hemoglobin level were not significant predictors of ACS events. The rate of pain was not increased in those with asthma diagnosis (0.72 events per patient year for those with asthma and 0.60 events per patient year for those without asthma, p value=0.53). Furthermore, baseline white blood cell count, percent fetal hemoglobin and baseline hemoglobin were not significant predictors of pain episodes (Table 2). When compared to the remaining group of children without asthma (n=280), children taking daily inhaled corticosteroids (n=17) had an increased rate of ACS (0.43 events per patient-year *vs.* 0.16 events per patient-year; p-value=0.002) and no significant increase in rate of pain (0.99 events per patient-year *vs*. 0.59 events per patient-year; p=0.122) .

Evidence from previous studies suggested that asthma is associated with increased rates of ACS events[2,3,4] and pain episodes.[2] The results of this study confirmed previous data indicating an association between asthma and ACS events, but did not reveal an association between asthma and pain events. The reasons for the lack of association between asthma and pain in the Créteil population are not known, but may be related to differences in how care is delivered in that center and/or unmeasured environmental factors. Two studies have assessed the impact of the environment on SCD-related pain episodes.[5,6] Both studies demonstrated that local environmental factors may contribute to the rate of hospitalization for pain.[5,6]

The background rate of asthma among the children with SCA in France, 8.4%, was not significantly different from a comparable cohort of children of African descent living in France, 9.1%.[7] Taken together, these studies provide no evidence that a physician diagnosis of asthma occurs more frequently among children with sickle cell disease when compared to children without sickle cell anemia.

In summary, we provide further support that asthma is a potentially treatable risk factor associated with ACS. Future prospective studies to classify lung disease associated with SCA and to determine the effectiveness of asthma management in preventing SCA-related morbidity are warranted.

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Funding: Burroughs-Wellcome Foundation.

Key words: sickle cell anemia, acute chest syndrome, vaso-occlusive episode, asthma.

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Citation: Bernaudin F, Strunk RC, Kamdem A, Arnaud C, An P, Torres M, Delacourt C, DeBaun MR. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study. Haematologica 2008; 93:1917-1918. doi: 10.3324/haematol.13090

References

1. Phillips KL, An P, Boyd JH, Strunk RC, Casella JF, Barton BA, et al. Major gene effect and additive familial pattern of inheritance of asthma exist among families of probands with sickle cell anemia and asthma. Am J Hum Biol 2008; 20:149-53.
2. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood 2006;108:2923-7.
3. Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. Pediatr Pulmonol 2004;38:229-32.
4. Nordness ME, Lynn J, Zacharisen MC, Scott PJ, Kelly KJ. Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. Clin Mol Allergy 2005;3:2.
5. Yallop D, Duncan ER, Norris E, Fuller GW, Thomas N, Walters J, et al. The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment. Br J Haematol 2007;136:844-8.
6. Jones S, Duncan ER, Thomas N, Walters J, Dick MC, Height SE, et al. Windy weather and low humidity are associated with an increased number of hospital admissions for acute pain and sickle cell disease in an urban environment with a maritime temperate climate. Br J Haematol 2005;131:530-3.
7. Moreau D, Ledoux S, Choquet M, Annesi-Maesano I. Prevalence and severity of asthma in adolescents in France. Cross-sectional and retrospective analyses of a large population-based sample. Int J Tuberc Lung Dis 2000;4:639-48.

Clinical and biological features of acute promyelocytic leukemia patients developing retinoic acid syndrome during induction treatment with all-trans retinoic acid and idarubicin

Although all-trans retinoic acid (ATRA) is generally well tolerated, some patients develop a potentially severe and life-threatening complication referred to as retinoic acid syndrome (RAS). We analyzed here the biological and clinical characteristics of 110 consecutive patients with genetically proven APL, with the aim of identifying predictive features of developing RAS.

