cell inoculum was used in APL patients in second (n=5) or fourth (n=1) molecular remission. In this series all patients had a first CR lasting for more than one year and this may have accounted for the favorable results, given the pivotal prognostic role of the duration of the first CR in acute myeloid leukemia.[10] No transplant-related deaths occurred and extra-hematologic toxicity was mild. Five out of 6 patients (83%), including one who relapsed after alloSCT, are alive with no evidence of molecular disease after a median follow-up of 33 months from ASCT and 57 from diagnosis. Of note, in four out of five cases, the duration of second molecular remission is longer than two years and a sustained molecular remission has also been achieved in the patient who relapsed after alloSCT. These results suggest that ASCT performed with a molecularly negative graft in APL patients in second molecular remission offers a valid chance for achieving cure. Such an approach should be also considered in relapsed patients with an HLA compatible donor, namely in those with a first CR lasting more than one year or in elderly individuals.

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Acute Leukemia

Analysis of fatal intracranial hemorrhage in 792 acute leukemia patients

Forty-one of 792 acute leukemia patients suffered fatal intracranial hemorrhage (FICH). Acute promyelocytic leukemia was the most common subtype. Achievement of complete remission in AML was significantly influenced by FICH. FICH accounts for about half of deaths from hemorrhage and this proportion has not changed despite improvements in leukemia management.

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Hemorrhagic complications are common in patients with acute leukemia, constituting the second most frequent cause of death in such patients.[1,2] Intracranial hemorrhage (ICH) is the most common hemorrhagic complication in acute promyelocytic leukemia (APL)[3] and is also associated with other acute leukemias such as acute monocytic leukemia and acute lymphoblastic leukemia.[4-8] We examined the features of hemorrhage and ICH in 792 patients with acute leukemia diagnosed between July 1998 and March 2003. Fatal ICH (FICH) was defined as an ICH which was a leading cause of death. Early FICH (group 1) was defined strictly as an event that occurred within seven days of diagnosis of acute leukemia and included cases that presented with FICH. FICH which occurred more than seven days after diagnosis was defined as late FICH (group 2). In all cases, radiological imaging studies such as computed tomography or magnetic resonance imaging were required for confirmation of ICH. The median follow-up was 45.6 months, and 67 (8.5%) patients were lost to follow-up. By the reference date, 419 (52.9%) patients had died. The cause of deaths was hemorrhage in 79 (18.9%) of these patients. At the time of diagnosis, 158 (19.9%) patients presented with various hemorrhagic problems such as epistaxis and petechiae.

Analyzable FICH occurred in 41 (51.9%) of the 79 patients who died from hemorrhage. There were 6 non-fatal symptomatic cases of ICH. Twenty-seven of the FICH were early and 14 were in group 2. At presentation, 13 patients already had signs of ICH which was then fatal. ICH significantly shortened the probability of overall survival in acute leukemia patients. The most common subtype of leukemia in which FICH occurred was APL (n = 18, 43.9%). DIC was the most common probable cause of FICH in all patients and in group 1 patients (n = 17, 41.5%; n = 16, 39.0%, respectively). The patients' status at FICH were: CR in two patients (4.9%), relapse in six (14.6%), and post-SCT relapse in two (4.9%). Patients in group 1 showed a more prolonged PT ($p < 0.001$) and lower serum fibrinogen levels ($p = 0.032$) than did those in group 2. While the time from diagnosis to hemorrhage was longer in group

Table 1. Basic characteristics of fatal intracranial hemorrhage patients.

Characteristics	*All*	*Group 1 (early)*	*Group 2 (late)*	*P**
Gender, n (%)				NS
Male	13 (31.7)	10 (24.4)	3(7.3)	
Female	28 (68.3)	17 (41.5)	11 (26.8)	
Age, median (range)	34 (16-75)	32 (16-75)	35.5 (22-74)	NS
Proportion of all deaths from any cause, %	9.8	6.4	3.3	
Proportion of all death from hemorrhage, %	51.9	34.2	17.7	
Days from diagnosis to hemorrhage, median (range)	2 (0-1826)	1 (0-7)	247 (16-1826)	<0.001
Days from hemorrhage to death, median (range)	2 (0-20)	2 (0-8)	1.5 (0-20)	0.674
Disease status prior to FICH (prior to first CR), n (%)	31 (75.6)	27 (100)	4 (28.6)	<0.001
White blood cells ($\times 10^3/\mu L$), median (range)	36.2 (0.1-752)	64.7 (1.1-752)	7.5 (0.1-250.6)	0.018
Platelet ($\times 10^3/\mu L$), median (range)	20 (2-108)	24 (6-108)	19 (2-95)	NS
Peripheral blasts (%), median (range)	53 (0-96)	74 (0-96)	1 (0-92)	0.005
Prothrobin time (INR), median (range)	1.6 (1.0-6.6)	1.7 (1.3-6.6)	1.2 (1-2.7)	<0.001
aPTT (sec), median (range)	40.2 (17.2-107.4)	40.2 (17.2-107.4)	40.2 (31.9-72.6)	NS
Fibrinogen (mg/dL), median (range)	206 (64-483)	150 (64-368)	430 (377-483)	0.032
Hemorrhage score[11] at presentation	0 (0-3)	1 (0-3)	0 (0-3)	NS
Induction chemotherapy, n (%)	25 (61)	14 (34.1)	11 (26.8)	NS
Surgery for ICH, n (%)	2 (4.9)	1 (2.4)	1 (2.4)	NS

