ONCOLOGY AND HAEMATOLOGY

G81 EFFECTS OF GROWTH HORMONE TREATMENT ON SELF-ESTEEM AND MOOD IN CANCER SURVIVORS WHO ARE GROWTH HORMONE DEFICIENT

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Aim: To investigate the effects of commencing growth hormone treatment, in growth hormone deficient cancer survivors, on selected measures of body image, self-esteem and mood.

Method: 21 Patients aged between 8 and 18 years who were starting growth hormone replacement were recruited from childhood cancer survivors in the Yorkshire and Trent regions. Disfigured and significantly disabled patients were excluded from this study. Questionnaires were administered before and 8 to 10 weeks after starting growth hormone replacement therapy. Battle and Harter scores were used for self-esteem and PANAS scores for mood respectively. The study received ethical approval from St James University Hospital.

Results: All patients who were recruited completed the study. The mean pre-treatment standard deviation score for height was -2.0. At assessment there was a slight improvement in the score (-1.8) but this was not significant statistically.

Self-esteem: The mean pre-treatment Battle score was 45 (SD 7.7), the mean post treatment score was 63 (SD 7.2). There was a significant improvement ($P<0.001$) on paired t Testing. On the Harter scale only the Global Self Worth subsection ($P<0.01$) showed any significant change. The correlation coefficient for Harter versus Battle was 0.89 showing the Battle score to be a reliable assessment of self-esteem in this group of patients.

Mood: The PANAS measures positive and negative aspects of mood. The positive mood scores showed a significant improvement with pre-treatment mean (27.4) versus post-treatment mean (35.3), $p<0.01$ for paired t Tests. Negative mood scores fell (pre-treatment mean 14.4 and post-treatment mean 13.9) but this change was not statistically significant.

Conclusions: Initiation of growth hormone therapy leads to significant early improvements in measures of mood and self-esteem before the physical effects of therapy occur.

G82 COCHRANE REVIEW: THE PREVENTION OF MUCOSITIS AND ORAL CANDIDIASIS FOR PATIENTS WITH CANCER

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Aims: This systematic review of randomised trials aimed to determine whether oral agents are superior to placebo/no treatment in preventing oral mucositis and candidiasis for cancer patients.

Methods: We reviewed randomised trials of cancer patients receiving prophylactic oral therapy, searching computerised Medline, Embase, Cinahl, Cancerlit, the Cochrane controlled trials register and oral health group specialist register up until July 1999. Authors of eligible studies were contacted to confirm trial data and obtain additional information.

Results: Of 1605 abstracts and 108 papers identified only 26 studies were truly randomised. 11 were included in the meta-analysis for mucositis. Of the six prophylactic agents used only ice chips were effective (relative risk 0.57, 95% CI 0.43 to 0.77). The number needed to treat (NNT) to prevent one extra case of mucositis was 4 (95% CI 3-7). 15 studies were included for oral candidiasis. Non-absorbable anti-fungal agents were not effective; those partially or fully absorbed were capable of preventing oral candidiasis with partially absorbed more effective (relative risk 0.13, 95% CI 0.06 to 0.27) with an NNT to prevent one extra case of 3 (95% CI 3-5).

Conclusions: Ice chips may prevent mucositis, and prophylactic absorbed or partially absorbed anti-fungals can reduce overt candidiasis. There is little evidence to support the use of standard therapy with oral nystatin.

G83 THE USE OF MAGNETIC RESONANCE IMAGING IN DETECTING BONE MARROW DISEASE IN NEUROBLASTOMA

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Many operators do not obtain adequate bone marrow biopsy specimens, in particular in infants. We therefore evaluated the ability of magnetic resonance imaging (MRI), at diagnosis, to detect bone marrow metastases in 25 children with neuroblastoma and compared it with bone marrow aspiration and biopsy. Previous studies had demonstrated the ability of MRI in detecting bone marrow involvement in multiple myeloma. Bone marrow aspirates and biopsies, and MRI were retrospectively blindly assessed for involvement and adequacy by RW and NW respectively. Twelve of the 43 (28%) bone marrow biopsies available were inadequate and in 16 patients bone marrow biopsies and/or aspirates demonstrated metastases. In 12 of these 16 patients MRI demonstrated infiltration with neuroblastoma. No MRI showed evidence of infiltration without metastases in either their aspirate or biopsy, hence MRI had a sensitivity in detecting bone marrow disease in neuroblastoma of 75% with a specificity of 100%. We conclude that MRI is highly specific in detecting bone marrow metastases and may add to bone marrow aspirates and biopsies, particularly in infants. As the MRI were not specifically performed to assess marrow disease further prospective studies are required to assess if the sensitivity of MRI can be improved.

