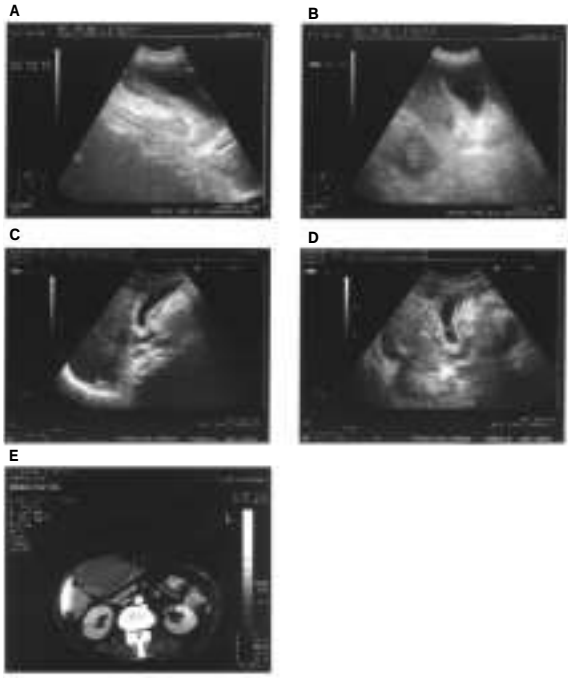


**Figure 1. Abdominal US findings in representative cases of immunocompromised patients: overdistended gallbladder with striated wall thickening (A) containing biliary sludge (B) in patient #1; marked striated thickening of gallbladder wall in patient #4 (C and D). Gallbladder CT scan of patient #1, confirming the US findings (E).**

to infectious causes, even in the absence of calculi or of bile duct abnormality, has a significant prevalence in a group of patients suffering from hematologic malignancies complicated by FUO.[4,5] In these cases, as in other settings,[6-8] abdominal US scan proved to be a valuable tool for rapid detection of the infection site, thus moving a number of patients from FUO to clinically documented infection and ultimately leading to more appropriate treatment.[9] In our small series, one patient had gallbladder empyema; the others had a clinical syndrome characterized by high fever, moderate right abdominal pain, serositis and US findings strongly suspicious of gallbladder distress.[3] In this group of patients, close US follow-up associated with correct antibiotic therapy, supportive treatment and bowel rest were an effective method to avoid potentially dangerous surgery.[10]

We see US examination as the natural continuation and extension of the physician's manual action, and a potentiation of his semeiotic sensitivity. It is a rapid, safe, effective and inexpensive diagnostic tool for detecting the site of infection in immunocompromised patients with FUO, with special attention to the gallbladder.

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***Key words***

*Acute acalculous cholecystitis, gallbladder abnormality, ultrasound scan, immunocompromised hosts, FUO*

***Contributions and Acknowledgments***

*MP designed the study and performed the ultrasound examinations. CS, CC and AC were responsible for patient care and follow-up. BR was responsible for data interpretation and revising the paper.*

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## References

1. Cappell MS. Hepatobiliary manifestations of the acquired immune deficiency syndrome. Am J Gastroenterol 1991; 86:1-9.
2. Murakami CS, Louie W, Chan GS, et al. Biliary obstruction in hematopoietic cell transplant recipients: an uncommon diagnosis with specific causes. Bone Marrow Transplant 1999; 23:921-7.
3. [anonymous]. Trattato Italiano di Ecografia. SIUMB: Poletto ed. Milan, Italy; 1993; vol. 1.
4. Wiboltt KS, Jeffrey RB Jr. Acalculous cholecystitis in patients undergoing bone marrow transplantation. Eur J Surg 1997; 163:519-24.
5. Jacobson AF, Teefey SA, Lee SP, Hollister MS, Higano CA, Bianco JA. Frequent occurrence of new hepatobiliary abnormalities after bone marrow transplantation: results of a prospective study using scintigraphy and sonography. Am J Gastroenterol 1993; 88:1044-9.
6. Picardi M, Morante R, Rotoli B. Ultrasound exploration in the work-up of unexplained fever in the immunocompromized host: preliminary observations. Haematologica 1997; 82:455-57.
7. Picardi M, Selleri C, Camera A, Catalano L, Rotoli B. Early detection by ultrasound scan of severe post-chemotherapy gut complications in patients with acute leukemia. Haematologica 1999; 84:222-5.
8. Picardi M, Selleri C, De Rosa G, Califano C, Camera A, Rotoli B. Previous occurrence of life-threatening abdominal infection is not a contraindication to bone marrow transplantation. Haematologica 1999; 84: 764-5.
9. Takada T, Yasuda H, Uchiyama K, Hasegawa H, Asagoe T, Shikata J. Pericholecystic abscess: classification of US findings to determine the proper therapy. Radiology 1989; 172:693-7.
10. Chirletti P, Barillari P, Sammartino P, et al. The surgical choice in neutropenic patients with hematological disorders and acute abdominal complications. Leuk Lymphoma 1993; 9:237-41.

