PLENARY SESSION VI
MANAGEMENT OF APL IN DEVELOPING COUNTRIES

EPIDEMIOLOGICAL OBSERVATIONS ON A SPECIFIC MOLECULARLY-DEFINED SUBTYPE OF ACUTE MYELOID LEUKEMIA

Douer D

Division of Hematology, University of Southern California Keck School of Medicine Los Angeles California, USA

Despite the fact that acute myelogenous leukemia (AML) is a heterogeneous disorder almost all descriptive epidemiological studies consider AML as a single entity.[1,2] Large tumor registries such as U.S. NCI Surveillance Epidemiology and End Results (SEER) Program use the ICD-0 coding system that until recently are based on the FAB classification; FAB subgroup (with very few exceptions) are not homogenous biological entities. As a consequence, information on specific homogenous subtypes is very limited and etiological clues of homogenous AML subsets are likely to have been masked by studying AML as a whole. Characterization of AML patients by specific chromosomal aberrations divides the subgroups into true homogenous entities. Further, the different chromosomal abnormalities result in specific gene rearrangements that are often involved in the etiology and the pathogenesis of the disease.[3]

The specific chromosomal abnormality of APL allows us to study the epidemiology of a homogeneous AML subtype, and the distinct PML-RARα molecular abnormality, may enable us to better decipher its etiologies causes. Further, APL or FAB M3 is fairly easy to recognize by morphology criteria with minimal error and therefore the translocation t(15:17) can be identified in most patients without actually performing a cytogenetic analysis. Thus large databases of AML can be used to study the epidemiology of APL and circumventing the lack of cytogenetic information. Since 1972, APL has been coded in SEER registries separately and distinctly from all other AML cases, by the morphological features of the leukemia cells. Another source of gathering epidemiological information in APL and comparing it to non APL is databases of large clinical trials although they could be biased by patient selection and differences in the eligibility, for example age limitation and inclusion of de novo AML only.

Incidence and secular trends

Approximately 11,000 new cases of AML are diagnosed in annually U.S. The overall incidence of AML in the U.S. is 2.7 per 100,000 populations. It increases with age and at age 55-60 the incidence the increase is exponentially, the disease changes its biology and becomes less responsive to treatment.[4] This could imply a change in etiology at this age. Several large studies in USA and Europe with a total of 4639 AML patients demonstrated than that 500 patients (10.8%, range 5-13%) had APL.[5-11] Similarly, among a total of 3229 AML cases registered in all Italian GIEMEMA clinical trials conducted in adults between 1992 and 1997, 335 patients were classified as APL (10.4%).[12] Thus, one would estimate approximately 1,000 new case of APL per year in the U.S. We used the Cancer Surveillance Program (CSF) of the Los Angeles County which is a SEER database to perform a population-based epidemiological survey of APL.[14,15] Between 1972 through 1995 the CSP collected data on all 6108 cases of AML in Los Angeles County, which included 256 cases (4.2%) diagnosed as APL. The year-specific age-adjusted incidence rates (AAIR) showed no change in the overall incidence rates of AML or AML after exclusion of APL since 1972. In contrast, a hike in the AAIR of APL was observed in late 1970s. It was felt that this change in secular trend occurring around the year 1980, is artificially due to more accurate distinction of APL from other AML subtypes and recognizing the hypogranular M3 variant (M3V). Therefore our population-based analyses in Los Angeles County were confided to patients diagnosed on 1980 or later. During 1980-1995 no change in the incidence of APL was seen in Los Angeles County. The average AAIR for all APL cases was 1.7 per 1 million males and 1.5 per 1 million females in this population and the frequency of APL would be approximately 5% of all AML cases. A case-control study on APL was carried out in patients seen in three large hematology centers in Italy, and reported an annual incidence of APL of approximately 0.6 cases per 1 million people. However, this study included only patients who were 15 years or older.[13]

Gender

Throughout the world, registries report a higher incidence of AML in males than in females.[14] Similarly the Los Angeles CSF reported for non-APL AML, a higher AAIR male to female ratio (1.5:1). In contrast the AAIR of APL for females and for males was equal (ratio 1:1). Two reports from Italy - the GIEMEMA Group data[16] and the case control study [13] - also showed no such difference between males and females.