G84 THE USE OF DISTORTION PRODUCT OTOACOUSTIC EMISSIONS IN SCREENING FOR DRUG INDUCED HIGH FREQUENCY HEARING LOSS

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High frequency hearing loss is an important complication of treatment with drugs such as platinum chemotherapeutic agents. Early high frequency hearing loss is often difficult to demonstrate in young or sick children who cannot co-operate pure tone audiometry (PTA).

Distortion product otoacoustic emissions (DPOAE) are sounds generated by the precise cochlear structure affected by ototoxic drugs. DPOAE are detected by a non-invasive technique, requiring minimal patient co-operation. There have previously been no significant clinical studies of DPOAE in normal children or those receiving ototoxic drugs.

Normal data were collected from a control group of 102 children. Risk factors for sensorineural hearing loss and middle ear disease were excluded. Assessment included PTA (or age appropriate techniques), DPOAE growth rates and DP-grams. This control data was then used to evaluate the results of a prospective group of 36 children receiving platinum chemotherapy and a retrospective group of 55 children previously treated with platinum agents.

Twenty-six children (21 retrospective and 5 prospective) had evidence of significant high frequency hearing loss (PTA threshold >40dB at or above 4kHz), with corresponding loss of DPOAE at the affected frequencies in all patients. Children studied prospectively demonstrated a significant decrease in amplitude of DPOAE before DPOAE disappeared and before there was a change in PTA threshold (paired t test $p<0.05$). 8 children with normal PTA showed abnormal DPOAEs. These children had higher cumulative drug doses and may represent a group with early cochlea damage.

DPOAE provide a feasible, frequency specific, test of cochlea function in children with the potential to detect early cochlear damage at a stage when action to reduce the severity of hearing loss may be possible.

G85 RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (RTPA) THERAPY FOR HEPATIC VENO-OCCLUSIVE DISEASE (VOD)

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VOD is a common early complication of Bone Marrow Transplantation (BMT), and when severe has a very high mortality. rTPA has been used to treat severe VOD, but little information about its use is available in children. Over 3 years we have given rTPA to 10 patients (pt) (age 2 months-14 years) with severe VOD after allogeneic or autologous BMT for congenital immunodeficiency (8pt) or malignancy (2). Conditioning included alkylating agents in all pt. Treatment with rTPA was started when the predicted risk of developing severe VOD was > 30% (using the Bearman model, plotting bilirubin (bili) against % weight gain). All 10 pt were given rTPA, 0.2 mg/kg/day for 4 days, and Heparin 5 units/kg/hour for 10 days. rTPA was commenced between day +5 and + 19, given for 4-11 days and the dose doubled in 5 pt after 4 days. Mean peak bili was 315 (range 21-832) μmol/l. 5 pt required abdominal paracentesis, 3 also needed cardio-respiratory and renal support. 5 pt responded with resolution of clinical and biochemical signs by day +61; 1 of these had anicteric VOD with tender hepatomegaly, gross ascites and 19% weight gain. 3 pt with Omenn's syndrome died from multiorgan failure (MOF), but bili had decreased to <80 μmol/l in 2 after rTPA; capillary leak syndrome leading to respiratory and renal failure, rather than liver damage was the major factor leading to death. 1 patient failed to respond to rTPA and died after a liver biopsy, which confirmed severe VOD. The other pt stabilised initially after starting rTPA, but then had progressive liver failure due to biopsy proven acute GvHD. rTPA was stopped in 1 pt after 7 days because of worsening of pre-existing gastrointestinal bleeding. No other toxicity due to rTPA was seen. Overall 7 of 9 patients with VOD showed improvement after rTPA was started and 5 recovered fully. rTPA and heparin may be an effective treatment for severe VOD if started before development of MOF.