All patients described were treated with AIDA[1] or AIDA 2000[2] protocols, between January 1993 and December 2005 at the University "La Sapienza" of Rome. Diagnosis was confirmed at the genetic level by RT-PCR identification of the PML/RARa hybrid as previously described.[1] The presence of FLT3 internal tandem duplication (ITD) was investigated in 80 cases using the technique previously reported.[3] Immunophenotype was performed by flow-cytometry using a wide panel of monoclonal antibodies including CD13, CD33, HLA-DR, CD34, CD2, CD7, CD15, CD9, CD117, CD56, MPO (Becton Dickinson, Mountain Flow, CA, USA), considering a sample antigen-positive if >20% of the cells reacted with a specific monoclonal antibody, whereas for CD34 a cut-off of >10% was used. According to Frankel *et al.*[4], the diagnosis of *definitely present* RAS was clinically established by the presence of at least three of the following signs: weight gain, respiratory distress, unexplained fever, interstitial pulmonary infiltrates, pleural or pericardial effusions. For statistical analysis, the Wilcoxon-Mann-Whitney test was per-

Table 1. Clinical manifestations and outcome of patients developing retinoic acid syndrome.

	Time to initial symptoms (days)	Respiratory distress	Fever	Renal failure	Pulmonary infiltrates	Pulmonary edema	Pleural effusions	Bone pain	Headache	Weight gain	Outcome
1	5	+	+	–	+	–	–	–	–	+	Alive in CR
2	4	+	+	–	+	–	–	–	–	+	Alive in CR
3	4	+	-	–	+	–	+	–	–	+	Alive in CR
4	3	+	+	–	+	–	+	–	–	+	Alive in CR
5	5	+	-	–	+	+	–	–	–	+	Died in relapse
6	3	+	+	–	+	–	–	–	+	+	Died in relapse
7	5	–	+	–	–	–	–	+	+	+	Alive in CR
8	5	+	+	–	+	–	–	–	–	+	Alive in CR
9	4	+	+	–	+	–	–	–	–	+	Alive in CR
10	4	+	+	–	+	–	–	–	–	+	Died in relapse
11	3	+	+	–	+	–	–	+	+	+	Died in relapse
12	5	–	+	+	+	–	–	+	–	+	Alive in CR
13	4	–	+	+	+	–	–	+	+	+	Alive in CR
14	5	+	+	–	+	–	–	–	–	+	Alive in CR
15	4	+	–	–	+	–	–	–	–	+	Alive in CR

formed for comparison of non-parametric series and Fisher's exact test was used to compare categories. Values of $p<0.05$ were considered as statistically significant. Overall survival was measured from the time of diagnosis to death or last follow-up.

Median time elapsed between treatment initiation and first symptoms of RAS was four days (range 3-5). At the time of initial suspect of RAS, the median WBC count was 2.9×10^9/L; in 5/15 patients RAS was accompanied by an increase of WBC up to 10×10^9/L. Median peak WBC was 5.3×10^9/L and median doubling time was four days. Respiratory distress was the first manifestation of RAS in 12/15 patients (80%, Table 1). CT scan was performed at the earliest manifestation of respiratory distress in all patients. Pulmonary infiltrates were documented in 14/15 patients and in 3 of them without dyspnea. Fever was present in 12 patients, weight gain in all, renal failure in 2, pleural/pericardial effusions were present in 3 patients.

Treatment of RAS consisted of dexamethasone 10 mg/m^2/bid until complete disappearance of symptoms, administered for a median of six days. ATRA was discontinued only in 2 cases in which RAS was considered life-threatening and did not improve with dexamethasone.