Age

In the Los Angeles CSF the incidence rates of APL increased until age 20, and remained relatively stable after then. An analysis from four British Regional Leukemia Registries confirmed this observation of a relatively low incidence rate of APL in childhood and then constant rate over the rest of the life span.[17] A similar age distribution was shown in a retrospective analysis of 256 APL patients diagnosed in 1980-1988 in the Italian GIEMEMA study group [16]. This stable age distribution in APL is in contrast to the well known increase in the incidence rates of non-APL AML with age that is seen the Los Angeles CSF, other SEER databases and other registries.[4,14] The increase rate with age of AML, is believed to result from the multi-step process of accumulation of mutations during a life long exposure to environmental leukemogenic causes.[18] In contrast, the relatively constant incidence of APL with age, could imply that less genetic mutations are required, suggesting different etiology of APL than other AML subtypes.

Ethnicity

In the mid 1990s, our group noticed a high frequency of APL cases among Latino patients with AML diagnosed in Los Angeles County (LAC) - USC Medical Centre in Los Angeles.[19] Of 80 cases of AML among patients originating in Latin America countries, 37.5% had the APL subtype as opposed to only 6.5% of 62 all other non-Latino patients with AML.[20] In a selected sample of well characterized AML patients from the county of Los Angeles, 24.3% of Latino patients had APL compared to 8.3% of non-Latinos.[20]This observation was subsequently confirmed by a report from Lima Peru (22%).[21], in Mexican Mestizo patients in Puebla (20%),[22] among Children in Mexico City (21%)[23] and Texas.[24] "Latinos" are not a single racial or ethnic group and could be defined in different ways. In our large population-based survey of the Los Angeles CSF database of the entire AML population of the County we found that the proportion of APL in Latinos with AML was 9.1% compared to 4.2% for non Latinos.[14] Ruiz-Arguelles[22] suggested that Latino populations are people speaking the Spanish language. Our definition of *Latinos* is a geographic one that includes people who originated in Latin America (Mexico, Central or South America).

In a population-based study in Mexico City the AAIR of APL in children younger than 15 years was 2.21 cases per 1 million children compared to a lower rate (0.2- 0.9 cases per 1 million) among non Latino APL children in Los Angeles county.[23] Another ethnic difference between APL and other subtypes of AML was found in children. In Italy, a single institute in the north,[25] and the Pediatric Hematology Oncology Group,[26] reported a high frequency (17%-30%) of APL among children with AML, while the proportion of APL in large pediatric AML studies from Germany [26] and the United states[25, 27-29] has been low (3.8%-8.7%).

The reason for the high frequency of APL is Latinos is unclear and could be explained by environmental factors or genetic predisposion. We reported that the APL specific PML-RARα gene rearrangement and specific breakpoint region (bcr subtypes) in the PML gene is different in Latinos and non-Latinos. The percentage of bcr1 patients has consistently been reported as 50%-55% in several large studies, which include patients from Europe (including Spain) [30-33] and from non-Latinos in the USA.[33] In contrast, we found a statistically significant higher rate (75%) of the bcr1 subtype among APL patients originating in Latin America compared to rate published in Europe and non-Latinos in USA.[33] This was found independently in two groups of APL patients from Latin America: one group diagnosed in the Los Angeles area, and the other group diagnosed in Lima, Peru. This finding was confirmed in Mexican Mestizo patients with 63% brc1 cases.[34] Thus, the overrepresentation of APL among Latin American patients with AML may be accounted for by an increase in a single isoform, bcr1, rather than an equal increase in all three bcr isoforms. For unknown reasons, APL patients from Latin America may have a predilection for a break at intron 6 in the PML gene. Since the PML-RARα fusion protein gene is involved in the pathogenesis of APL[35] the particular breakpoint site of the PML gene (for example in intron 6 in Latinos) might be associated with an etiology that may be determined genetically [33].

