case each). The presence of bone involvement was observed in 23.7% of the patients and 3.9% presented CNS involvement. Time to diagnosis ranged from 1 to 210 days (mean = 47.1 days). The mean LDH was 2,014 U/mL (range 91U to 36,599U). 51 patients had immunephenotyping, 23 confirmed B (Burkitt´s) NHL, 13 T NHL patients, 2 T angiocentric NHL patients (one nasal e one testicular), 2 mediastinal diffuse large cell NHL patients (B), 4 abdominal diffuse large cell NHL patients (B), 7 large cell anaplastic lymphoma patients (T). 51 (67.1%) patients are alive and with no evidence of disease, 22 (28.9%) were dead, 2 (2.6%) alive (but with short follow-up) and 1 patient was lost of follow-up. The causes of deaths were: progressive disease (13; 59.1%), sepsis (7; 31.8%) and deep venous thrombosis and cardiogenic shock (1; 4.5% each).

Treatment of B Non-Hodgkin's Lymphoma in Children: The Experience of Multicentre Studies and Brazilian National Cancer Institute's Experience

Claudete Klumb

Pediatric lymphomas are the third most common neoplasm in children and adolescents. Unlike lymphomas in adults, childhood non-Hodgkin's lymphomas (NHL) are diffuse, aggressive neoplasms with a tendency to widespread dissemination. The outcome in childhood lymphoma non-Hodgkin's (NHL) has improved steadily over the past decade through the incremental development of multiagent chemotherapeutics regimens. At present, 80-90% of children are cured with intensive risk-adapted chemotherapy. The most recent era advance is chemotherapy directed toward both stage and histology, an approach that has been validated in randomized multicenter clinical trials. Nevertheless, in developing countries there are many obstacles to treatment of childhood lymphomas. The most important are late diagnosis, low socioeconomic status and under-nourishment . In developing countries patients with these conditions may be at increased risk for therapy-related toxicity, including life-threatening infections.

In more recently trials, Patte et al. and Reiter et al., reported higher long term EFS in children with advanced stages of B-NHL using short intensive multiagent chemotherapy. However, the application of these regimens in developing countries may result in severe and life-threatening toxicity. Previously, our group reported 86.7% (SE=0.87) and 64% (SE=0.78) pEFS for children with early and advanced stage of non-lymphoblastic lymphoma, respectively. At that time, our results confirmed that a short duration therapy was effective to treat most children with non-lymphoblastic lymphoma in Brazil. Our following objective was to treat non-Hodgkin's B cell lymphoma in children with manageable toxicity-related morbidity without detriment of survival results. Between January 1998 to April 2003, 53 consecutive patients (age $\leq$ 16 years), from National Cancer Institute, Brazil were stratified by risk factors (Stage and LDH level) and treated with BFM 86/90 (Berlin-Frankfurt-Münster) based protocol with reduction of metotrexate dose from 5 mg/m^2 to 2mg/m^2. The mean age of patients was 6 years (range: 1 to 16 years). Seventy 2% of patients had lymphomas classified as Burkitt type; 11% as diffuse large cell lymphoma, 6% as Burkitt-like lymphoma, and 11% were not classified. At a median follow-up time of 35 months 44 patients (83%) survive in complete remission. The event free survival for all patients was 78% (SE= 0.07), 100% (SE=0.0) for stage I/II patients, and 74% (SE= 0.08) for stage III/IV disease. Six patients suffered from initial treatment failure, 1 patient relapsed, all of whom died. There was only one death for sepsis related to treatment. This strategy was very effective for the treatment of B-NHL in setting of a developing country. Our results were comparable to BFM 90 study and other contemporary groups and represent an advance of the cure rates in childhood B-NHL from Brazil. However, despite dramatic improvements in the treatment of childhood NHL, approximately 20% of patients either do not achieve a complete remission, or develop recurrent disease. The identification of clinical and biologic features that are predictive of treatment failure may help in the development of more effective therapeutic strategies.