G86 NEUROBLASTOMA TUMOURS WITHOUT MYCN AMPLIFICATION AND WITH LOSS OF HETEROZYGOSITY AT CHROMOSOME 11q COMPRISE A DISTINCT GROUP OF AGGRESSIVE TUMOURS

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Amongst the heterogeneous group of neuroblastoma tumours, stage 3 and 4 tumours and especially those with MYCN amplification and loss of heterozygosity (LOH) at 1p are associated with a poor survival rate. We investigated whether chromosomal abnormalities other than MYCN and LOH at 1p may be involved in the aggressive behaviour of the tumour. LOH and CGH studies report that loss of heterozygosity is most frequent at the chromosomal regions 3p, 4p, 11q and 14q. Therefore we studied 25 tumours for LOH at these regions. The tumours comprise 8 stage 1, 1 stage 2, 1 stage 4S, 2 stage 3 and 12 stage 4 and stage was unknown in 1. MYCN amplification was observed in 6 tumours. Matched pairs of tumour and constitutional DNA were analysed using polymorphic markers on 3p21.31-3p24.3, 4p16.1, 11q14.3-11q24.2 and 14q32.11-14q32.32. In 10 tumours (40%) LOH at 11q was observed accompanied by LOH at 1 or more of the chromosomal regions 3p, 4p or 14q in 7 of those. LOH at 11q occurred in non-MYCN amplified tumours only, often stage 3 or 4. Our data showed that among patients without MYCN amplification, those with deletion of 11q had a significantly worse outcome. Taken together, a group of aggressive neuroblastoma tumours are characterised by absence of MYCN amplification and LOH at 11q often accompanied by LOH at 3p, 4p or 14q.

G87 ETOPOSIDE-INDUCED CLEAVAGE OF THE *MLL* GENE: POTENTIAL APPLICATION IN PREDICTING INDIVIDUAL SENSITIVITY TO TOPOISOMERASE 2 INHIBITOR THERAPY IN CHILDHOOD CANCER

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Treatment-related leukaemia (TRL) is a growing and the most serious complication of effective childhood cancer chemotherapy with topoisomerase 2 (topo-2) inhibitors such as etoposide. These TRLs frequently carry rearrangement of the Mixed Lineage Leukaemia (*MLL*) gene, resulting from drug-induced gene cleavage. Molecular analysis of *MLL* cleavage may offer a way to determine and compare patient sensitivity to topo-2 inhibitor therapy and indirectly predict the risk of TRL.

We have studied cleavage in the Breakpoint Cluster Region (BCR) of the *MLL* gene in normal lymphoid and leukaemic cell lines exposed to etoposide using a hybridization assay with a cDNA probe. *MLL* cleavage fragments were quantified by real-time autoradiography. Etoposide concentrations and exposure times for maximal *MLL* cleavage were determined for each cell line and their sensitivity to etoposide was estimated and compared.

Two *MLL* cleavage fragments (~6.8 and 1.5kb) were consistently induced *in vitro* by etoposide. The combined size of these fragments suggested that most cleavage occurred at a specific site in the BCR and was consistent with double-strand DNA breakage. The proportion of cleavage fragments ranged from 30-80% of total *MLL* BCR signals. Exposure to etoposide of 10 μM for 5-7 hours gave maximal cleavage of the gene but differences were detected in the susceptibility of cell lines to *MLL* cleavage.

Detection and quantification of etoposide-induced *MLL* cleavage has potential in predicting individual sensitivity to topo-2 inhibitors. Collection and analysis of blood and bone marrow samples from children receiving topo-2 inhibitor therapy are in progress.

G88 A COMMON PATHWAY OF DRUG RESISTANCE IN LEUKAEMIA?

