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Tailored treatment of childhood ALL

M. Schrappe[1], A. Moericke[1], A. Schrauder[1], M.G. Valsecchi[2], M. Zimmermann[3], A. Biondi[4], V. Conter[4]. [1]*University Medical Center Schleswig-Holstein, General Pediatrics, Kiel, Germany;* [2]*Medical Statistics Unit Univ. Milano-Bicocca, Clinical Medicine and Prevention, Milano, Italy;* [3]*Medical School Hannover, Statistics at Dept. Ped. Hematology, Hannover, Germany;* [4]*Univ. Milano-Bicocca, Dept. of Pediatrics Ospedale S. Gerardo, Monza, Italy*

Childhood ALL is characterized by a wide range of clinical and biological features at time of diagnosis. Age, leukemic cell count, CNS involvement, immunphenotype, 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 immunglobuline 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 hematopoetic 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

A. Biondi[1], G. D'Amico[1], E. Biagi[1]. [1]*Centro M. Tettamanti, Clinica Pediatrica Universita Milano-Bicocca, Monza, Italy*

Even tough 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 contest 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 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 lymphocitic 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 agasint 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

288 Distinguished Merit Award

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

J. Foubert[1]. [1]*Erasmushogeschool, Gezondheidszorg, Brussels, Belgium*

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

A. Molassiotis[1], S. Brearley[1], M. Saunders[2], O. Craven[2], A. Wardley[2], C. Farrell[2], C. Todd[1], K. Luker[1]. [1]*University of Manchester, School of Nursing, Manchester, United Kingdom;* [2]*Christie NHS Foundation Trust, Oncology, Manchester, United Kingdom*

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

patients are at home. The aim of the present RCT was to assess the effectiveness of a home care nursing programme compared with standard care in the management of treatment toxicities, anxiety, depression and quality of life in colorectal and breast cancer patients receiving oral capecitabine (Xeloda®).
Standard care involved patient education at hospital and medication for common toxicities. The home care programme additionally consisted of a home care nurse visit during the first week of chemotherapy, which provided patients with education about symptoms and their management. Weekly phone calls assessed and monitored symptoms, and provided emotional support and reassurance. Patients were assessed using weekly CTC toxicity scales, with anxiety, depression and quality of life scales administered every 6 weeks. Patients were followed up for 18 weeks (6 cycles). In this trial, 164 patients were randomised to receive either home care nursing (n = 83) or standard care (n = 81).
Results: Patients in the home care arm experienced significantly lower symptoms (composite score of all symptoms). More specifically, the had lower oral mucositis (P = 0.003), diarrhoea (P = 0.008), constipation (P = 0.008), nausea (P = 0.003), vomiting (P = 0.041), pain (P = 0.003), fatigue (P = 0.018) and insomnia (P < 0.0005), the majority of symptoms maintaining the improvement over the 6 cycles. There were also trends towards lower anxiety and indications of less service utilization in the home care group. No difference between the two groups was seen for hand-and-foot syndrome, quality of life and depression.
Conclusions: A nursing symptom management regimen-focused home care programme was able to better assist patients in managing treatment-related toxicities and support them during the treatment period than receiving standard care alone.

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Cancer supportive care – creating opportunities within the DRG-system

