Ministry of Health - Italy

MEDITERRANEAN BOOKLETS SERIES

# TUNISIA

# Abstract Book

## Italian-Tunisian Workshop on Diagnosis and Treatment of Acute Myeloid Leukemia

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**Editor**

Patrizia Parodi, Ministry of Health, Rome

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# 1. Italian-Tunisian partnership in the field of health

***Pietro Malara*[1]**

*Memorandum of Understanding in the field of health and medical sciences*

- Signed in Tunis on July 11, 1998.
- Main activities:
  - promotion of exchanges of experiences and programmes of cooperation;
  - study and scientific visits;
  - cooperation between Hospitals;
  - exchange of documentation, health legislation and epidemiologic data ;
  - Monitoring and coordination group.

Since now, the collaboration developed in a number of sectors, among which :

- **Hematology –** Workshop on hematologic diseases in Tunisia (2005).
- **Mother and child health –** Workshop in Tunisia (2006) and in Italy (2007).

  Exchange of documents concerning Mother and Child Health policies (2007).

  Stage in Italy of three Tunisian gynecologists on breast cancer (2008) and participation in the 5° International Congress of Senology.

  Stage in Italy on cervix cancer (2010)
- **Epidemiology -** participation in:

  Workshop Epidemic Intelligence in the Mediterranean Basin (Marrakech, Morocco 3-4 November 2008).

  Workshop for the preparation of the 3° Project Meeting EPISOUTH (Sofia, Bulgaria 12-13 January 2009).

  3° Project Meeting EPISOUTH (Sofia, Bulgaria, 30 March – 1 April 2009).

  5° Steering Committee Project Meeting EPISOUTH (Venice, Italy, 12-13 November 2009)
- **Environmental Health** – Presentation of the Italian experience in the hospital waste management during the 15° National Days on Hygiene (Hammamet, Tunisia, 9-10 December 2009) and publication of the Booklet no. 4 on "Hospital Waste Management".

- **Nurse and Health Personnel Training** – 31 and 60 Tunisian academic qualifications recognised respectively in 2008 and 2009.
- **Organ Transplantation -** participation in:

  3° Meeting France-Maghreb (Tunis, Tunisia, 29 November 1 December 2007).

  Meeting in Tunis for the design of a joint training project (Tunis, Tunisia, 17-18 March 2008).

  1°, 2° and 3° Meetings of the « Mediterranean Transplant Network » (Rome, Italy 31 October 2008; Palermo, Italy 2 March 2009; Beirut, Lebanon, 30 September 2009).

[1] Directorate General for EU and International Affairs, Ministry of Health, Rome, Italy

Preparation of a joint project for the exchange of researchers within the Italian-Tunisian Scientific and Technologic Collaboration Programme 2009-2012.

Preparation of a joint proposal on organ transplantation under the ENPI programme.

- **Training** – Signature of an Agreement between Cardarelli Hospital and Charles Nicolle Hospital. Realisation in Tunisia of:

  Workshop on Neurology (2007)

  Workshop on Hypertension (2007)

  Workshop on Hepatic Surgery (2007).

The collaboration in the health sector between the two Countries is still increasing and we wish to continue and to improve exchanges of experiences, expanding priority sectors in the next Action Plan.

## 2. Molecular, Cytogenetic and Phenotypic Diagnosis of Acute Myeloid Leukemia

*Francesco Lo Coco*[2]

Over the past two decades, relevant insights into AML biologic and genetic characterization have allowed considerable progress in the management of this leukemia by better defining distinct prognostic groups for patient stratification and by identifying new targets for tailored therapies. Among clinical and biological features associated with AML, genetic aberrations represent most powerful predictors of prognosis and therefore the most reliable markers for tailoring treatment in the individual patieent. In particular an integrated phenotypic, cytogenetic and molecular approach to unravel cytogenetically silent lesions (such as mutation in *FLT3*r or *NPM1* genes) significantly improves AML genetic characterization for better therapeutic stratification and routine screening for these abnormalities is now recommended for all newly diagnosed patients (Dohner et al., Blood 2009). Some of the newly described genetic lesions (e.g. *FLT3*) may be targeted by specific inhibitors which have shown anti-leukemic efficacy in preliminary studies and are currently being evaluated in phase III clinical trials (Sanz et al., 2009; Cheson et al., 2003).

Finally, some of the AML genetic alterations have been exploited to better assess response to therapy through the study of minimal residual disease (MRD) employing sensitive assays such as Q-PCR. These include fusion genes (AML1/ETO, PML/RARA, CBFb/MYH11, BCR/ABL) and evaluation of copy numbers of genes overexpressed in AML such as WT1. However, while these molecular signatures certainly improved upfront prognostic evaluation in AML, their relevance in predicting response/resistance to chemotherapy is modest. Likewise, the clinical impact of detecting MRD through measuring these alterations in the post-remission phase is still debated.