The two populations in our study and study from Mexico share a high frequency of *Mestizos*, meaning different degrees of genetic mixture of Caucasian and Indian races. Because these patients originated from places, which are far apart in the American Continent, it is suggest that the higher rate of bcr1 might be genetic than environmental. In Peru, as in several other Latin American countries, the population is composed of pure Indians, pure Europeans and mostly Mestizos. Because of the different distribution of the bcr subtypes between Europe (including Spain) and Latin America, we suggest a hypothesis that the higher rate of bcr1 APL subtype in Latin American patients might be related to a non-European genetic factor, possibly originating in Native Americans, in the ethnically mixed Latin American genetic pool. Interestingly, in a small cohort of Chinese APL patients and in a Japanese group[36,37] the bcr1 rates were the closer to Latin American patients in Los Angeles, Peru and Mexico. One could speculate that a non-European genetic factor might have migrated from the East Asia through the Behring Straits into America approximately 12,000 years ago.[33]

Etiological Factors

Although several etiologies have been considered, in most case the cause of AML in general and APL in particular is unknown. Very little has been studied or published on the possible etiologies of APL. Two reports from china have shown than exposure to bimolane – a drug used there to treat psoriasis – can be associated with development of APL.[38,39]AML but not APL was found to be associated with smoking in.[40,41] Possibly toxins present in tobacco may not play a role be in the pathogenesis of APL as in other types of AML, again implying different etiologies. A. The case control Italian study [13], suggested a possible selective role for certain environmental and/or occupational factors in APL development. Because of the small number of APL patients we could not identify in the CSP database of the Los Angeles County any high-risk groups. Therapy Related APL: The most common known etiology of AML is prior treatment with chemotherapy and or radiotherapy that accounts for 10-20% of all AML cases. The Italian GIEMEMA Group [42] and French study[43] have shown that approximately 5% of APL cases occur as a second tumor. Interestingly, In the GIEMEMA population only 37 of 51 APL patients could be labeled as *therapy-related*since 27% of them were treated for the primary tumor with surgery alone, without chemotherapy or radiotherapy. More recently the European APL group reported that therapy-related APL (t-APL) accounted for 22% of all cases and its incidence is rising in last decade.[44] The hematological characteristics and response to treatment in t-APL, are not different from de-novo APL

t-APL is more prevalent in females, approximately 70% of the patient[42,44] which is higher than the 50% rate of de novo APL. The most common primary tumor is breast cancer. It is difficult to determine the pathogenetic role of each of the previous treatments since it included various combination of chemotherapy, radiotherapy and in some cases surgery. However, in recent studies from Europe it appears that topoisomerase II inhibitors such as anthracyclines and etoposide, in particular prior mitoxantrone are the most common antecedent drugs.[44,45] This may explain why breast cancer which is often treated in Europe with mitoxantrone is the most common primary in the European studies. It is intriguing that in non APL AML the male/female ratio is high, compared to the lower ratio (1:1) in APL,[13,14,16] and very low in t-APL. One can also speculate that it is possible that certain etiological factor(s) exist in females that predispose them to develop APL, which are influenced by prior treatment or cancer.