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Background: Glucocorticoids have been used in the treatment of acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) for many years, initially as the only agent and then as part of multiagent chemotherapy in ALL and in CLL either alone or with chlorambucil. In ALL 20% of patients are resistant to glucocorticoids at presentation but on relapse this rises to above 70%. The mechanism of this resistance remains unknown despite much work in this field, theories however abound which include alternative splicing of the glucocorticoid receptor, number of glucocorticoid receptors and inhibition of factors responsible for cell survival. Other agents used in the treatment of ALL include daunorubicin and in CLL chlorambucil and fludarabine.

Aim: To investigate whether there is cross-resistance between drugs with different mechanisms of action used in the treatment of haematological malignancies in the form of ALL and CLL.

Methods: *In vitro* sensitivity to glucocorticoids and daunorubicin in ALL and prednisolone, fludarabine and chlorambucil in CLL were measured using the MTT assay.

Results: MTT assays on 71 ALL samples were analyzed for LC_{50} values to prednisolone and daunorubicin in ALL. The LC_{50} values for these 2 drugs in the same sample showed a strong correlation ($r_s = 0.52$, $p<0.0001$). Blasts from 46 patients with CLL were analyzed, *in vitro* sensitivity of prednisolone strongly correlated with both fludarabine ($r_s = 0.631$, $p<0.001$) and chlorambucil ($r_s = 0.692$, $p<0.0001$). Sensitivity to chlorambucil and fludarabine also correlated ($r_s = 0.692$, $p<0.0001$).

Conclusion: These data show that sensitivity of leukaemic blasts to *in vitro* drugs suggests a common mechanism of resistance despite their different mechanisms of action. This is likely to involve downstream aspects of the apoptotic pathway.

G89 TEMPORAL INCREASE IN THE INCIDENCE OF CHILDHOOD PEAK COMMON ACUTE LYMPHOBLASTIC LEUKAEMIA (c-ALL) SEEN IN NORTH WEST ENGLAND

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Aims: To examine temporal trends in incidence in acute leukaemia by age,sex and immunophenotype.

Methods: Cases were ascertained from the Manchester Children's Tumour Registry. Immunophenotyping is available for all cases since 1980. Incidence rates were calculated using annual mid-year population estimates as denominators.Log-linear modelling was used to analyse temporal trends.

Results: Out of 435 cases of ALL diagnosed between 1980 and 1998, 339 were classified as precursor B-cell ALL(c-ALL),52 T-ALL,31 Null-ALL and 13 other. There was significant increase of 3.0% per annum in the childhood peak of c-ALL(ages 1-4;p=0.025). Female rates increased more rapidly than male (3.6% versus 2.6% per annum). There was no increase in other age-groups for c-ALL, nor in other sub-groups of leukaemias.

Conclusions: These observations suggest that c-ALL has a different aetiology to other subtypes of childhood leukaemia. Recent observations suggest that involvement of infections in the aetiology of c-ALL. If the observed increase is due to such a mechanism it is unlikely to involve a new infection. More probably there has been a change in patterns of exposure.

G90 THROMBOCYTOPENIA WITH ABSENT RADII (TAR) SYNDROME: NOMINALLY A HAEMATOLOGICAL SYNDROME IN WHICH ORTHOPAEDIC AND GASTRO-INTESTINAL PROBLEMS PREDOMINATE

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We present a series of 6 TAR patients who presented to our institution over the past ten years. Summary of haematological data:

Age now (years)	Platelet count (birth) x10^9/l	Months until plts>40	Significant bleeds	Prophylactic plt support
4	46 (19 at 2/52)	22	Nose bleed x1	Nil
4	10	30	? PV bleed[+]	3 months
4	15	39	Nil	Nil
6	26	15	Nil	Nil
8	N/A	8	Nil	Nil
10	5	96	Intracranial *	9 months

[+]Possibly just "normal" loss in first week of life. Transfused before referral.
*Fall from 1.3m window—full recovery with conservative management.

All patients had bilateral radial aplasia, 1 had true phocomelia of the arms. 3 have marked deformities of the lower limbs that have required & will require further operation. One cannot yet walk because of his disabilities.

Varying degrees of cow's milk intolerance were present in 6/7 cases. All appeared to settle over the first few years of life, although the final case required naso-gastric feeding in infancy for a steroid-responsive enteropathy.