Multiparametric flow cytometry (MPFC) is an alternative method to quantify MRD. It consists of the combination of 4-5 surface markers (usually cross-lineage or asynchronous ones) and/or flow-cytometric physical abnormalities that characterize the leukemia blasts and are absent or very infrequent in normal bone marrow (leukemia associated phenotypes; LAIPs). We and others have shown that a specific LAIP can be found in up to 85-90% of AMLs patients.

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Using a cut-off value of $3.5x10^{-4}$ residual (LAIP-positive) leukemic cells to discriminate MRD-negative from -positive cases, we found that persistence of LAIP-positive MRD predicts clinical outcome in a consistent manner especially when measured at the post-consolidation time-point (Buccisano et al., 2009; Maurillo et al., 2008; Buccisano et al., 2006).

Based on the above considerations, it is conceivable that an improved initial characterization and outcome evaluation in AML may emerge from the combination of the above techniques which should be integrated to allow most reliable prognostic evaluation. Our laboratory, together with a network of other national Italian laboratories has long since been involved in this activity within the clinical cooperative group GIMEMA.

## 3. Contribution of flow cytometry in the diagnosis of Acute Myeloid Leukemia

*Emna Goudier*[3]

Biological diagnosis of acute myeloid leukemia is based on cytology and flow cytometry.

Nowadays, cytology alone for diagnosis is insufficient. Flow cytometry is an essential tool for typing leukemia and identification of some prognosis markers.

Specimens are obtained through a bone marrow aspiration in EDTA tube.

After washing cells and lyses of red blood cells, incubation with monoclonal antibodies is performed.

Then acquisition is done by a flow cytometer Beckman Coulter XL MCL©. Monoclonal antibodies are coupled with fluorochrome: FITC, PE or PC5. Intracytoplasmic markers need a permeabilization step that is realized by the coulter kit Intra prep©. Blasts are gated on the expression of CD45.

Diagnosis of AML is based on the EGIL score.

From April 2005 to September 2009, 346 AML were diagnosed in our laboratory. Panmyeloid profil was found in 8,5% of case. cMPO, CD65, CD117 was expressed in respectively 93%, 80%, 67%, 40%, and 39% of cases, HLA DR and CD34 in 68% and 49%.

The concomitant negativity of HLA-DR and CD34 was correlated with the diagnosis of AML3.

The co expression of CD56 was seen in 15,5%. Lymphoid markers were observed in 12% of cases with predominance of T markers.

Some markers seem to have a prognosis impact.

Flow cytometry is an essential tool for the diagnosis of leukemia in order to adapt chemotherapy.

## 4. Current International Clinical Trials in Acute Myeloid Leukemia

*Francesco Buccisano*[4]

Curative treatment in acute myeloid leukemia (AML) depends on successful induction therapy to achieve a complete remission (CR) and subsequent post-remission therapy to prevent relapse.

While about 60-80% of young adults and approximately 50% of fit older adults can achieve a CR, only a proportion of these patients will be cured with current post-remission strategies.

Thus, the greatest challenge in AML is to maintain the remission. Among patients

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younger than 55 to 60 years old, about one third of all AML patients can be cured, whereas among older patients only about 10-20% are long-term survivors.

**Younger patients**

Several major studies, particularly CALGB 9621 and the French ALFA 9000 study, have demonstrated that higher doses of DNR up to 80 or 90 mg/m$^2$ can be administered safely.

Eastern Cooperative Oncology Group (ECOG) studied younger patients up to age 60 and very recently reported a significantly higher CR rate for patients receiving 90 mg/ m$^2$ 72% versus 57% (P = .004). More importantly, the OS was also significantly prolonged among patients receiving the higher dose of DNR, particularly among patients with favorable or intermediate cytogenetics. In the Medical Research Council (MRC) AML15 study of younger adults, 1115 patients were randomized in induction to receive, or not, gemtuzumab ozogamicin (GO) in addition to the induction regimen. The post-remission therapy was identical in both arms of the study. The data were initially presented in 2006, reporting a similar CR in both arms, but a significantly improved DFS among patients receiving GO 51% versus 40% at 3 years (P = .008).

Disappointingly, these improvements in induction therapy, increasing the DNR dose or the addition of GO, do not seem to benefit patients with unfavorable cytogenetics. A trial by the CALGB studied post-remission therapy in young adults up to age 60 and compared 3 different doses of cytarabine given for 4 cycles followed by maintenance therapy.

The data from this prospective study demonstrated a significant improvement in the OS for patients less than 60 years of age when a high dose of cytarabine, at 3 g/m$^2$ for 6 doses, was given. Of note, in the CALGB study the impact of cytarabine dose on long-term survival was most marked among patients with favorable cytogenetics.