Molecular Biology

Cases of t-APL provide us with a unique opportunity to investigate potential etiological factors in relationship to specific changes in the rearranged PML-RARα gene and the pathogenesis of the disease. It is suggested that topoisomerase II inhibitors may cause leukemia that are characterized by balanced chromosomal translocation-such as t(15;17)-by increasing the chance of illegitimate joints between two non homologous chromosomes.[46] A recent study showed that that in mitoxantrone-related APL the breakpoints in intron 6 of the PML gene were clustered in a short 8 bp while the breakpoints in other t-APL and de novo APL were more dispersed in the intron. The specific region of PML was a particular *hot spot* for mitoxantrone- induced topoisomerase II cleavage.[45,46] This finding might have broader implication in understanding the epidemiology of APL. For example, in Latinos APL with a high frequency of bcr 1 subtype, the genomic breakpoint of intron 6 may be clustered in a specific region that is diffent from that of bcr 1 APL in Europeans. Such finding could suggest a genetic predilection of this population for DNA breakage in specific sites. An example for environmental exposure is the report that maternal exposure in-uteri to natural topoisomerase II inhibitors especially dietary flavonoids, is associated with increase risk of infantile leukemia.[47]

Summary

APL, with its unique and well-defined chromosomal aberration and PML-RARα gene rearrangement, provides an excellent model to study a homogenous subtype of AML.

APL has distinct epidemiological characteristics, namely a relative constant incidence with age, equal incidence in males and females, and higher frequency among patients originating in Mexico, Central and South America. Future molecular biology investigations should explore the relationship between epidemiological observation and the specific PML-RARα gene rearrangement. Eventually we would be able to find possible etiological factors in the pathogenesis APL. Finally, studying the epidemiology of APL could serve as a model for studying and better understating the etiology of other AML subtypes that express different specific chromosomal aberrations and are currently being identifying and documented by the several large cancer registries

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INTERNATIONAL CONSORTIUM FOR THE CLINICAL MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA: A PILOT PROJECT

Lowenberg B

Dept of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

In acute promyelocytic leukemia (APL) a high cure rate can be obtained when the disease is properly diagnosed and treated. Lack of infrastructure and funding has prohibited clinical studies of APL in less privileged countries. In these countries a relatively high frequency, up to 20-25%, of APL is noted among acute myeloid leukemia (AML) patients, most notably in Latin-American Mestizo. To facilitate clinical networks for APL in these countries the American Society of Hematology (ASH) has taken the initiative to foster a collaboration among interested research investigators from Brazil, Jordan, and Mexico and APL experts from the US, Europe, and Asia. During a December 1-2, 2004 workshop in San Diego, USA, the International Consortium on APL was organized (IC-APL).

Purpose

The goal of the IC-APL network is multifold: (a) to initiate clinical collaboration, (b) to improve the care and survival of patients with APL in the participating countries, (c) to foster clinical and laboratory research in APL, and (d) to promote drug availability where such are typically not.

Once successfully established, this collaborative model can be extended to other countries and potentially include other diseases as well.

Plan

Experts on APL from the US, Europe, South and Central America, and Asia are actively participating in this endeavour. The work of the IC-APL is primarily done through five subcommittees: Protocol, Add-on Studies, Web Registration & Auditing, Funding, and Drug Availability. A collaborative international cooperative treatment protocol for APL has been drafted for patients treated at 12 international sites in three countries: Brazil (7), Jordan (1) and Mexico (4). The St Jude Children's Hospital International Outreach Program provides active support with respect to funding, web registration, and data management. In fall of 2005, the treatment protocol will be finalized and presented for ethical approval; Web registration training will be completed; an add-on studies manual will be written to include information on addressing coagulation issues, molecular diagnosis, biobanking DNA, RNA and plasma; all Web-based forms will be created and prepared for use; and funding will be acquired.

In early December, prior to the ASH annual meeting, the IC-APL will meet to finalize the preparative process for patient enrollment to begin in March 2006 and to develop a plan to consider engaging other partners.

This initiative may serve as a paradigm for establishing clinical collaboration and stimulating hematological research around the world.

