induction is a powerful adverse prognostic factor. However, the mechanisms by which glucocorticoids induce cytotoxicity are poorly understood. Using the T-lymphoblastic cell line CCRF CEM C7, we have demonstrated the involvement of a novel gene with proposed thioredoxin function in the response to the glucocorticoid, prednisolone.

Global gene expression profiles were examined in sensitive and resistant populations of CCRF CEM C7 using the technique of differential display. Quantitative RT-PCR was used to confirm altered gene expression.

Using differential display, apparent down-regulation of the novel gene CGI-31 was seen in sensitive but not resistant leukaemia cells during 6 hours of prednisolone exposure and this was confirmed using quantitative RT-PCR.

638 POSTER

Pharmacodynamics of aplidinR (APL) in experimental models of haematological malignancies (HAMA)

B. Debabrata[1], G. Kaspers[2], E. Erba[3], A. Grossi[4], M. D'Incalci[3], J. Jimeno[5], J. Bertino[1]. [1] *Cancer Institute of New Jersey, Medicine, New Brunswick, USA;* [2] *VU Med Center, Amsterdam, The Netherlands;* [3] *Mario Negri Institute, Milan, Italy;* [4] *Florence University, Florence, Italy;* [5] *PharmaMar R&D, Madrid, Spain*

APL is a marine derived COMPARE negative cyclodepsipeptide isolated from the tunicate *A. albicans*. The phase I program has been completed being muscular tox the dose limiting factor with lack of bone marrow suppression; In contrast APL has been shown to inhibit the VEGF secretion and to block the VEGF/VEGFR1 loop in the acute lymphoblastic leukaemia (ALL) MOLT-4 cells. Such evidence is consistent with the induction of apoptosis and % cell death (median 97%) in ALL *de novo* and relapsed fresh patient's blasts at 0.5nM. Extended studies in ALL and AML pediatric samples have confirmed *in vitro* cytotoxicity at concentrations (CO) achievable below the recommended dose. In contrast supraphamacological COs are needed to induce cytotox against normal bone marrow progenitors and peripheral lymphocytes; Cross resistance studies have failed to demonstrate a pattern of resistance between conventional antileukemic agents and APL. Comparative studies demonstrate that APL is 10 fold more potent than Idarubicin in a panel of AML patient's blasts with respective median IC50s= 0.048uM and 0.357 uM. Moreover, clinically relevant CO of APL are also able to induce cytotoxocity against fresh samples from patients with CLL and against samples from multiple myeloma resistant to dexamethasone. In addition, *in vitro* combination studies in AML, ALL and non-Hodgkin lymphoma indicate statisitcally significant synergistic effects when sub-toxic CO (IC20) of APL are combined with standard agents.

Additional drug	IC50 DOXO	IC50 MTX	IC50ARA-C
-APL	18nM	5nM	30nM
+IC20APL	1nM	500pM	6nM.

In conclusion the available data with APL, a non myelotoxic drug, indicates selective cytoxity against a set of experimental models of HAMA at COs that are achievable well below the RD. Such evidence supports the clinical development of APL in these settings.

639 POSTER

Ganglioneuroma in childhood: the Italian experience

P. Angelini[1], C. Carlini[2], M. Conte[1], M. Testa[1], S. Biasotti[1], B. De Bernardi[1]. [1] *Giannina Gaslini Children's Hospital, Paediatric Haematology and Oncology Department, Genoa, Italy;* [2] *Giannina Gaslini Children's Hospital, Surgery Department, Genoa, Italy*

Ganglioneuroma are benign neuroblastic tumours. Few informations about optimal treatment and outcome of this tumour are currently available.

We searched the Italian Neuroblastoma Registry for cases of ganglioneuroma and sent a questionnaire to all Italian Paediatric Oncology Centres. Questions concerned sex, age, symptoms at diagnosis, surgery and follow-up. We also asked the participant Centres to send the surgery description and the histological report of each patient.

Since 1976, January 1 to 2002, December 31 159 cases were diagnosed. 66 were males, 93 females. Median age was 5 years and 11 months (range 0- 14 years and 5 months). Of 141 evaluable cases, 70 had a thoracic tumour, 53 an abdominal one, in 12 the tumour was pelvic and in 6 latero-cervical. In 2 cases the mass had an intraspinal extension.