The final analysis of EORTC-GIMEMA AML-10, comparing the antitumor efficacy of three different anthracyclines in combination with cytarabine and etoposide in adult patients with newly diagnosed AML, has been recently published 2,157 patients (age range, 15 to 60 years) were randomly assigned to receive intensive induction-consolidation chemotherapy containing either daunorubicin, idarubicin, or mitoxantrone. After achieving CR, patients were assigned to undergo either allogeneic stem-cell transplantation (allo-SCT) or autologous stem-cell transplantation, depending on the availability of a sibling donor. The overall CR rate (69%) was similar in the three groups. However, the disease-free survival (DFS) and survival from CR were significantly shorter in the daunorubicin arm: the 5-year DFS was 29% versus 37% and 37% in mitoxantrone and idarubicin, respectively, and the 5-year overall survival rates were 34%, 34%, and 31%, respectively. In conclusion, adult patients with AML who do not receive an allo-SCT, the use of mitoxantrone or idarubicin instead of daunorubicin enhances the long-term efficacy of chemotherapy.

The future EORTC-GIMEMA trial (AML-14) has been designed to test clofarabine in combination with a standard remission induction regimen (AraC and Idarubicin) in patients 18-60 years old with untreated intermediate and poor risk AML or high risk MDS.

Despite the efforts produced by many groups, many questions about the optimal frontline induction-consolidation therapy remain unsolved. In particular, the better post-consolidation therapy is still matter of debate.

Allo-SCT provides the better anti-leukemic effect. Nevertheless, some important issues are still discussed:

1. Which patients should be offered this in CR1?
2. How much, if any, additional post-remission therapy should be administered prior to allo-SCT?
3. Should patients who do not have an HLA-matched sibling be offered a transplant from a matched unrelated, a

genetically haploidentical donor or an unrelated umbilical cord?

4. Given the high procedural mortality, should such a procedure be preferably reserved for patients in second remission or at relapse?

Table 2 summarizes possible indication for allo-SCT in CR1. EORTC-GIMEMA is actually planning a prospective protocol where the post consolidation therapy is decided according to the biological risk assignment of AML patients. The risk of each patient is determined combining baseline parameters (cytogenetic/genetic) with determination of minimal residual disease.

Patients presenting with high-risk cytogenetic/genetic pattern (Complex cytogenetics (>1, ≥2 monosomies CN-AML with FLT3-ITD, MLL-PTD, ↑ BAALC and c-kit positive core binding factor AMLs) should be addressed to allogeneic transplant procedure or investigational therapy; in this group of patients the role of determination of minimal residual disease is meaningless.

Patients with low-risk (core binding factor without c-Kit mutations cytogenetically normal-AML with NPM1 mutated and FLT3-wt CBPA mutated) intermediate-risk (patients not fulfilling criteria for high- or low-risk assignment should receive standard chemotherapy and submitted to a MRD evaluation after induction and/or consolidation.

At this stage, patients who are MRD positive should be treated on the same strategy of high-risk patients, whereas those who gain a MRD negativity should receive additional consolidation, autologous or reduced intensity stem cell transplantation.

**Elderly patients**

Table 2 summarizes the larger cooperative clinical trials in elderly AML. The overall CR rate ranges between 49-59% with an induction death rate ~15-25% and a median disease free survival of 6-9 months. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON)/Swiss Group for Clinical Cancer research (SAKK) recently completed a study in older adults administering 45 mg/m$^2$ or 90 mg/m$^2$. The CR rate for patients receiving the 90 mg/m$^2$ dose was superior to that of patients receiving 45 mg/m$^2$, 64% versus 54%, respectively (P = .002), with a greater percentage of patients achieving remission after only one course of treatment, 52% versus 35%, respectively (P ≤ .001).

There were no significant safety issues in the high dose. Thus, based on historic trials and the most recent data, it appears probably fair to say that 45 mg/m$^2$ should no longer be considered as the standard of care. For induction therapy, also for older patients, the dose should be clearly higher, somewhere between 60 and 90 mg/m2 for 3 days, and the optimal dose has not been established.

Regarding older adults, the issues concerning post-remission therapy are even more fundamental. Unlike induction therapy, dose attenuation is critical when administering post-remission therapy to older patients.

The gastrointestinal and central nervous system toxicity from high-dose cytarabine is prohibitive at the standard doses given to young adults.

Furthermore, as opposed to younger adults, the benefit of any post-remission therapy has never been unequivocally established for older patients. It has never been shown that any form of post-remission therapy makes a difference; although in common practice, fit older adults almost always receive consolidation therapy.

What is also not known is the number of cycles that should be given. The largest study of older patients with AML was the MRC AML 11, which was published 8 years ago. Essentially this trial compared older patients who went into CR with induction therapy, got one course of consolidation with daunorubicin, cytarabine and 6-thioguanine (DAT) and were then randomized to 3 further cycles versus observation only.