INTERNATIONAL NETWORKING STRATEGIES FOR THE MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA IN DEVELOPING COUNTRIES

Ribeiro RC, Razzouk B

From the Department of Hematology-Oncology and the International Outreach Program, St. Jude Children's Research Hospital; the Department of Pediatrics, University of Tennessee College of Medicine, Memphis, Tennessee, USA

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Since 1994, St. Jude Children's Research Hospital, through its International Outreach Program (St. Jude IOP), has partnered with public hospitals in developing countries to improve the cure rates for children with cancer.[1] The focus of this program has been to create local capacity for the proper diagnosis and treatment of childhood malignancies through training and education of health care providers and the transfer of technology. This program is a modification of the *twinning program* conceived by Massera *et al.*[2] When a partnership is established between St. Jude IOP and a public hospital in a developing country, the first step is to facilitate the creation of pediatric cancer units (PCUs) by developing a critical mass of specialized health care providers.[3] To complement the medical services delivered by the pediatric cancer units, it is essential to establish a private non-governmental foundation dedicated to providing psychosocial and economic support for children with cancer and their parents.[4] These foundations provide domiciliary care for families that must relocate from their homes for the duration of treatment and economic support that allows the hospitals to purchase diagnostic services and antineoplastic and antimicrobial drugs. In addition, foundation members advocate for the rights of children with cancer and establish public campaigns to educate communities about the unique characteristics of pediatric malignancies.

The results of these partnerships have been outstanding. The cure rates of children with acute lymphoblastic leukemia (ALL), Burkitt lymphoma (BL), and other chemotherapy-sensitive malignancies have soared in the partner countries.[5] For children with ALL, the complications of intensive therapy can be relatively well managed in the PCU, even where hospital infrastructure is not optimal. Overall survival rate in these locales has reached 65%. About 15% to 20% of failures are due to infection. In some countries, abandonment of therapy is still a major problem, particularly in countries with high levels of poverty; anywhere from 1% to 20% of children who achieve complete remission may fail to complete treatment.

Management of childhood acute myeloid leukemia (AML) has been difficult at St. Jude IOP partner sites.[6] The long-

Table. Selected clinical and laboratory features and descriptive outcome measures for 121 children with promyelocytic leukemia.

Features	Culiacan	Guatemala City	Managua	Recife	San Salvador	San Jose	Tegucigalpa
Period	1989-2004	2000-2005	1995-2004	1997-2004	1998-2004	1996-2005	1998-2004
Number of patients	10	16	36	21	14	12	12
Age, years median (range)	6.8 (11.1-16.0)	8 (2.0-16.0)	9 (2.7-16.4)	11.4 (0.1-16.2)	7.7 (0.8-17.7)	7 (1.7-11.9)	10.2 (2.6-16.1)
Sex (M/F)	7 / 3	8 / 8	18 / 18	13 / 8	10 / 4	4 / 8	7 / 5
% AML	17.2	22.0	28.5	16.6	13.6	15.2	15.9
WBC x 10^9/L, median (range)	45.6 (1.3-189.0)	8.5 (1.1-143.0)	10.0 (0.1-100.1)	17.7 (1.1-121.3)	11.9 (1.5-165.9)	19.2 (0.8-124.0)	17.7 (0.5-279.6)
Platelets x 10^9/L, median (range)	56.3 (22.0-100.0)	30.0 (7.5-180.0)	21.0 (1.3-54.0)	18.0 (6.0-157.3)	15.5 (1.3-143.4)	32.5 (7.0-91.0)	28.1 (4.0-160.0)
DIC (%)	5 (50.0)	7 (43.7)	8 (22.2)	4 (19.0)	6 (42.8)	4 (33.3)	6 (50.0)
CRR (%)	6 (60.0)	7 (43.7)	20 (55.5)	16 (76.1)	7 (50.0)	8 (66.6)	5 (41.6)
Early Death (%)	1 (10.0)	8 (50.0)	6 (16.6)	3 (14.2)	4 (28.5)	2 (16.6)	4 (33.3)
Abandonment/ refusal (%)	2 (20.0)	1 (6.2)	4 (11.1)	2 (9.5)	1 (7.2)	0	5 (41.6)
Relapse (%)	2 (20.0)	1 (6.2)	14 (38.8)	5 (23.8)	2 (14.2)	4 (33.3)	0
Other failures (%)	1 (10.0)	1 (6.25)	6 (16.6)	2 (9.5)	1 (8.3)	2 (16.6)	2 (16.6)
Alive (%)	4 (40.0)	6 (37.5)	6 (16.6)	9 (42.8)	6 (42.8)	6 (50.0)	1 (8.3)