All appear to be developing normally & have remarkable function in their upper limbs. All have required orthopaedic surgery to maximise function. This has been performed safely with appropriate donor platelet cover.

Conclusions: TAR is a multi-system disease in which non-haematological problems may dominate. Failure to thrive is common & may represent food intolerance or more severe gut disease. The platelet count eventually reaches a safe level. The mortality figures of 25% in the literature are no longer justified. Prophylactic platelet support is not usually necessary & may be dangerous because of allo-immunisation. HLA matched platelets should be considered in this situation. Corrective surgery is safe & appropriate.

G91 ASSESSING THE IMPACT OF GUIDELINES IN THE REQUESTS FOR COMMON HAEMATOLOGICAL INVESTIGATIONS

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Introduction: Requests for common haematological investigations ie. full blood count (FBC), Urea and Electrolytes (U&E's and C-Reactive Protein (CRP) have been increasing by mean of 20% each year over the previous 2 years in the Paediatric Department of our District General Hospital. However, no significant rises have been observed in the number of patients seen. The first six months of 1997 saw a request of the above investigations asked in

almost every third child seen in the department. Guidelines were therefore put in place and the aim of this prospective study was to determine the impact of such guidelines on future requests for the above investigations.

Methods: Requests for FBC, U&E's and CRP were monitored for a period of 10 months from August 1997 until May 1998.

Results: The total number of patients seen in the Paediatric Department recorded a rise of 31.3% during the period of study. However, requests for FBC decreased by median 21.7% (range 16% - 24%), U&E's by median 38.2% (range 7% - 47%) and CRP by median 26.3% (range 10% - 38%). These were significant decreases ($P<0.05$). Requests for *other* haematological investigations ie. blood cultures, serum bone profile and liver function tests also recorded significant falls ($P<0.05$). Mean number of hospital admissions as a measure of morbidity were not significantly affected ($P>0.2$).

Conclusions: Significant reductions in the requests for common haematological investigations can be achieved. Such changes in practice could potentially result in less invasive procedures associated with considerable parental anxiety and hospital costs.

G92 SICKLE CELL CRISES AND NOCTURNAL HYPOXAEMIA

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Aims: Acute painful crises cause considerable morbidity in children with sickle cell disease (SCD) but are difficult to predict or prevent. Adenotonsillar hypertrophy, upper airways obstruction and nocturnal hypoxaemia are common in children with SCD. This study was designed to test the hypothesis that the frequency of acute painful crisis is related to upper airways obstruction and associated nocturnal hypoxaemia.

Methods: In 107 unselected children from a defined population of children with SCD (age range 1-17 years, Females 51%), mean nocturnal oxygen saturation (MNO_2) was recorded using overnight pulse oximetry. In 61 of these patients, clinical questionnaire data on upper airways obstruction (tonsillar size, snoring, mouth breathing and disturbance of sleep) were also recorded and were summated. MNO_2 and the summated questionnaire data were compared with the frequency of hospitalisation for acute painful crises obtained from the hospital notes.

Results: Mean nocturnal oxygen saturation ranged from 85 - 99.7%. Using simple linear regression there was a significant inverse relationship between MNO_2 and number of hospitalisations for painful crisis ($r = -0.37$, $r^2 = 0.14$, $p = 0.002$). Analysis of variance showed a significant difference between groups for number of crises and increasing tonsillar size ($p = 0.04$), severity of snoring ($p = 0.03$), severity of mouth breathing ($p = 0.05$) and disturbance of sleep ($p = 0.05$) but these clinical data did not predict nocturnal hypoxaemia as measured by oximetry.

Conclusion: This study suggests a relationship between relative nocturnal hypoxaemia and increased hospitalisation for vaso-occlusive crises. A combination of questionnaire and overnight pulse oximetry may be required for screening. Interventions designed to relieve upper airways obstruction, e.g. adenotonsillectomy, and to correct chronic nocturnal hypoxaemia, eg. domiciliary oxygen or nasal continuous positive airways pressure, may reduce the frequency of acute painful crisis in SCD.

