The initial advances were made in identifying genes that predispose to a greatly increased risk of childhood cancer. Such genes included RB, WT1 and p53. These illustrate the varied contribution of somatic mutation of predisposition genes to specific childhood cancers. Mutation in the RB1 gene seems to account for nearly all cases of retinoblastoma with heritable mutations occurring in approximately 40% and tumour specific defects in the remaining allele found in nearly all. By contrast, heritable mutations in WT1 occur in less than 5% of children with Wilms tumour and somatic mutations occur in only a further 10-20% of tumours. Mutation of the p53 gene, which underlies the Li Fraumeni syndrome, is very common as a somatic event in many adult tumours. However, this is not the case in childhood cancer, where somatic p53 mutations are unusual except in certain subtypes such as anaplastic Wilms tumour and some sarcomas.

Analogous to leukaemias, several childhood solid tumours have been shown to carry balanced chromosomal translocations resulting in fusion genes and chimeric proteins with novel, oncogenic properties. Examples include the EWS-FLI1 fusion in Ewing family tumours and the PAX3/7-FKHR fusion characteristic of alveolar rhabdomyosarcoma. Development of molecular methods to detect these fusion genes has led to a new era of molecular diagnostic pathology and also clinical research on the significance of micro-metastases and minimal residual disease. Mutation of the INI1 gene in rhabdoid tumours illustrates their common biology despite their varying anatomical sites. INI1 is an important component of chromatin remodelling complexes, suggesting a target for therapeutic intervention.

The study of the molecular biology of childhood cancers continues to bring broader insights into the biological control mechanisms of cellular proliferation and differentiation. Ultimately this should point the way towards novel therapeutic strategies.

14

The status of bone marrow transplant clinical trials

T. Demirer[1], J. Ledermann[2], S. Leyvraz[3], D. Niederwieser[4], D. Blaise[5], M. Aglietta[6], N. Ueno[7], G. Rosti[8]. [1] *Ankara University Ibn-i Sina Hospital, Hematology/Oncology, Ankara, Turkey;* [2] *University College London Hospital, Hematology, London, United Kingdom;* [3] *Centre Pluridisciplinaire d'Oncologie, Oncology, Lausanne, Switzerland;* [4] *University Hospital Leipzig, Internal Medicine, Division of Hematology/Oncology, Leipzig, Germany;* [5] *Institut Paoli Calmettes, Marseille Cedex 9, France;* [6] *Ospedale Regina Margherita, Oncology/Hematology, Torino, Italy;* [7] *MD Anderson Cancer Ctr., Houston, USA;* [8] *Ospedale Civile, Oncology/Hematology, Ravenna, Italy*

The purpose of this teaching letter is introduction of the ongoing trials related to EBMT STWP. Currently, EBMT STWP has 7 prospective studies. These studies: 1) HIDOC European intergroup study that is a randomized phase III trial of sequential HDC or conventional chemotherapy (CC) for advanced ovarian cancer in the de novo setting. J. Ledermann, from London, is conducting this trial. To date, 136 patients have been accrued. 2) Randomized phase III trial of HDC with ASCT versus CC in platinum sensitive relapsed ovarian cancer. This study is being conducted by T. Demirer, from Ankara and started to accrual in the beginning of 2003. 3) Phase III randomized trial of sequential HDC versus CC for the treatment of small cell lung cancer. S. Leyvraz from Lausanne is conducting the study. To date, 114 patients have been accrued. 4) Phase I study of allogeneic stem cell transplantation with reduced conditioning for the treatment of the patients with advanced solid tumors. D. Niederwieser from Leiden is conducting this study. This is a hot topic in the field of transplantation and oncology in recent years. Therefore, study has a fast accrual rate compared to the other ongoing studies. Until now, 36 patients from 12 transplant centers have been reported. The vast majority of the patients were treated from renal cell carcinoma (RCC) (n=22) and for breast carcinoma (n=7) and remaining 7 patients were treated for other diseases. Of 36 patients, 19 received cyclophosphamide (Cy), fludarabine (Flu) and ATG, 10 patients received thiotepa, Cy and Flu and 4 received 200 cGy-TBI and Flu as conditioning regimen. This interim report shows that RCC is the most frequent indication and Cy Flu ATG is the most frequent conditioning used in this study. For patients with renal and breast cancer, the trial will be closed probably by the end of 2003. We'll start to phase II randomized studies by the end of this year. 5) A phase II study of intra-familial allogeneic stem cell transplantation for patients suffering from metastatic RCC, which is a joint protocol of the EBMT STWP and French national group. D. Blaise from Marseille will conduct this study and it will be launched soon. 170 patients will be accrued, 60 in transplant group and 110 in control group. 6) A phase III randomized clinical trial for metastatic breast cancer patients achieving complete response to CC. This study will start this year and be conducted by Drs. N. Ueno and G. Hortobagyi from MDACC in Texas. 7) Same as study 6, a randomized trial for metastatic breast cancer patients achieving partial response to CC will be started soon. This will be conducted by M. Aglietta from Turin and will be a joint protocol of EBMT STWP and Italian GITMO Group. We believe that introduction of current ongoing EBMT studies to medical oncology society will increase the cooperation between oncologists and transplanters on the way to have fast answer whether HDC can be a tool for the treatment of some solid tumor.