Abbreviations: AML, acute myeloid leukemia; WBC, white blood cell; DIC, disseminated intravascular coagulopathy; CRR, complete remission rate.Values shown are median (range).

term survival of children with AML is only around 25% in these countries. Management of AML in children is complex even in industrialized countries and requires easy access to intensive care, timely availability of blood products, and a broad range of antibiotic and antifungal agents. Moreover, effective therapy for AML results in prolonged bone marrow aplasia and a wide variety of infectious complications. Therefore, the majority of our partner sites have been unable to treat pediatric AML adequately.

The introduction of all-*trans* retinoic acid (ATRA) for the management of acute promyelocytic leukemia (APL) has been a major landmark in the treatment of this disease. The high rates of complete remission and long-term disease-free survival associated with the introduction of ATRA raised the expectation that, at least in this subtype of AML, patients treated in developing countries would be among those who would benefit most. There was hope that the frequency of early mortality associated with disseminated intravascular coagulation (DIC)-a common problem in newly diagnosed APL-would be reduced. However, it is uncertain whether the introduction of ATRA has improved the overall survival of children with APL in developing countries as it has done in North America and Europe. In developing countries, the supply of ATRA has been irregular, and its therapeutic benefit may not be appreciated, as many children die of hemorrhage within a few hours of admission. To determine the impact of modern treatment, including ATRA, on the clinical features and outcome of childhood APL, seven sites in countries with limited resources were surveyed. Six of these sites (in San Jose, Costa Rica; San Salvador, El Salvador; Guatemala City, Guatemala; Tegucigalpa, Honduras; Recife, Brazil; and Culiacan, Mexico) have been St. Jude IOP partners for more than 5 years; the remaining site (Manuel de Jaesus Rivera Hospital, La Mascota, Managua, Nicaragua) has had a twinning program with Monza (Giuseppe Masera, Mario Negri Institute for Pharmacological Research, Milan, Italy) for more than a decade. The entry criteria were morphological/cytochemical diagnosis of APL, age less than 18 years at diagnosis, and admission to the PCU between January 1995 and June 2005.

The table lists selected clinical and laboratory features and descriptive outcome measures of 121 children with APL who were admitted to PCUs in the seven regions with limited resources. ATRA was used in the management of most of these cases, except in Culiacan, where 9 of the 10 patients received intensive chemotherapy without ATRA. The median age of the children with APL in the seven PCUs was 9 years (range, 0.1 to 17.7 years). There was a slight predominance of boys (M:F ratio, 1.2). APL represented 13.6% (in San Salvador) to 28.5% (in Managua) of cases of childhood AML (median, 16.6%). The median white blood cell count at diagnosis varied from 8.5×10^9/L to 45.6×10^9/L, and the median platelet count from 15.5×10^9/L to 56.3×10^9/L. The frequency of laboratory evidence of DIC varied from 19.0% in Recife, Brazil to 50.0% in Tegucigalpa, Honduras. Death within 14 days of diagnosis (early death) was observed in 28 (23.1%) cases. Rates of complete remission (CR) ranged from 76.1% in Recife to 41.6 % in Tegucigalpa. Relapse was observed in 29 of the 69 patients who entered remission (42.0%). Death due to infectious complications was observed in 11 children. Abandonment or refusal of treatment was documented in 15 cases. At the time of this report only 37 of 122 (30.3%) children with APL remained alive in first remission. An additional two children treated in San Jose survived in second remission. One child from Guatemala City is receiving palliative care after relapsed APL. These findings suggest that the outcome of children with APL continues to be very poor in developing countries. Although most of these children received ATRA during remission induction, the CR rates are much lower than the