## Fludarabine-containing regimen followed by autologous peripheral blood stem cell transplantation in unselected patients with acute myeloid leukemia: a single center experience

**Fludarabine has been recently reported as ineffective in mobilizing peripheral blood stem cells (PBSC) in acute myeloid leukemia (AML) patients. We report herein on 27 AML patients, 9 of them being eligible for peripheral blood stem cell transplantation (PBSCT). Eight of the 9 successfully**

**mobilized after two courses of a fludarabine-containing regimen and the administration of CTX at a dose of 4 g/m².**

Sir,

Fludarabine, in combination with Ara-C and anthracycline, has proven to be a highly effective regimen in patients with high-risk AML.[1-4] To date, however, few studies in unselected patients with *de novo* AML are available and in those that are a shorter duration of remission or an impairment of immune surveillance of the disease were often reported.[5-7] It is also still unclear whether fludarabine may exert an adverse effect on PBSC mobilization following induction treatment.[8] The purpose of the study was to evaluate the feasibility of a fludarabine-containing regimen prior to PBSC transplantation in unselected AML patients.

Since 1996 twenty-seven AML patients, 16 males and 11 females, entered a multidrug protocol based on fludarabine (30 mg/m²/d, days 1-5), idarubicin (10 mg/m²/d, days 1, 3, 5) and aracytin (2 g/m²/d, days 1-5) (FLAI) as induction therapy; patients aged >60 years received the same drugs over three instead of five days (FLAI-3). Patients with peripheral blasts <25x10³/μL received a pre-phase therapy with ATRA 45 mg/m² 5 days before and 5 during chemotherapy in order to induce a recognizable maturation of blasts. Patients who obtained complete remission (CR) underwent a second identical treatment; those who did not were salvaged by MEC therapy (mitoxantrone 10 mg/m², VP-16 100 mg/m², Ara-C 3g/m² over 5 days). Patients < 60 years in CR underwent high dose therapy followed by PBSC transplantation or autologous bone marrow transplantation in case of unsuccessful mobilization. Two individuals with a compatible related donor underwent bone marrow transplantation. Mobilization therapy was cyclophosphamide 4 g/m² plus G-CSF 5 μg/kg/d. PBSC collection was obtained by leukapheresis with a Cobe-Spectra Separator.

Overall, 23 out of 27 patients achieved CR after induction; 4 patients needed salvage therapy. Eight patients underwent successful CD34⁺ mobilization (mean 6.3×10⁶/kg; range 2.7-12.5×10⁶/kg); one patient underwent marrow aspiration. Recovery of neutrophils occurred after a mean of 11.6 days (range 9-16) whereas platelet transfusion independence required a mean of 22.0 days (range 11-60). Toxicity consisted of mild mucositis in most patients. As of writing, 4 of 9 patients are alive and disease free after a mean follow-up of 13.5 months; 5 patients died because of relapse within a mean of 6.8 months.

In our experience almost all patients (89%) were successfully mobilized following fludarabine; remarkably, time for mobilization was relatively short: CD34⁺ collection often occurred between day +10 and +11 after chemotherapy. This early and transient mobilization may explain the unsuccessful PBSC collection experienced by some authors.[8] Despite an increase of infections and relapses having been reported,[9] we did not observe major infections or a higher incidence of relapses. In conclusion, our results support the use of fludarabine in combination with Ara-C and anthracyclines in newly diagnosed AML; the toxicity is acceptable enabling most patients to receive further treatment such as high dose therapy followed by peripheral blood stem cell transplantation.