**p value indicates the significance of differences between groups 1 and 2. NS: not significant; INR: international normalized ratio; aPTT: activated partial thromboplastin time.*

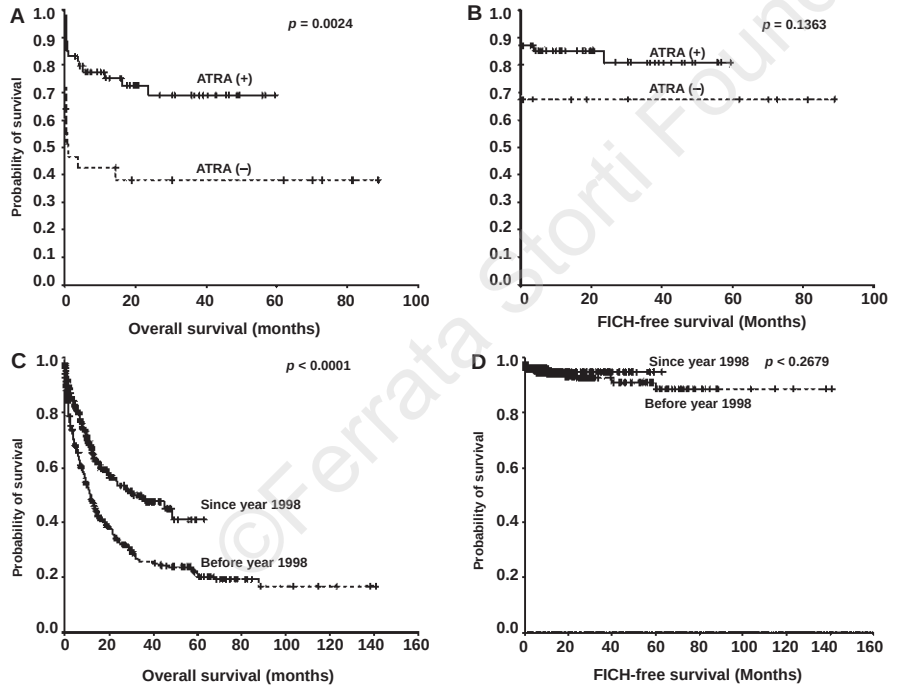

Figure 1. Overall survival (a) and FICH-free survival (b) in relation to use of all-trans retinoic acid (ATRA) in patients with acute promyelocytic leukemia. ATRA patients (n = 54, solid line); non-ATRA patients (n = 25, dotted line). Overall survival (c) and FICH-free survival (d) in relation to date of diagnosis. After January 1998 (n = 406, solid line); before January 1998 (n = 386, dotted line).

2 patients by definition, there was no difference in the length of time from FICH to death ($p = 0.674$). Table 1 presents the characteristics of the patients with FICH.

The cerebral parenchyma was the region most commonly involved in FICH, being the site in 22 of all 41 cases (53.7%) and in 15 of the group 1 cases. The next most involved regions were the cerebellar parenchyma and the subdural space. The most common radiologically identifiable type of bleed in all patients and group 1 patients was a single hematoma, which occurred in 18 (43.9%) and 12 (29.3%) patients, respectively. There were more unilateral locations, but the frequency of these was not significant different between groups ($p = 0.084$). Intraventricular hemorrhage was fatal in all patients (n = 8, 19.5%; group 1: n = 3, 7.3%). Induction chemotherapy had been discontinued in 25 (61%) FICH patients and had been completed as intended in 9 (22%). Achievement of CR in AML was significantly influenced by FICH ($p < 0.001$), whereas CR in ALL was not associated with FICH ($p = 0.143$).

