second molecular relapse, occurred after autologous peripheral blood stem cell transplantation. Among 60 APL patients treated in our Institution with AIDA regimen from 1993 till 2005 (AIDA0493 till 2000, than AIDA 2000), 9 had a medullar relapse and 3 (5%) presented CNS relapse, while before the introduction of ATRA in the APL treatment only one out of 81 APL patients had CNS localization.[9-10] However, the survival of APL patients before ATRA treatent was probably too short to develop any extra medullar relapse. CNS localization in our series has a frequency of 5%, that is comparable with the percentage of CNS localization in the other AML subtypes. Therefore, CNS localization might be related not to the ATRA introduction but to a prolonged survival of APL patients in ATRA era and CNS could be a leukemic "sanctuary" as in other AML. Our finding highlight the importance of better defining patients with high-risk of CNS disease and of carrying out CNS prophylaxis in these subset of APL patients

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Table 1. Main characteristic of 3 APL patients with CNS relapse.

	Patient 1	*Patient 2*	*Patient 3*
Hemoglobin (g/dL)	8.5	11.9	5.3
WBC (/mcL)	8600	4230	9300
Platelets (/mcL)	14000	9000	53000
Risk group	intermediate	intermediate	low
Bone marrow morphology	M3	M3v	M3
Bone marrow immunophenotype	CD13+; CD33+, CD34-; HLA-DR-; MPO+; CD2-; CD56-	CD13+; CD33+; CD34-; HLA-DR-; MPO+; CD2+; CD56+	CD13+; CD33+; CD34-; HLA-DR-; MPO+; CD2-; CD56+
PML/RARA isoform	bcr1	bcr3	bcr1
ITD-FLT3	Y	Y	Y
ATRA toxicyty	Respiratory distress; epatotoxicity	epatotoxicity	no

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