Resolution of RAS occurred in a median time of four days (range 2-8 days) from dexamethasone initiation. All patients achieved complete hematologic remission after a median of 30 days (range 28-45), were given 3 cycles of consolidation and obtained molecular remission at the end of consolidation. Five patients (33%) underwent disease relapsed at a median time of 22 months (range 12-32). Four patients died in second relapse whereas one patient is alive after allogeneic stem cell transplantation after 72 months. Presenting features and treatment outcome of the 15 patients who developed RAS and of the 95 who did not are shown in Table 2. Significant differences were observed in the prevalence of M3v FAB subtype (50% *vs.* 26%, p=0.02), median WBC count (6×10^9/L *vs.* 2.8×10^9/L, p=0.01), prevalence of high relapse risk (46% *vs.* 24%, p=0.001), bcr3 PML/RARα (66% *vs.* 44%, p=0.001), FLT3-ITD (54% *vs.* 36%, p=0.002), expression of CD2 (54% *vs.* 12%, p=0.0001) and CD15 which was only detected in patients developing RAS (p=0.0001). No differences in CR rate and in overall survival were observed between the two groups (40 *vs.* 45 months, p=0.35). Finally, patients who experienced RAS had a 33% rate of morphological relapse as

Table 2. Comparison of clinical/biological features in patients with and without retinoic acid syndrome.

		With RAS	Without RAS	p
Sex	m/f	9/6	40/45	0.577
Age	(median) year	45.5	37	0.456
FAB	M3/M3v	10/5 (50%)	67/18 (26%)	0.02
WBC	(median)x10^9/L	6	2.8	0.01
Hb	(median) gr/dL	10	9.1	0.877
Plts	(median)x10^9/L	29	28	0.344
Risk	Low	2 (13%)	24 (26%)	0.001
	Int	6 (40%)	40 (44%)	
	High	7 (46%)	21 (24%)	
Type of bcr	bcr1	5 (33%)	44 (48%)	0.001
	bcr3	10 (66%)	38 (44%)	
FLT3-ITD	pos/neg	8/7 (54%)	24/41 (36%)	0.002
CD34+	pos/neg	12/3 (80%)	26/59 (28%)	0.012
CD2+	pos/neg	8/7 (54%)	11/74 (12%)	0.0001
CD15+	pos/neg	9/6 (60%)	-/85 (0%)	0.0001
CR rate	%	100%	100%	0.653
Morphological relapse	yes/no	5/15 (33%)	11/95 (11%)	0.002
Molecular relapse	yes/no	5/15 (33%)	18/95 (18%)	0.07
Overall survival	months	40	45	0.358

compared to 11% of patients who did not (p=0.002).

We report here an incidence of RAS of 13.6% from which none of the patients died. The difference in the reported RAS frequency and mortality among different series may reflect several variables including its definition and recognition criteria, type of concomitant therapeutic protocol for APL and RAS treatment itself.[5,6] To better define biological features associated with bona fide RAS, we included in the present study only patients in which a *definitely present* RAS could be diagnosed according to the criteria of Frankel *et al*.[4] As to the absence of deaths due to RAS in our series, this may reflect improvements in early recognition of the syndrome and prompt institution of dexamethasone. As reported by Vadhat *et al*.[7], we found a significant correlation with WBC count at presentation; however, we did not find that WBC count above 5×10^9/L on day 1, or above 6×10^9/L, 10×10^9/L, 15×10^9/L, on days 5, 10 or 15 of ATRA treatment respectively, was predictive for the development of the syndrome as observed by Fenaux *et al*.[8] We documented an aberrant phenotype in all patients who developed RAS, in particular a strong associations with CD2 and CD15 expression. CD2 can mediate the adhesion to several molecules such as the ubiquitously expressed CD58 or CD59 expressed on platelets and erythrocytes, and may play a role in leukoagglutination, contributing to tissue damage by microvascular occlusion.[9] As to CD15, it is known that this antigen mediates the adhesion to activated endothelial cells through selectins ligand, and favors the first rolling event.[10,11] Although in the present study we did not evaluate the *in vivo* induction of CD2 and CD15 levels during treatment, others have reported that both CD2 and CD15 expression are modulated by ATRA suggesting a role for these antigens in the development of RAS.[11]

The frequent association of the FLT3-ITD mutation in APL blasts at presentation and its correlation with elevated WBC count and the PML/RARa bcr3 isoform is well known.[12] Recently, Marasca *et al*.[12] reported gene expression profiling and FLT3 mutational status in a series of APL patients, and found that patients ITD$^+$ had increased expression of genes regulating blood coagulation (*CD97, PTX3, H963*) and cell adhesion (AMIGO2, LGALS 1-2) suggesting a role for FLT3-ITD in the development of RAS during induction.