Only two (4.9%) of 41 FICH patients underwent surgical procedures. The reasons for not undergoing surgery were as follows: 13 (31.7%) patients died before surgery, four (9.8%) had a poor performance status and were not suitable for surgery, 16 (39%) had an unacceptably high surgical risk because of coagulopathy or cytopenia, and six (14.6%) had no proper surgical target lesion. Overall survival in APL patients receiving ATRA treatment was significantly longer than in patients treated before ATRA therapy was available ($p = 0.0024$, Fig-

ure 1A). FICH-free survival was not different between pre- and post-ATRA era patients with APL ($p = 0.1363$, Figure 1B). Considering all patients with acute leukemia, there was significantly longer overall survival in patients diagnosed after January 1998 ($p < 0.0001$, Figure 1C) but no difference was found in FICH-free survival despite a plateau in patients diagnosed after January 1998 ($p = 0.2679$, Figure 1D).

Graus *et al.*[9] reported on intracranial hemorrhage in 425 leukemia patients after hematopoietic stem cell transplantation (11 subdural and 5 brain hematomas): these patients differed from our series in terms of common location of hemorrhage, population and procedure-related events. In spite of the improved survival in acute leukemia, achieved through advances in understanding leukemia pathophysiology and the introduction of ATRA treatment for APL,[10] because most FICH (65.9%) occur within seven days of diagnosis and there have been few improvements in treating FICH, a special effort is required to decrease the frequency and mortality of FICH in this early period.

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Malignant Lymphomas

BCL-6 gene mutations in primary cutaneous B-cell lymphomas

We analyzed mutations in the 5' non-coding region of the *BCL-6* gene in 46 cases of primary cutaneous B-cell lymphomas (PCBCL), using a polymerase chain reaction single strand conformation polymorphism (PCR-SSCP) method. The results indicate that PCBCL display a low frequency of mutations and support a marginal zone B-cell origin for most of these neoplasms.

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Primary cutaneous B-cell lymphomas (PCBCL) comprise entities morphologically similar to their nodal counterparts, but with a more favorable clinical behavior and prognosis. According to the EORTC classification, PCBCL generally do not express immunohistochemical markers such as CD5 and CD10 and only rarely show rearrangement of the *C-MYC*, *BCL-1*, *BCL-2* and *BCL-6* genes.[1]

In contrast, more recent studies have reported CD10 expression in the great majority of primary cutaneous follicular lymphomas and the presence of the t(14;18) translocation in about 30% of these cases.[2] The *BCL-6* gene is a proto-oncogene functioning as a transcriptional repressor and mutations of the 5' non-coding region are reported to be a potential mechanism for deregulating *BCL-6* expression, thus playing a role in the pathogenesis of non-Hodgkin's lymphomas (NHL).[3]

We extensively analyzed these molecular alterations in PCBCL. Forty-six cases of PCBCL (32 males and 14 females; age range: 31-86 yrs; mean age: 66 yrs) were examined. According to the EORTC classification there were 11 cases of primary cutaneous immunocytoma/marginal zone B-cell lymphoma (Ic/MZBCL), 31 cases of primary cutaneous follicle center cell lymphoma (FCCL) and 4 cases of large B-cell lymphoma of the leg (LBCL).

BCL-6 gene mutations were detected with non-radioiso-

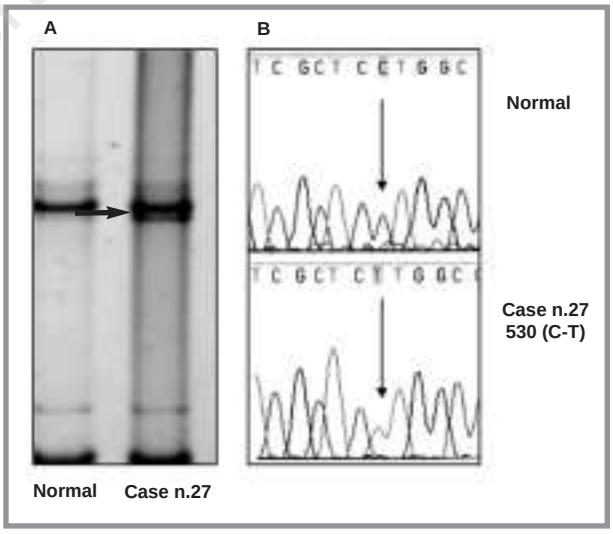

Figure 1. Case #27: A) SSCP analysis showed an anomalous migration pattern in fragment E1.12 of case #27, in comparison to the normal specimen. The arrow indicates the band used for sequencing analysis. B) Sequencing analysis identified a point mutation (530 C-T).