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Tailored treatment of childhood ALL

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Childhood ALL is characterized by a wide range of clinical and biological features at time of diagnosis. Age, leukemic cell count, CNS involvement, immunophenotype, and genetic subtype may be relevant for a first assessment of the immediate disease-related risk for the patient, and for determining the treatment strategy. Systematic evaluation of these features in the setting of cooperative clinical trials, however, has revealed the limitations to predict the risk of relapse. Therefore, the detailed analysis of early treatment response since the 1980's has revealed the large heterogeneity of *in vivo* treatment sensitivity, not only between the various ALL subgroups, but more importantly even within ALL subgroups. Initially, response was determined through cytological blast count in the peripheral blood (e.g. Prednisone response on day 8 after a prednisone prephase), or in the bone marrow aspirate (on days 8 or 15 of induction therapy). Later, more sensitive techniques allowed to detect minimal residual disease at end of induction or even several weeks later. They utilized either a PCR-based detection of fusion genes, or of the individual T-cell receptor or immunoglobulin gene rearrangements, or a flow-cytometry based detection of leukemia-specific antigen expression.

When reviewing the results of clinical trials which have utilized one or the other technique for *in vivo* response evaluation, it is evident that the benefit of each approach mainly depends on the study questions and endpoints chosen for a given trial. For example, in the recent AIEOP-BFM ALL 2000 study, we wanted to determine the relapse risk with the most sensitive technology available. This was needed to determine the subgroup of patients with the lowest relapse risk in order to ask a randomized question regarding reduction of therapy. Besides the patients with a slower MRD response (intermediate risk group) we utilized MRD detection at week 12 of therapy to detect the subgroup with the highest relapse risk, and to determine if modified chemotherapy and allogeneic hematopoietic stem cell transplantation can reduce the risk of recurrence. We succeeded to utilize the PCR-based MRD assessment with the high standards for quality assessment and sensitivity prescribed by the protocol upfront (Flohr et al. Leukemia 2008;22:771-82). Most surprisingly, even within so-called high-risk groups (e.g. in patients with inadequate early prednisone response, or with Ph+ ALL) MRD revealed major heterogeneity. Recently, several study groups focussed on the underlying biology. The aim is to identify genetic signatures at time of initial diagnosis which may be predictive of subsequent *in vivo* response to a given chemotherapy. For example, Cario et al. (Blood 2005; 105: 821-826) have determined potential mechanisms in initial blasts which may be responsible for the large treatment resistance identified by MRD later during therapy. Similar investigations will be essential to develop novel preventive and therapeutic strategies.

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Perspectives in cell and gene therapy of childhood leukaemia

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Even though tumor immunotherapy represents one of the most attracting and fascinating fields of modern medicine, clinical applications in humans have shown a limited number of significant responses and they demonstrated, on the contrary, the existence of many scientific and practical difficulties related to the translation of apparently flawless *in vitro* or animal models to the context of human cancers. Leukemic cells, in fact, evade the recognition and the elimination by immune effectors by many ways: (i) low or absent expression of tumor-specific antigens; (ii) expression of antigens that are shared with normal cells at certain developmental stages, so that the immune system has become self-tolerant or anergic; (iii) down-regulation of surface expression of MHC molecules; (iv) defective pathways of antigen processing and presentation; (v) absence of appropriate costimulation to deliver a complete activation stimulus to effector T cells; (vi) the presence of inhibitory molecules actively secreted by the tumor itself or the tumor microenvironment (such as IL-10 and TGF-beta); (vii) the expansion of naturally occurring or tumor-induced T cells with regulatory activity. Besides being capable of efficiently overcoming these multiple mechanisms of immune escape, any application of immunotherapy must consider all the practical issues related to the production of immune cells for clinical use. Chimeric T-cell receptors (ChTCRs) represent a valuable tool to overcome the above mentioned obstacles and certainly are an

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attracting and promising line of medical research, whose clinical application in the near future may give new prospects to tumor immunotherapy. The main characteristic of ChTCR is their ability of redirecting T-cell specificity and their killing/effector activity toward a selected target in a non MHC-restricted manner, exploiting the antigen binding properties of monoclonal antibodies. ChTCR are, in fact, artificial T-cell receptors constituted by an antigen-recognizing antibody moiety linked to a T-cell triggering domain. Several CARs have been described so far, directed against various tumoral antigens. Our group is focused on the development and optimization of CAR-mediated approaches for the targeting of different haematological malignancies, including acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (B-CLL), and acute lymphoblastic leukaemia (B-ALL). In fact, for all this kind of leukaemias, a consistent number of patients are still refractory or relapse after standard treatments, therefore supporting the development of innovative anti-tumoral approaches. Different antigens can be exploited to generate specific CARs for these malignancies: the myeloid antigen CD33 could represent an optimal target for AML -as also supported by the development of the gentuzumab ozogamicin monoclonal antibody-, while CD23 could be a valid alternative to CD19 and CD20 for the targeting of B-CLL, since it would allow a more selective action of CAR-transduced T cells against blast cells, whereas CAR specific for the B-lymphoid antigen CD19 have been extensively studied for ALL. A European consortium, *Childhope*, was established in 2006 as a Specific Targeted Research Project funded by the European Community (www.childhope.eu), is now strictly involved in the set up of a phase I clinical trial with anti-CD19 chimeric-receptor modified T cells for the treatment of relapsed transplanted children affected by high-risk ALL.

Society session (Wed, 23 Sep, 14:45-16:45)**EONS session – The future is ambulatory care**

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Distinguished Merit Award

From baby to granny: why do we consider older persons living with cancer different?

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Worldwide more than 11 million people are diagnosed with cancer every year and in developed countries more than 55% of these individuals are over 65 years.

Childhood cancer incidence rates have remained relatively stable over the last decade. The overall incidence rate is 127 per million children.

It is anticipated that by the year 2020, 60% of all malignancies will affect this age group. Given the rising number of older adults in society the management of cancer in older people will be an increasingly common aspect of oncology practice. It is well documented that compared to their younger counterparts older people are likely to receive inadequate treatment and care and this situation varies internationally. A number of factors contribute to this situation including the lack of adequate knowledge in relation to management of older people generally including the management of multiple co-morbid conditions. Inadequacies in the care and treatment received by older people with cancer as opposed to their younger counterparts is well documented. These include under diagnosis, ineffective symptom management and lower survival rates. This situation reflects the ageism within society generally but is particularly concerning within cancer care given the demographics of our patients. Despite the significant population of older people with cancer, there is limited research on older peoples' perspectives regarding their cancer diagnosis and treatment further compounding the lack of awareness of the needs of this patient group. This presentation will consider emerging information on the needs of older people with cancer and consider the challenges for professionals in providing care for older people with cancer. In particular it is a reflection from a pediatric nurse who is asking himself why we consider children with cancer different from older people with cancer.

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A randomised controlled trial of a symptom-orientated home care nursing programme in patients with colorectal and breast cancer receiving oral chemotherapy

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Oral chemotherapy is now commonly used with colorectal and breast cancer patients, and there appears to be considerable toxicity when