90% overall rate of CR obtained in developed countries. The main cause of failure during the remission induction phase was death due to bleeding. Early mortality continues to be very high, even in places such as Recife, where the CR rates for ALL and BL exceed 90%. It is possible that the delay between diagnosis and the start of ATRA therapy partially accounts for the low CR rates. In some of the PCUs, ATRA is not stocked by the hospital pharmacy and there is a delay between diagnosis and the start of treatment. Moreover, because childhood APL is less common than other leukemias, health care providers in many of these centers may lack expertise in diagnosing it and in anticipating the complex clinical problems that may occur. Early mortality may be reduced by treating childhood APL as a medical emergency, initiating ATRA as soon as the diagnosis is suspected, administering platelet transfusion prophylactically, and treating ATRA syndrome at the prodromal stage. In addition, establishment of a focus APL study group among partner sites to discuss all new patients in real time with an expert in APL may help to increase the collective experience and reduce early mortality. Inexpensive computer-based technologies that support communication among clinical investigators are readily available. IOP clinicians at St. Jude have used the web site *www.cure4kids.org* as a platform for live meetings to discuss cases with partners and offer suggestions on clinical care. As the initial management issues are addressed, relapse of APL is expected to become an important cause of failure. For example, in San Jose, which has had the lowest rate of early mortality, relapse accounted for 38% of all failures. Intensified therapy for selected children at high risk of relapse may increase overall survival, but it will require further improvement of hospital infrastructure for supportive care and diagnostics.[8]

In summary, the availability of ATRA and the knowledge and skills required to treat APL have not been fully transferred from developed countries to many developing Latin countries, where the incidence of APL is high. Improving cure rates in these regions will require access to drugs, improved supportive care, and the broad participation of clinicians from different parts of the world. The American Society of Hematology has started a focus group composed of experts in APL and primary care providers in developing countries to improve the survival of patients with APL. Treatment guidelines were collaboratively developed by the participants, taking into account the resources of the different countries. The hope is that this project will identify and resolve the main obstacles to the transfer of effective curative therapy to countries with limited resources.

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DEVELOPMENT OF THE IC-APL PROJECT IN BRAZIL

Rego EM

Medical School of Ribeirão Preto University of São Paulo, Brazil

Acute Promyelocytic Leukemia (APL) is a distinct subtype of Acute Myelogenous Leukemia (AML) genetically characterized by chromosomal translocations involving the *Retinoic Acid Receptor* α locus on chromosome 17.[1-3] In the vast majority of APL cases, the t(15;17) is detected, leading to the fusion of RARα with the Promyelocytic Leukemia (PML) gene localized on chromosome 15.[4] On the epidemiological point of view, APL is also distinct from other AML subtypes for its higher incidence in individuals older than 20 years, equal incidence in males and females and higher frequency among patients originating in Latin America.[5] In addition, studies analyzing APL patients mainly from México and Central America countries showed that there is a relative excess of PML breakpoint region of the subtype one (bcr1) among Latinos.[6] Brazil has a peculiar ethnic distribution and previous studies of the frequency some markers suggested that genetic background of the Brazilian population is distinct from other South American countries, moreover it varies according to the region of the country (e.g. northeastern and southern states).[7-9] Unfortunately, there is a lack of epidemiological studies on acute leukemia incidence in Brazil, and the available data from the National Registry is hampered by inaccuracy of the classification system, by which acute lymphoid and myeloid leukemias were computed together. Nevertheless, the frequency of APL relative to other AML subtypes is increased in Brazil compared to developed countries, ranging from 7,8% to 24%, with most figures above 12%.[10-12] Another interesting peculiarity is the increased frequency of APL in Brazilian children. Mendes et al. analyzed 45 children with AML genetically characterized by the Brazilian Group for Infant Acute Leukemias Studies and detected five (11%) with t(15;17).[13] Nevertheless the frequency of APL variant translocations is similar to that reported in Europe, our group detected only two cases with t(11;17)/PLZF/RARα among 73 APL patients, and none with t(5;17)/NPM/RARα; t(11;17)/NuMA/RARα nor t(17;17) /STAT5b/RARα.[14,5] On the other hand, Chauffaille et al. described a higher incidence of additional cytogenetic abnormalities in Brazilian patients. In order to better characterize APL in Brazil and determine the feasibility of a multicenter clinical trial, we conducted a survey in seven University Hospitals localized in five Brazilian states from the Northeastern (1), Southeastern (3) and Southern (2) regions of the country. Between September 2002 and September 2004 667 consecutive AML cases were diagnosed, of which 143 (21.4%) cases were classified as APL with genetic confirmation by RT-PCR or FISH. All patients were treated with ATRA associated with chemotherapy, but the choice of anthracyclines varied, in part due to unavailability of idarubicin in all hospitals. Ninety-two of the 143 patients with APL were treated with PETHEMA 96 or AIDA regimens, and 21 (22.8%) died within the first seven days of treatment, mainly due to hemorrhagic events. Therefore, it was possible to estimate that between 40 to 70 APL patients per year could be enrolled

