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)

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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

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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

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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

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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