The data demonstrated clearly that within the range of doses given in this study there was no particular value for further intensification

after a single course of consolidation therapy. Studies from other groups, such as the German AML Cooperative Group (AMLCG) or CALGB also suggested that there is no benefit to giving more than one cycle of intensive chemotherapy.

A possible exception may be for the relatively uncommon older patients with favorable cytogenetics, among whom 20% to 30% may be cured with maximally tolerated post-remission therapy. EORTC-GIMEMA is actively researching in this category of patients. AML-19 trial has been designed to compare GO monotherapy versus best supportive care for previously untreated AML in older patients not considered fit for intensive chemotherapy.

For elderly patients considered eligible for standard chemotherapy, Phase 1 study investigating the combination of RAD001 (mTOR inhibitor) with standard induction and consolidation therapy in older patients with AML will be explored with the objective to establish the feasible dose level of the mTOR inhibitor RAD001 in combination with standard induction chemotherapy based on the evaluation of safety.

For refractory-relapsed elderly patients with the purpose of determining the efficacy and toxicity of the combination Clofarabine+Temsirolimus (1 or 2 courses)

**Conclusions**

While there has been impressive progress in the treatment of AML, the majority of patients still die from this disease. Clearly, the major curative potential is while patients are in CR1; once in relapse, the options are very limited. Multiple studies have attempted to define the optimal strategies for post-remission therapy.

Nevertheless, much uncertainty and controversy persists, especially among patients with the intermediate cytogenetics.

This group comprises a heterogeneous population that only recently is becoming more clearly defined based on molecular prognostic groups.

The major areas of uncertainty relate to the type of post-remission therapy that should be offered. In our opinion, the combination of frontline parameters (genetics, cytogenetics) and parameters assessing the quality of remission (minimal residual disease) should be included in prospective treatment algorithms of AML patients, allowing a proper intensity of treatment to be delivered, avoiding over or under treatment.

**Table 1: indication for allogeneic transplantation in CR1**

1. t(9;22), deletion 7/7q-, monosomy 5 or del(5q),
2. alteration 3q26, complex Karyotype (≥3 abnormalities), FLT-3 - ITD.
3. CR1 achieved with >1 induction course.
4. Flow-Cytometry MRD ≥ $3.5x10^{-4}$ after consolidation therapy.
5. Secondary AML

**Table 2: selected clinical trials in elderly AML**

| Study | Year | Median age, y | CR, % | Overall survival, mo |
|---|---|---|---|---|
| ECOG 1490 | 1995[36] | 64 | 52 | 7.8 |
| CALGB 8293 | 1995[37] | 69 | 52 | 9.6 |
| SWOG 9031 | 1998[38] | 68 | 45 | 8.5 |
| HOVON AML 9 | 1998[17] | 68 | 42 | 9.5 |
| MRC AML 11 | 2001[12] | 66 | 55 | 10% - 5 yrs |
| CALGB 9720 | 2002[39] | 70 | 46 | 10 |
| SWOG 9333 | 2002[40] | 68 | 43 | 9 |
| ECOG 3993 | 2004[15] | 68 | 42 | 7.5 |
| AMLCG | 2009[41] | 66 | 59 | 16% - 4 yrs |

Induction death ~15%-25%
Disease-free survival ~6-9 months

# 5. Acute Myeloid Leukemia, a prospective study of 83 Tunisian patients

*Ramzi Ben Amor*[5]

**Objective:** The main objective of this study was to evaluate the therapeutic results in AML young patients treated according the national Tunisian protocol and to compare the prognostic to literature and suggest any changes to improve their issue.

**Patients and Methods:** In our prospective study, between January 2003 and December 2006, 83 de novo AML patients aged between 18 and 55 years were included (acute promyelocytic leukemia was excluded).

They were diagnosed and treated, according to the national protocol, in the Hematology Clinical Unit of AZIZA OTHMANA hospital.

**Results:** The median age of our patients was 41 years.

The karyotype was normal in 47.2 % of cases.

According to "the Medical Research Council cytogenetic risk group": 13.5% of patients were low-risk, 77% intermediate risk and only 9.5% were high risk.

The Complete induction-remission rate was 75.9%. Among clinical and biological parameters analyzed at diagnosis, only karyotype influenced the achievement of complete remission: 100 % in low risk group, 82.6% in intermediate risk group and 28.5 % in high risk group ($p = 0.006$).

Induction mortality was 16.8% caused by an infectious cause in 71% of the cases.

The 4-years overall survival was 48.6%.

The 4-Years relapse-free survival was 34.9%.

The global relapse rate was 41.2%.

Relapse-free survival at 18 months was 55% in intermediate risk, 0% in high risk and only 18.5% in low risk ($p = 0.05$).