63 patients were asymptomatic. The most frequent symptom was pain (23 cases), followed by cough (16) and fever (12). In 10 cases the mass was found at a routine physical examination. Interestingly, 4 patients had scoliosis at diagnosis, 5 presented with urinary symptoms (haematuria, disuria), 3 had Claude-Bernard-Horner syndrome as first sign, and 3 had neurological symptoms (paraplegia, neurologic bladder). Information about surgery was available for 144 cases. 130 underwent a radical or partial tumour excision. In 14 cases only a biopsy was performed at first, and it was followed by radical or partial excision in 8/14 cases. In the remaining 6/14 patients the tumour was not removed and a careful follow-up was started. Early complications of surgery occurred in four cases (pleural effusion, chilothorax, aortic rupture, and mild hischemic suffering of the spinal cord). 13 patients had permanent Claude-Bernard-Horner syndrom after surgery. Nephrectomy was performed in 3 patients, to achieve a complete resection of the tumour. Only one case was treated with chemotherapy and one received radiotherapy (2750 Rad). Median follow-up is 4 years (range 1 month- 15 years, 98 patients available). 103 patients are alive without disease and 15 are alive with stable residual disease. 2 patients underwent disease progression (one had a partial resection at diagnosis, the other had only a biopsy). Both are alive and well after secondary surgery. 4 patients relapsed. All are alive and free of disease after surgery.

Our data demonstrate that ganglioneuroma is a benign disease. The extent of surgery at diagnosis does not correlate with the outcome, although it might be useful to perform at least a partial resection of the tumour, to allow discrimination between ganglioneuroma and nodular ganglioneuroblastoma. Surgery can be difficult and complete resection might require an aggressive approach. We recommend to avoid aggressive surgery, even if complete resection is not otherwise possible.

640 POSTER

Delay in diagnosis of children with cancer: a retrospective study of 315 children

M. Weyl Ben Arush[1], M. Haimi[1], M. Peretz Nahum[1], H.F. Rennert[2], K. Katz[3]. [1] *Meyer Children's Hospital, Pediatric Hematology Oncology, Haifa, Israel;* [2] *Carmel Medical Center, Epidemiology, Haifa;* [3] *Diagnostic Statistical Institute, Statistic, Haifa*

Objectives: Cancer in children can be difficult to diagnose in the primary setting leading to some delay in diagnosis. Our aim was to determine the demographic and systemic parameters in children with solid tumors and to ascertain which of them affected the delay in diagnosis.

Methods: Lag time' was defined as the interval between onset of symptoms and final diagnosis. A retrospective study was performed on 315 children diagnosed with a solid tumor between 1993-2001 at the Department of Hemato-Oncology at Rambam Medical Center. A questionnaire was completed for each child, including epidemiological, social and medical issues concerning the family, the child, the medical system and the tumor. Lag time, including parent delay and physician delay, was estimated for each case.

Results: Mean lag time: 15.75 weeks, median: 7 weeks, range: 0-208 weeks. Lowest mean values appeared in kidney tumors, highest values for epithelial tumors, brain tumors and soft tissue sarcomas. Mean parent delay: 4.42 weeks, median: 1 week, range: 0-130 weeks. Mean physician delay: 11.17 weeks, median: 4 weeks, range: 0-206 weeks. One-quarter of patients were diagnosed within 3 weeks, 50% within 7 weeks, and 75% within 15 weeks.

Multi-variant analysis: Five factors were found to be strongly associated with lag time: age of child (older children presented later), ethnic origin of father (greater delay if he was 'Sephardic'), family religion (greater delay in Jews), serial number of the child in the family (greater diagnosis delay in families with one child) and family place of residence (shorter diagnosis delay in the village). Among the demographic and personal parameters, the best predictors for diagnosis delay were age of child and father's ethnic origin.

Conclusions: This work demonstrated that there are several factors influencing the diagnosis delay of childhood solid tumors. Recognizing these factors coul d minimize the diagnosis delay, hence improving the chances of the child survive.

641 POSTER

Seeking for a second opinion in paediatric oncology

M. Weyl Ben Arush[1], R. Levy[2], J. Eid[1], S. Makhoul[1]. [1] *Meyer Children's Hospital, Pediatric Hematology Oncology, Haifa, Israel;* [2] *Research Promoting Center, Statistic, Tivon*

Objectives: the number of second opinions consultations in pediatric oncology is increasing, yet the grounds on which families decide to seek a second opinion have been little studied. The goal of the study was to identify

patients and families factors that appeared to contribute to a second opinion being sought and the correlation with internet and alternative medicine use.