The *TP53* gene encodes a nuclear protein implicated in the regulation of the cell cycle, DNA repair, and apoptosis. *TP53* mutations and other alterations have been described in numerous types of tumors, and some of these have been associated with poor prognosis. Some reports in the literature have indicated a relationship between *TP53* status and prognosis especially in non-small-cell lung cancer, breast cancer and NHL.

In order to characterize these molecular abnormalities and their clinical significance in prognosis, we also have analyzed the possible correlation between mutations in *TP53* gene, clinical findings, response to chemotherapy and survival in 49 children of our series. The mutations of *TP53* gene were analyzed by single-strand conformation polymorphism analysis (SSCP) of exons 5 through 9 and direct sequencing. Mutations of *TP53* were detected in 11 of 49 (22.5%) patients and more specifically in 20% of Burkitt's lymphoma. No significant correlation was found regarding age, gender, clinical stage and LDH level and *TP53* gene mutations. The comparison of EFS curves using the Log-Rank test were also not significant. However, the analysis of the effects of mutations on the core p53 structure identified biological and biochemical mutants with phenotypes probably related to different response to chemotherapy. Our data suggest that some types of mutants can alter the protein distinctly and may be associated with a more aggressive phenotype.

HTLV-1 $p12^{I}$ and $p30^{II}$ Proteins in Viral Persistence and Pathogenesis

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HTLV-1 is the only retrovirus known to be the etiologic agent of a human cancer, adult T cell leukemia/lymphoma (ATLL). HTLV-1 as well as some DNA viruses cause lifelong infections. In the case of DNA viruses, the inability of the host's immune response to clear virus-infected cells has been associated with viral latency and/or the ability of viral-encoded proteins to interfere with the host's immune response to the virus, particularly to evade CTLs, which play a major role in cellular immunity against cell-associated viruses.

We hypothesized that this may be the case also for HTLV-1 and focused on both the $p12^{I}$ and $p30^{II}$ proteins encoded by alternatively spliced mRNAs from ORFs I and II, respectively, within the 3' end of the viral genome. The HTLV-1 $p12^{I}$ protein localizes to the ER and Golgi, exhibits weak oncogenic activity, shares aa similarities with the bovine papillomavirus type 1 E5 oncoprotein, and binds to the IL-2R $ and ($_c$ chains. The spliced mRNA encoding $p12^{I}$ has been detected in *in vitro* and *ex vivo* HTLV-1-infected T cells and macrophages. Sera from rabbits experimentally infected with HTLV-1, as well as sera from humans infected with HTLV-1, have been shown to recognize the ORF I product , and a CTL response to ORF I products can be detected in HTLV-1-infected individuals. Ectopic expression in Hela-Tat cells or overexpression of $p12^{I}$ in PBMCs is associated with enhancement of STAT5 activation and decreased IL-2 requirement for proliferation. This effect however is strictly dependent on activation of T cells by both ligation of TCR and PHA stimulation and is not observed in HTLV-1-immortalized T cells since culture conditions (IL-2 addition) likely compensate for ORF I expression. The work of others has demonstrated that, in the presence of PMA, $p12^{I}$ induces calcium release and NFAT activation and transcriptional modulation of cellular genes. A seminal finding was that the ablation of $p12^{I}$ in an infectious clone impairs viral infectivity of primary lymphocytes *in vitro* and, importantly, in rabbits *in vivo*. A recent report suggested that $p12^{I}$ may not be essential for viral transmission. However, this conclusion was drawn from the finding of *in vivo* $p12^{I}$ mutations that preserve 84% of the $p12^{I}$ protein. The HTLV-1 $p30^{II}$ is a nuclear/nucleolar protein [5] and contains a highly conserved bipartite nuclear localization signal (NLS) between aa 71 and 98, which can be functionally substituted for the NLS of Rex. In addition, $p30^{II}$ contains serine- and threonine-rich regions that share distant homology to the activation domain of transcriptional activators, such as Oct-1/2, Pit-1, and POU-1, that modulates cell gene expression and is important for *in vivo* infectivity. Thus, both $p12^{I}$ and $p30^{II}$