Univariate study revealed that; age between 18-50 years ($p = 0.05$), myelo-peroxydase positivity ($p = 0.04$) and nonexistence of a HLA identical donor ($p = 0.03$) influenced favorably the overall survival.

Multivariate study revealed that mortality relative risk was 3.96 for patients older than 50 years.

**Conclusion:** We note that our results are approximating those reported in literature data (excluding the worse issue of our low risk group patients).

We also believe that these results could be improved by: increasing alloSCT number, a better supportive care and a better molecular follow up.

Finally, we have to re-consider the place of AutoSCT, as an alternative post induction therapy, because of the poor development and the limited indications of allograft in our country.

[5] Clinical Hematology Service, Aziza Othmana Hospital, Tunis, Tunisia

# 6. The Significant of Minimal Residual Disease in Acute Myeloid Leukemia

*Adriano Venditti*[6]

The current management of adult with acute myeloid leukemia (AML) is still largely based on the "one fits all" principle in designing either induction therapy, not significantly evolved from the standard 3+7 schedule, or post-remissional approaches whose choice often does not rely on a comprehensive biological risk stratification.

This has produced disappointing long-term results; in fact, in spite of complete remission rates of 50%-80%, roughly 40% of younger and less than 20% of elderly patients are cured of their disease. In recent years several evidences have been generated about the role of chromosome abnormalities in influencing

[6] Complex Operative Unit of Hematology, Policlinico Tor Vergata, Rome

remission achievement and long term outcome.

However, in particular biological subsets like cytogenetically normal and core binding factor AML, superior refinements of prognosis have been achieved by investigating specific gene mutations (FLT3, NPM1. CEBPA, KIT).

Even more recent observations have made clear that demonstration of an efficient disease eradication in specific phases of the treatment, may represent an important predictor of long term cure.

Accordingly, measurement of minimal residual disease after induction or consolidation course has become a reliable tool to stratify patients belonging to homogeneous cytogenetic/genetic subsets.

We will examine the evidences supporting the usefulness to incorporate in a common treatment algorithm, upfront biological data, such as cytogenetic and genetic profile, and those defining the quality of response, such as minimal residual disease.

Such a comprehensive approach would eventually allow risk-tailored induction and post remissional treatments to be adapted, avoiding situations of therapeutic under or overexposure.

# 7. Diagnosis, Monitoring and Treatment of Acute Promyelocytic Leukemia

*Giuseppe Avvisati*[7]

**Introduction:** Acute promyelocytic leukemia (APL) is a biologically and clinically distinct variant of AML.

APL was classified as AML-M3 in the older French-American-British (FAB) classification system and is currently classified as acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARA in the WHO classification system. APL represents a medical emergency with a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy.

It is critical to start treatment with a differentiation agent (e.g., all-trans retinoic acid) without delay as soon as the diagnosis is suspected based upon cytologic criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made.

**Diagnosis:** The diagnosis of APL is suspected by the characteristic morphology of the leukemic cells, immunophenotype, or the presence of severe coagulopathy. The leukemic cells are represented by atypical promyelocytes in the peripheral blood and bone marrow in which the cytoplasm is filled of granules.

One-quarter of patients will have a microgranular variant where the granules are not as pronounced. The immunophenotype of APL cells reveals a characteristic surface antigen profile with a strong positivity for CD33, expression of CD9 and CD13 , infrequent expression of CD34 and HLA-DR, and do not express CD7, CD11a and CD11b.

The diagnosis is then confirmed by the identification of the PML-RARa fusion gene or the associated chromosomal translocation.

This genetic confirmation serves to differentiate APL from other forms of acute leukemia.

A rapid diagnosis can be achieved by using an anti-PML monoclonal antibody on dry smears of bone marrow or peripheral blood, this technique is highly specific for presence of an underlyining PML-RARa fusion protein.

**Monitoring:** Molecular biology for PML-RARa fusion gene should be performed at diagnosis, at the end of the consolidation phase , every 2-3 months during the first two years of follow-up and every 3 months for additional 3 years.

After 5 years from the achievement of molecular Complete Remission (mCR)

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monitoring of the fusion gene will be performed only if clinically required . The goal of APL treatment is the achievement of a mCR as defined by the absence of the PML-RARa fusion transcript using RT-PCR methods.

Patients who have a positive RT-PCR test should have a second bone marrow aspirate and biopsy with RT-PCR testing repeated in two to four weeks. If this second test were negative, the patient may proceed to maintenance therapy. If the second RT-PCR were still positive, the patient should proceed to salvage treatment.

**Treatment:** ATRA plus daunorubicin (with or without Ara-C) or idarubicin is the standard of care as initial induction treatment of newly diagnosed APL. With such strategies, overall survival is excellent.

The Italian cooperative group GIMEMA prefers as initial induction treatment the combination ATRA plus idarubicin (well known in the world as the AIDA protocol).