Methods: 86 parents (43 from jewish origin, 43 from arab origin) of children with cancer recently treated in the Hematology Oncology Pediatric Department were interviewed by the social workers of the department. The questionnaire included epidemiologic data, details about the disease, timing of the second opinion consultation, reasons for seeking a second opinion and the risk/benefit of the consultation.

Results: 22 parents out of 86 (25%) had sought a second opinion,with 39.5% of the Jewish families, 11.6% of the arab families (p=0.003), 36% of the working mothers, 18% of the housekeeping mothers (p=0.058),72.7% of the internet user,and a higher academic and socioeconomic level (p=0.05).Most of the second opinion were performed at diagnosis after advices from family physician (32%), Rabbi (27%), friends (27%) and family (18%).Most of the parents sought a second opinion because they wanted confirmation about the treatment protocol and the professional level of the hematologist oncologist / surgeon and the institution.A few wanted more information about the child's condition and its treatment. First opinions consultants were usually aware of these communication issues. There was a slight correlation between the worse prognosis of the child's disease and the second opinion consultation. In 6 cases the parents were proposed to stay in the second institution.In 5 cases, the therapeutic approach proposed by the second consultant was different.In most of the cases (86%), mandatory second opinions helped the family confidence in the first physician and decrease confusion and anxiety helping to accept decision making.

Conclusions: The duties of collegiality has to include ethical obligations to collegues, moral enterprise, recommending the best treatment for the child with a cooperative interaction among colleagues. Seeking an open and trusting communication process between the family and the treating physician may certainly contribute to improve the second opinion process.

642 POSTER

Use of high dose fractionated cyclophosphamide and coordinated high dose methotrexate and cytarabine in childhood B cell Non Hodgkin's Lymphoma.

S. Sandip[1], N. Shah[2], P. Shah[2], K. Patel[2], S. Shukla[2], B. Parikh[2], A. Anand[2], S. Talati[2], H. Panchal[2], A. Patel[2]. [1] *Gujarat Cancer & Research Institute, Medical & Pediatric Oncology Department, Ahmedabad, India;* [2] *G.C.R.I., & Pediatric Oncology Dept., Ahmedabad, India*

Non-Hodgkin's Lymphoma (NHL) in children has varied presentation. Disease localized to the abdomen is often of B Cell origin. Every immunophenotyping markers are not available in developing countries. Therapeutic decisions are therefore based on the clinical presentation. In treating B Cell NHL progress has been made by a trend toward the use of intensive short duration therapy.

Objective: To determine the efficacy of high dose fractionated Cyclophosphamide and co- ordinated high dose Methotrexate and Cytarabine a protocol used by Murphy et al.

Methods: During July 1997 to December 2002, 30 children from 3-14 years age group with B cell NHL (boys 25, girls 5) were treated with Murphy's protocol. It consist of fractionated schedule of intravenous (IV) Cyclophosphamide (300mg/m2 every 12 hours for six doses) followed immediately by doxorubicin (50 mg/m2) and Vincristine (1.5 mg/m2) with combine intrathecal (IT) Methotrexate and Cytarabine cycle A. Immediately on hematological recovery iv high dose Methotrexate (1000 mg/m2 over 24 hours) followed by iv Cytarabine (400 mg/m2 over next 48 hours) was administered with leucovorin rescue and repeated IT cycle B. This sequence is repeated four times with the escalating dose of Cytarabine in successive courses up to 3200 mg/m2. The entire duration is approximated 24 weeks.

Results: Out of 30 cases 20 were stage III, 2 with stage IV and 8 with stage II by St. Jude staging system. According to site of presentation 8 were having intra abdominal resectable mass,16 with unresectable abdominal mass,2 with head & neck mass and 4 other (1 epidural and 3 bone). Total 140 cycles of chemotherapy were given.42 episodes of grade III and IV Neutrogena (30%) were observed following cycle A and 15 episodes (11%) after cycle B.5 patients (17%) were lost to follow- up during the treatment course and 5 patients (17%) expired due to toxicity and progressive disease. After follow up range of 4 months 72 months 17 patients (57%) are in remission and 3 patients (10%) are on treatment.

Conclusion: Use of sort-term intensive chemotherapy is feasible tolerable and effective in childhood B cell NHL in developing countries with good supportive care.