in a multicentric study, but many of them may present overt disseminated intravascular coagulation (DIC) when first evaluated by a hematologist. To foster the formation of clinical networks on APL in developing countries, the American Society of Hematology through its International Members Committee (IMC) sponsored the creation of the International Consortium on APL (IC-APL) gathering centers from Brazil (n=7), Mexico (n=4) and Jordan (n=1). As the host committee, the IMC is catalyzing the process of conceiving, planning and establishing the initial infrastructure necessary for the clinical network. As a result of this endeavor the IC-APL 2006 protocol was created and the first patients are expected to be enrolled in March 2006. The IC-APL 2006 protocol is an adapted version of the PETHEMA/HOVON LPA2005 protocol, in which idarubicin for induction and consolidation therapy has been substituted by daunorubicin (equivalence, DNR 5 mg equal to IDA 1 mg). This study is chaired by Dr. Miguel Sanz and incorporated the risk criteria described by the PETHEMA group.[16] The schema of the IC-APL 2006 protocol is shown in Figure 1.

Figure 1..

An important obstacle to development of clinical networks in Brazil (and in developing countries in general) is the lack of trained data managers and experienced statisticians. The St Jude Children's Research Hospital through its International Outreach Program is collaborating with the IC-APL project by providing and customizing a software written and in use by St Jude's staff to IC-APL protocol data collection and analysis. It will also offer initial data manager training through workshops to be held in Mexico, Brazil and at St. Jude for the Jordan data manager. Finally, Dr Haesook Kim from Dana-Farber Cancer Institute is collaborating with the project by coordinating the statistical analysis. Despite the fact that the IC-APL Protocol will begin enrolling patients in March 2006, the acquired experience in the build up of an International Clinical Network focused on developing countries has been most rewarding. It is foreseen that once the initial experience in these three countries is successfully established, the IC-APL project may be extended to other interested countries and also be applied to other selected hematological diseases. The IC-APL Protocol Chairman is Dr Miguel Sanz (Spain); the Add-on studies subcommittee is chaired by Dr Francesco Lo-Coco (Italy); the Web Registration and Auditing subcommittee by Dr Raul Ribeiro (USA) and the Funding subcommittee by Dr Martin Tallman (USA); the National Coordinators are: Eduardo Rego (Brazil), Huda Salman (Jordan) and Guilhermo Ruiz-Arguelles (Mexico). The IC-APL centers in Brazil are: HEMOPE (Raul Melo/Fernanda Souto), Federal University of Minas Gerais (Evandro Fagundes/Henrique Bittencourt), Federal University of São Paulo (Maria de Lourdes Chauffaille), Santa Casa de São Paulo (Claudia Bortolheiro), Federal University of Paraná (Ricardo Pasquini / Rodrigo Bendlin), Federal University of Rio Grande do Sul (Rosane Bittencourt) and University of São Paulo (Eduardo Rego).

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