However, the standard of care has begun to change with the introduction of ATO in the treatment of newly diagnosed patients.

**Conclusion:** During the past 2 decades, progress in biology and treatment of APL has contributed to the transformation of this once rapidly fatal disease into the most curable acute leukemia.

In the future, the development of risk-adapted strategies to minimize treatment related toxicities, together with the extension of these clinical results to less privileged countries remain the major challenges for improving the therapeutic results in APL.

# 8. ATRA plus Chemotherapy-based Treatment of Acute Promyelocytic Leukemia. Tunisian experience with two successive protocols APL93 and LPA99

*Ramzi Jeddi*[8]

**Background.** Before 1998 in Tunisia, acute promyelocytic leukemia (APL) was treated with standard AML « 3+7 » induction regimen combining daunorubicin and cytarabine.

In 1998, we started the ATRA era with two successive protocols, the European APL93 (1998-2004), based on the combination of ATRA, daunorubicin and cytarabine, and the Spanish PETHEMA LPA99 (from 2004), based on the combination of ATRA and anthracycline monochemotherapy with idarubicin.

We present here our experience with these protocols.

**Results.** Thirty four and 41 patients with genetically confirmed APL by t (15,17) or/and PML/RARA were treated respectively with the European APL93 and the Spanish PETHEMA LPA99 protocols.

Demographics and outcome are summarized in the table.

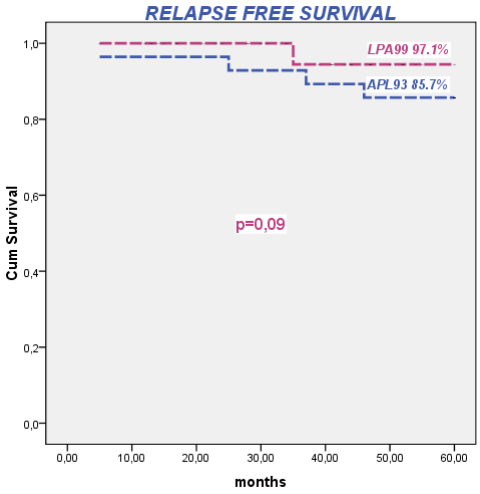
[8] Clinical Hematology Service, Aziza Othmana Hospital, Tunis, Tunisia

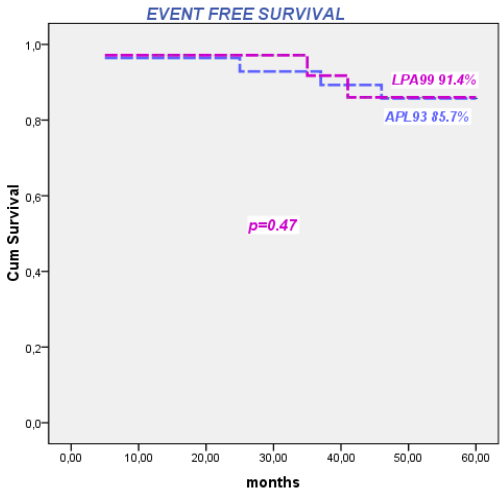
| | APL93, no. = 34 | LPA99, no. = 41 | p |
|---|---|---|---|
| Sex<br>- M, no.<br>- F, no. | 15<br>19 | 17<br>24 | 0.81 |
| Age, median (range) | 28 (6-60) | 26 (4-64) | 0.56 |
| Sanz's Score, no. (%)<br>- High<br>- Intermediate<br>- Low | <br>11 (15)<br>18 (53)<br>5 (32) | <br>16 (39)<br>24 (58.5)<br>1 | <br><br>0.13 |
| Complete remission rate | 82.4% | 85.4% | 0.72 |
| Induction mortality, no. (%)<br>- DS, no.<br>- Hemorrhage<br>- Infection<br>- Other | 6 (17.6)<br>2<br>2<br>1<br>1 | 6 (14.6)<br>3<br>3<br>-<br>- | 0.72 |
| Relapse, no. | 4 | 1 | |
| Relapse Free survival | 85.7% | 97.1% | 0.09 |
| Event Free survival | 85.7% | 91.4% | 0.47 |
| Overall survival (3 yr) | 76.5% | 82.5% | 0.55 |

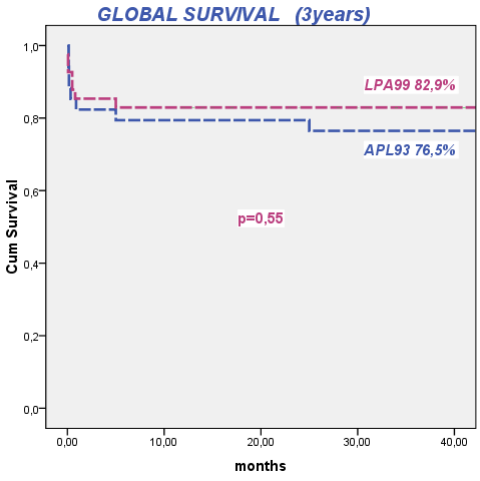
**Conclusion.** No cases of resistant disease were observed.