643 POSTER

Factors affecting the success or failure of sperm banking in adolescent male cancer patients.

G. Makin[1], B. Edge[1], D. Holmes[2]. [1] *University of Manchester, Medical School, Manchester, United Kingdom;* [2] *Christie Hospital, Young Oncology Unit, Manchester, United Kingdom*

Aims: Advances in the treatment of childhood cancer have resulted in many patients becoming long term survivors. This has lead to an increased focus on the cost of cure. Male infertility is a major long-term effect of chemo- and/or radiotherapy. A wide range of commonly used chemotherapeutic agents are gonadotoxic, including elements of protocols for the treatment of all the common tumours of adolescence. Sperm banking is a widely available method of maintaining post-pubertal male fertility. However the adverse impact of a diagnosis of cancer, and the evolving nature of many of these patients' sexual identities, mean that this facility is not always used. This study was conducted to identify those factors contributing to this failure.

Methods: Patients aged between 12-20 years at diagnosis, diagnosed between 1997-2001 at RMCH or the Christie were identified. Questionnaires were administered to those who had been offered sperm banking.

Results: 45 of 55 questionnaires were completed. The mean age at diagnosis was 17.1 years, and the mean interval between diagnosis and interview was 2.1 years. 67% of patients had been able to successfully bank sperm. Those who had been unsuccessful were younger (mean age 15.3y compared to 17.8y). This group of patients had significantly higher levels of anxiety at diagnosis and significantly greater difficulty in talking about fertility than those who were successful. They also had less understanding of sperm banking at the time of diagnosis.

Conclusion: The majority of adolescent cancer patients are able to bank sperm. However young age, high anxiety, lack of understanding of the process, and a difficulty in discussing fertility are associated with a failure to store semen. The provision of expert information and counselling to such individuals may increase their chances of successful sperm banking.

644 POSTER

Imminent ovarian failure in childhood cancer survivors

G.M. Lantinga[1], A.H.M. Simons[2], A. Postma[1]. [1] *University Hospital, Groningen, Dept. of Pediatrics, Div. of Pediatric Oncology, Groningen, The Netherlands;* [2] *University Hospital, Groningen, Dept. of Obstet. & Gynaecol., Groningen, The Netherlands*

Background: Although many female childhood cancer survivors apparently have normal ovarian function, there is increasing concern about the risk of subfertility and early menopause. The aim of this study was to investigate reproductive history and the prevalence of imminent ovarian failure (IOF) in young adult survivors. In the general population IOF is considered extremely rare before the age of 33.

Material and methods: Participants were * 18 yrs, had received chemotherapy with or without irradiation and were * 2 yrs off-treatment. Patients with hypothalamic/hypophyseal irradiation >25 Gy or with severe mental retardation were excluded. Ovarian function was evaluated by assessment of serum follicle stimulating hormone (FSH) and oestradiol (E2). Criteria for IOF were FSH >10,0 U/L or E2>0,28 nmol/L on day 3 of the menstrual cycle, or FSH >12,4 U/L on day 7 of the pill-free interval in women with oral contraceptives (Van Heusden, 1999). Data on reproductive histories were collected through questionnaires.

Results: Of the157 eligible patients (age at diagnosis 7.8 ± 5.3 yrs, age at the time of study 27.3 ± 6,0 yrs) 22 refused participation or were lost to follow-up, 12 were pregnant, 12 had primary ovarian failure after pelvic irradiation or were postmenopausal, 5 had depot-contraceptives and one was on hemodialysis. In addition hormonal assessment was incomplete in 12. In the remaining 93 patients (age at diagnosis 7.4 ± 5.3 yrs, age at the time of study 26.7 ± 5.7 yrs) IOF was found in 21 (23%). The prevalence of IOF under 33 years was 14/75 (19%). IOF correlated with age (p=.03) and was associated with peri- or postmenarchal treatment (p=.003) but not with alkylating agents or abdominal irradiation not involving the ovaries. 91 pregnancies in 55 women ended in 72 healthy babies, 1 stillbirth and 19 miscarriages ($p < 0.01$ vs normal population). The M/F ratio of the offspring was 0.76 (p=.04 vs normal population).

Conclusion: IOF appears to be a frequent complication in females treated for childhood cancer. Patients with menarche before or during treatment are more at risk. Once pregnant, there is an increased risk of miscarriages. The M/F ratio of the offspring is decreased.