To summarize, our study suggests that the risk of developing RAS in APL patients is associated with consistent phenotypic and genotypic features of leukemic cells. Further studies are warranted to investigate the mechanistic link between these features and the pathogenesis of RAS in these patients.

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Key words: acute promyelocytic leukemia, retinoic acid syndrome, immunophenotype, FLT3.

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Citation: Breccia M, Latagliata R, Carmosino I, Cannella L, Diverio D, Guarini A, De Propris MS, Petti MC, Avvisati G, Cimino G, Mandelli F, and Lo-Coco F. Clinical and biological features of acute promyelocytic leukemia patients developing retinoic acid syndrome during induction treatment with all-trans retinoic acid and idarubicin. Haematologica 2008; 93:1918-1920. doi: 10.3324/haematol.13510

References

1. Mandelli F, Diverio D, Avvisati G, Luciano A, Barbui T, Bernasconi C, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukaemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Blood 1997;90:1014-21.
2. Lo Coco F, Avvisati G, Vignetti M, Fioritoni G, Liso V, Ferrara F, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation: results of the AIDA-2000 Trial of the Italian GIMEMA Group. Blood 2004;104: [abstract 392].
3. Noguera NI, Breccia M, Divona M, Diverio D, Costa V, De Santis S, et al. Alterations of the FLT3 gene in acute promyelocytic leukemia: association with diagnostic characteristics and analysis of clinical outcome in patients treated with the Italian AIDA protocol. Leukemia 2002; 16: 2185-9.
4. Frankel SR, Eardley A, Heller G, Berman E, Miller WH Jr, Dmitrovsky E, et al. All trans retinoic acid for acute promyelocytic leukaemia. Results of the New York Study. Ann Intern Med 1994;120:278-86.
5. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Odgen A, et al. Clinical description of 44 patients with acute promyelocytic leukaemia who developed the retinoic acid syndrome. Blood 2000;95:90-5.
6. de Botton S, Dombret H, Sanz M, Miguel JS, Caillot D, Zittoun R, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1998;92:2712-8.
7. Vadhat L, Maslak P, Miller JR WH, Eardley A, Heller G, Scheinber DA, et al. Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PMN/RAR-α isoform, and CD13 expression in patients treated with all-trans retinoic acid. Blood 1994;84:3843-9.
8. Fenaux P, Castaigne S, Dombret H, Archimbaud E, Duarte M, Morel P, et al. All-trans retinoic acid followed by intensive chemotherapy gives a high complete remission rate and may prolong remissions in newly diagnosed acute promyelocytic leukemia: a pilot study on 26 cases. Blood 1992; 80:2176-81.
9. Claxton DF, Reading CL, Nagarajan L, Tsujimoto Y, Andersson BS, Estey E, et al. Correlation of CD2 expression with PML gene breakpoints in patients with acute promyelocytic leukaemia. Blood 1992;80:582-6.
10. Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis and treatment. Best Pract Clin Hematol 2003;16:453-61.
11. Di Noto R, Lo Pardo C, Schiavone EM, Ferrara F, Manzo C, Vacca C, et al. All-trans retinoic acid and the regulation of adhesion molecules in acute myeloid leukemia. Leuk Lymphoma 1996;21:201-9.
12. Marasca R, Maffei R, Zucchini P, Castelli I, Saviola A, Martinelli S, et al. Gene expression profiling of acute promyelocytic leukaemia identifies two subtypes mainly associated with FLT3 mutational status. Leukemia 2006; 20: 103-14.