Death during induction was the only cause of failure. Mortality rate during induction was 18% and 14.6% in APL93 and LPA99 protocols, respectively.

Relapses occurred less frequently with the LPA 99 (2.8%) compared with the APL 93 (14.3%) (p=0.09) which translates to better OS with the LPA 99.



# 9. The burden of Hematological Malignancies other than Granular Acute Leukemia in Aziza Othmana Hospital

*Balkis Meddeb*[9]

Three hematology department in Tunisian Aziza Othmana hospital: 60% Tunisians hematology patients (adult and children ≥ 2yeras), Sousse center 15 % patients, Sfax center 25% patients and 1 center for bone marrow transplant (CNGMO).

**Haematology department Aziza Othmana hospital**

Sterile Unit: 12 Rooms (1 bed) 2 Rooms (1 bed), Conventional unit: 20 Rooms (37 beds), Day hospital: 15 beds, Hemophilia center: 242 (145 H, others 97).

No. of hospitalization: 2400/y, no. of consultation: 15.000/y.

**New cases per 2009**

- AML < 60 years: 55 pts (adults 40, children 15 pts), (no treatment after 60 years);

- ALL: 48 pts (26 children, 12 adults, 10 pts adolescents);

- CML: 20 pts;

- Myeloma: 25 pts;

- Hodgkin: 53 pts;

- Lymphoma: 51 pts;

- Bone marrow failure: 10 pts, MDS: 20, Thalassemias, Sickle cell disease, TPI.

**Regimens**

AML adult: MRC 10 AML children: ELAM02 (French);

AML 3: LPA 99 PETHEMA;

ALL: Adult: GRAALL 2005 (French), children EORTC 58951;

Myeloma: ≤ 65 years: Thal – Dexa - autotransplant + Dexa Thal;

CML: Imatinib as initial treatment, ATK 2d gen resistant patients.

**Stem cell transplantation (1998-2008 in CGMO)**

* 378 Allo: 35% acute leukemia (132pts): 49 AML 1st remission: 27 y (16-42y ) ;

11% after (3 cons), 58% after (2 cons), 31% after (1 cons);

Results: relapse (19 %), TRM (22,4%);

Probabilities at 10 years OS and EFS (46 ± 8%).

* 419 Auto graft.

# 10. Organization and Programmes of GIMEMA

*Marco Vignetti*[10]

The "**G**ruppo **I**taliano **M**alattie **EM**atologiche dell'**A**dulto" (**GIMEMA**) was founded, in 1982, by Franco Mandelli together with 8 Italian hematologists (Giuseppe Papa e Giuseppe Leone, Roma; Alberto Neri, R. Calabria; Bruno Rotoli, Napoli; Vincenzo Liso, Bari; Mario Carotenuto, S. G. Rotondo; Massimo Martelli, Perugia; Glauco Torlontano, Pescara), to develop, promote, conduct and coordinate multicenter clinical trials in acute leukemias in Italy.

Since then, nearly all Italian hematologic centres have become members of this Group, whose research activities have also extended to other adult diseases, in particular non neoplastic diseases such as anemias and thrombocytopenias.

In light of the growing responsibilities and projects managed by the GIMEMA, as well as the demanding needs of the emerging

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international rules for clinical trials, in 1998 the GIMEMA Foundation was formally established to coordinates all the GIMEMA research activities. The President of the Foundation is Franco Mandelli.

Nowadays there are more than 140 Centres collaborating with GIMEMA and listed on the Group website www.gimema.org.

Since 2005, the original GIMEMA has been extended with the aim to cover all the hematological diseases in adults. After the historical "Acute Leukemia" and "Infection Program" Groups, also Multiple Myeloma, Chronic Myelogenous Leukemia, Chronic Lymphoproliferative Diseases, Chronic Myeloproliferative Disease, Anemias and Thrombocytopenias working parties have been developed under the GIMEMA Foundation umbrella. Each Group is chaired by outstanding opinion leaders in their respective field of research.

In addition to the task of managing clinical trials, the GIMEMA also set up a network of Centers in Italy able to apply common diagnostic and treatment procedures. This allow patients to be treated in a homogeneous way according to state of the art therapeutic strategies in all Centres throughout the Country. Moreover, in acute leukemias GIMEMA has also set up a network of laboratories able to centralize and review the most advanced diagnostic and monitoring examinations – i.e.- cytogenetics, molecular biology, up to genetic studies on neoplastic cells.