**Table 1. Fludarabine containing remission-induction therapy in 27 AML patients: data about diagnosis, karyotype and assigned therapy.**

| | |
|---|---|
| N° of patients | 27 |
| Mean age (range) | 53 (16-75) |
| Sex (M/F) | 16/11 |
| Karyotype | |
| t(8;12) | 1 |
| t(2;14) | 1 |
| complex karyotypes | 7 |
| normal | 16 |
| not evaluable | 2 |
| Diagnosis | |
| M0 | 1 |
| M1 | 5 |
| M2 | 2 |
| M4 | 15 |
| M5 | 4 |
| Induction therapy | |
| FLAI-5 | 16 |
| FLAI-3 | 11 |
| FLAI+MEC | 4 |
| Consolidation therapy | |
| PBSCT | 8 |
| ABMT | 1 |
| BMT | 2 |

**Table 2. Patients submitted to PBSC or ABMT transplantation: data on CD34⁺ mobilization and collection, haematologic recovery and current status.**

| *Pt* | *Age* | *Days to CD34 > 20/μL* | *Leuk-aphe-reses* | *CD34 reinfused (x10⁶/kg)* | *Days to PMN > 500/μL* | *Days to PLT > 20x10³/μL* | *Current status* | *Follow-up (mos.)* |
|---|---|---|---|---|---|---|---|---|
| 1 | 53 | 10 | 2 | 9.1 | 16 | 18 | CR | 21 |
| 2 | 51 | 10 | 2 | 12.5 | 9 | 14 | Dead | 10 |
| 3 | 40 | 11* | 2 | 3.2 | 10 | 15 | CR | 18 |
| 4 | 58 | 11 | 1 | 11.5 | 9 | 11 | Dead | 5 |
| 5 | 69 | 10 | 3 | 3.1 | 10 | 12 | Dead | 6 |
| 6 | 59 | 11 | 3 | 4.8 | 12 | 17 | Dead | 10 |
| 7 | 61 | 10 | 3 | 6.9 | 11 | 60 | Dead | 3 |
| 8 | 30 | –° | – | 2.7 | 16 | 34 | CR | 8 |
| 9 | 16 | 9 | 2 | 3.2 | 11 | 17 | CR | 7 |
| Mean values | | | | | | | | |
| | 48.5 | 10.2 | 2.2 | 6.3 | 11.6 | 22.0 | – | 13.5 (CR) 6.8 (died) |

**After 2nd mobilization; °marrow aspiration.*

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***Key words***

*Fludarabine, acute myeloid leukemia, peripheral blood stem cell transplantation.*

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## References

1. Vasova I, Penka M, Hajek R, Mayer J, Krahulcova E. A new purine analog in the treatment of haematologic malignancy. I. Fludarabine. Vnitr Lek 1997; 43:45-50.
2. Keating MJ, O'Brien S, Mc Laughlin P, et al. Clinical experience with fludarabine in hemato-oncology. Hematol Cell Ther 1996; 38:S83-91.
3. Clavio M, Carrara P, Miglino M, et al. High efficacy of fludarabine-containing therapy (FLAG-FLANG) in poor risk acute myeloid leukemia. Haematologica 1996; 81:513-20.
4. Visani G, Tosi P, Zinzani PL, et al. FLAG (fludarabine + high-dose cytarabine + G-CSF): an effective and tolerable protocol for the treatment of 'poor risk' acute myeloid leukemias. Leukemia 1994; 8:1842-6.
5. Estey E, Thall P, Kantarjian H, Pierce S, Freireich E. Role of fludarabine containing regimen in newly-diagnosed AML or MDS. Congress of the American Society of hematology 1998.
6. Russo D, Candoni A, Grattoni R, Bertone A, Zaja F. Fludarabine and cytosine-arabinoside for poor-risk acute myeloid leukemia. Haematologica 1998; 83: 281-2.
7. Tafuri A, De Felice L, Petrucci MT, et al. Multidrug resistance expression and proliferative studies in poor risk acute myeloid leukemia treated with the FLAG (G-CSF plus fludarabine and Ara-C) regimen. Cytokines Mol Ther 1995; 1:301-7.
8. Visani G, Lemoli R, Tosi P, et al. Fludarabine containing regimens severely impair peripheral blood stem cells mobilisation and collection in acute myeloid leukemia patients. Blood 1999; 23:S221.
9. Fleischhack G, Hasan C, Graf N, Mann G, Bode U. IDA-FLAG (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experiences of a phase II trial. Br J Haematol 1998; 102:647-55.