G93 THE MANAGEMENT OF ITP—FEW NEED ACTIVE THERAPY. AN 8 YEAR REVIEW OF CONSECUTIVE UNSELECTED CASES

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Although the course of childhood idiopathic immune thrombocytopenic purpura is usually short with few bleeding complications, many clinicians find it difficult to leave a child with a very low count untreated.

Aims: a retrospective review of the management of all children admitted with newly diagnosed ITP over an 8 year period to a single hospital.

Methods: Analysis of case notes of all children identified by the hospital coding system as having been admitted with acute ITP between January 1992 and October 1999. (This excludes children who were never admitted).

Results: 81 cases were identified; 17 with chronic and 64 with acute ITP. The majority (58/64) of children with acute ITP had only mild symptoms (cutaneous signs with or without minor mucosal lesions) and received no therapy. 78% of children with acute ITP had achieved a platelet count $>50x10^9$/l within 4 weeks of diagnosis. Two children had epistaxis requiring blood transfusion (severe ITP); one was treated with steroids. Four children had moderate symptoms—one required nasal packing for epistaxis and one received steroids for frank haematuria. The other 2 remitted without specific therapy. Of the 17 children with chronic ITP one third had presented aged less than 4 years, a third between 5-8 years, and a third aged 9-12 years. Five had received therapy elsewhere but most were symptom-free or had minimal symptoms with no therapy. Treatment with IVIG was reserved for accidents, essential surgery or long air flights, and courses of steroids were avoided because of significant side effects.

Conclusion: The majority of children with ITP have minimal symptoms despite very low counts and do not require specific therapy to raise the count unless there is significant bleeding or injury.

G94 USE OR ABUSE OF BLOOD PRODUCTS: ARE WE USING VALUABLE RESOURCES PROPERLY?

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Aims: To trace the fate of all platelets and fresh frozen plasma issued from the hospital blood bank over a 6 month period to assess the indications for use and the standard of documentation.

Methods: Two audit personnel collected records of units issued from the blood bank and followed their fate by examination of patient case notes. Data was collected on a standardised proforma and analysed using Microsoft Access.

Results: FFP - 115 orders were made for 81 patients; a total of 176 units were issued, 83% for cardiac surgery. 42 units (24%) were wasted, reasons unclear. Documentation was incomplete in a significant number, in particular 24% had no doctor's signature and only 29% had a record of the volume given. The rationale for transfusion of FFP was not clearly documented.

Platelets: 364 orders were made for 123 children; 514 packs were issued of which only 337 (64%) were transfused. 67% of the wasted units were ordered electively for cardiac surgery, and 23 % were for oncology patients. Transfusion documentation was moderate, but 20% had no doctor's signature. Indication for transfusion was most commonly a low platelet count with or without bleeding.

Conclusions: an unacceptable wastage of both FFP and platelets is occurring. Documentation of indications needs to be more explicit. Discussion with cardiac staff led to an immediate change in platelet ordering policy for elective cardiac operations leading to a significant reduction in the wastage of platelets. Changes in procedures on the oncology ward also led to rationalisation and a reduction due to over-ordering, particularly at weekends.

G95 CANCER PHENOTYPE ASSOCIATED WITH GERMLINE TP53 MUTATIONS: AN ANALYSIS OF 28 KINDREDS

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Aims: To establish the frequencies of specific cancers, in families with germline TP53 mutations relative to population cancer rates.

Methods: A cohort of individuals including first and second degree relatives of probands from cancer-prone families with germline TP53 mutations was established. Expected numbers of cancers were estimated from age,sex and morphological type-specific cancer registry rates and compared with the observed. Log-linear modelling was used to compare distributions of cancers in the families with those in the general population.

Results: The cancer distributions in TP53 mutation-carrying families was highly significantly different from the general population both for childhood ($p<0.0005$) and adult [$p<0.0005$] onset cancers. The main paediatric cancers were embryonal rhabdomyosarcoma (22%) and high grade gliomas (16%) adrenocortical carcinoma (67%) of children who survived their first cancer developed a second malignancy.

Conclusion: The effect of a germline TP53 mutation is not simply to increase the risk of all cancers, there is a tissue-specific cancer phenotype. The risk of multiple primary cancers is extremely high. Determination of constitutional TP53 status is of clinical importance in certain childhood cancers.