Currently, GIMEMA is sponsoring 16 multicentric phase II and III protocols which include about one hundred centres. Eight new protocols are under completion and will be started during 2010.

The scientific and operative management of clinical trials are guaranteed by the GIMEMA Data Centre in Rome, according to a certified QA system and to European and national rules for clinical trials.

The Data Centre includes several units, according to all the required activities needed to project and realize a clinical trial at national and international level.

Statistics, project management, data management, investigational drug management and safety, both with regulatory issues for the management of all legal procedures needed to finalize contracts with companies, investigators, other cooperative groups, and information technology are all fields covered by the personnel of the Data Centre.

Each Italian GIMEMA investigator can apply for a new trial to the Data Centre. The application is evaluated by the competent working party board and, if approved, the Data Centre starts to support the investigator in writing the protocol and for all the needed activities – CRF, contracts, insurance, database and so on.

In the last ten years, this organization permitted also to academic investigators to perform clinical trials at national and international levels with same efficiency and quality of those performed by large multinational industries, also cooperating with them in evaluating new drugs and new indications for already registered drugs.

# Annex

**Rapporteurs**

*William Arcese*, Département Biopathologie et Diagnostique pour Images, Université Tor Vergata, Rome

*Giuseppe Avvisati*, Département Hématologie, Université Campus Bio-Medico, Rome

*Meddeb Balkis*, Président de la Société Tunisienne d'Hématologie, et Chef de Service d'Hématologie Clinique de l'Hôpital Aziza Othmana Tunis

*Ramzi Ben Amor*, Service d'Hématologie Clinique de l'Hôpital Aziza Othmana Tunis

*Francesco Buccisano*, Unité Opératif Complexe Hématologie, Policlinico Tor Vergata, Rome

*Emna Gouider*, Laboratoire d'Hématologie Biologique Hôpital Aziza Othmana Tunis

*Ramzi Jeddi*, Service d'Hématologie Clinique de l'Hôpital Aziza Othmana Tunis

*Francesco Lo Coco*, Responsable du Laboratoire de Onco-hématologie, Policlinico Tor Vergata, Rome

*Pietro Malara*, Directeur Bureau V, Direction Générale pour les Affaires Communautaires et Internationales, Ministère de la Santé, Rome

*Adriano Venditti*, Unité Opératif Complexe Hématologie, Policlinico Tor Vergata, Rome

*Marco Vignetti*, Département Biotechnologie Cellulaire et Hématologie, Université La Sapienza, Rome

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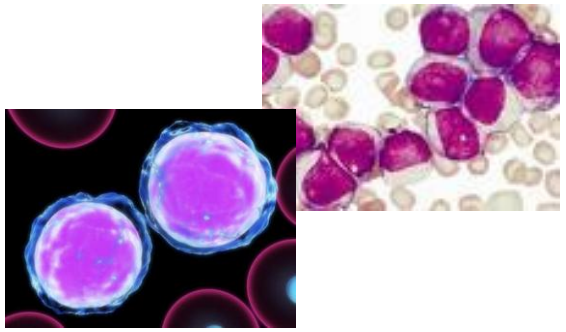
*Hôpital Aziza Othmana*



# Workshop Italo-Tunisien sur le Diagnostic et la Thérapie de la Leucémie Aiguë Myéloïde

**Rome, 15 Janvier 2010**

**Ministère de la Santé**
**Salle « Niglio »**

**15 Janvier 2010**

12.45 Registration

*Buffet*

13.30 Mots de bienvenue

13.45 Introduction sur le partenariat pour la santé entre Tunisie et Italie

**Session de travail : Le diagnostic et la thérapie des leucémies aiguës (LA) myéloïdes**
*Chairmen: Balkis Meddeb (Tunisie), William Arcese (Italie)*

14.00 Diagnose Moléculaire, Cytogénique et Phénotypique des LA myéloïdes
*F. Lo Coco*

14.20 Apport de la cytométrie en flux dans le diagnostic des LA granuleuses
*E. Gouider*

14.40 Actualité international sur les essais cliniques dans les LA myéloïdes
*F. Buccisano*

15.00 Résultats thérapeutiques des LA granuleuses
*R. Ben Amor*

15.20 L'importance de la maladie résiduelle dans les LAM
*A. Venditti*

*Coffee break*

16.10 Le diagnostic, le suivi et le traitement de la leucémie aiguë promyélocytaire
*G. Avvisati*

16.30 Résultats thérapeutiques des LA promyélocytaires
*R. Jeddi*

16.50 Prise en charge des hémopathies malignes autres que les LA granuleuses à l'HAO
*B. Meddeb*

17.10 Organisation et programmes du GIMEMA

**Session plénière**

17.30 Table Ronde: le plan de collaboration sur les LAM entre Tunisie et Italie

18.30 Remarques conclusives et clôture du Workshop