P. Riemer-Hommel[1]. [1]*HTW des Saarlandes, Institute of Health Research and Technology, Saarbrucken, Germany*

Treating cancer patients combines different professions and numerous transitions between in-patient and outpatient care settings. Awareness and continuity of supportive care are needed to improve the quality of the patients treatment experience and also clinical outcomes.
In this paper, first the reimbursement of supportive cancer care in the German DRG system in inpatient settings is analysed. Reimbursement opportunities and shortcomings are identified. In the second part, the traditional system is contrasted with the ongoing development of so-called flat fees for complex treatments ("*Komplexpauschale*") covering treatment both in ambulatory and in-patient care on a contractual basis between hopitals and ambulatory providers. For cancer care, so far a palliative care flat fee has been introduced allowing the reimbursment of integrated care contracts – these reimbursement rules are analysed towards their capacity to fulfill the need of cancer patients regarding access to and amount of supportive care offered as well as the capacity for guaranteeing continuity of care.
In the next part, the German developments on sector transcending flat reimbursment fees are contrasted with the international debate on evidence-based case rates and performance oriented multiple-sector reimbursement rates in cancer care. Problems and challenges remain when it comes to integrate an adequate level of supportive care into a system characterized by increasing economic pressures through flat fee reimbursements. With ever-increasing demands on nursing and medical care of cancer patients, the discussion of the role of specialized cancer nurses in providing supportive care in the German setting concludes the paper.

Special Session (Wed, 23 Sep, 17:00−18:00)
Circulating tumour cells

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Methods for detection of circulating tumour cells: potential & limitations

C. Panabieres[1], K. Pantel[2]. [1]*Immuno-Virology Department, Lapeyronie Hospital University Medical Center, Montpelier, France;* [2]*Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Metastasis is the main cause of death in patients with solid epithelial tumours (i.e. carcinomas), which represent the majority of cancers in industrialized countries.
Extremely sensitive immunocytochemical and molecular assays are required to allow the unambiguous identification and characterization of single circulating tumor cells (CTC) in the peripheral blood and disseminated tumor cells (DTC) in the bone marrow (BM) as a common and easily accessible homing organ for cells released by epithelial tumors of various origins. Detection methods are usually used in combination with tumor cell enrichment procedures, including density gradient centrifugation (Ficoll-Hypaque separation), immunomagnetic procedures or size filtration methods to enrich tumor cells prior to their detection.
These enrichment and detection methods currently used for the detection of CTC/DTC will be reviewed with their potential and limitations.

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Characterisation and monitoring of circulating tumour cells

K. Pantel[1], C. Alix-Panabières[2], S. Riethdorf[3]. [1]*Universitätsklinikum Hamburg-Eppendorf, Institute für Tumorbiologie, Hamburg, Germany;* [2]*University Medical Center, Lapeyronie Hospital, Montpellier, France;* [3]*Universitätsklinikum Hamburg-Eppendorf, Institute of Tumor Biology, Hamburg, Germany*

Early spread of tumor cells is usually undetected by current imaging technologies. Therefore, in patients with cancer and no signs of overt metastases, sensitive methods have been developed to detect circulating tumor cells (CTC) in the peripheral blood and disseminated tumour cells (DTC) in the bone marrow. These technologies can be classified into cytometric and/or immunological and molecular approaches. Interestingly, the bone marrow seems to be a common homing organ for cells derived from various epithelial tumors, and level 1a data from European and US groups have sustained the prognostic impact of DTC in the BM of breast cancer patients. Sequential peripheral blood analyses, however, are more convenient for patients than BM analyses in patients with solid tumours and many research groups are currently assessing the clinical utility of CTC for assessment of prognosis and monitoring of systemic therapy. In view of the plethora of prognostic indicators – especially in breast cancer – monitoring of CTC during and after systemic adjuvant therapy might provide unique information for the clinical management of the individual cancer patient and allow an early change in therapy years before the appearance of overt metastases signals incurability. There is an urgent need for biomarkers for real-time monitoring of the efficacy of systemic adjuvant therapy in individual patients. At present, the success or failure of anti-cancer therapies is only assessed retrospectively by the absence or presence of overt metastases during the post-operative follow-up period. However, overt metastases are, in general, incurable by most current therapies. The monitoring of CTC will provide new insights into the selection of tumor cells under biological therapies. Molecular characterization of DTC and CTC opens a new avenue for understanding early metastatic spread of tumour cells and might contribute to the identification of metastatic stem cells with important implications for future therapies.

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Detection and characterization of tumour cells in sentinel lymph nodes and bone marrow of patients with breast cancer

O. Fodstad[1], S. Tveito[1], H. Høifødt[1], D. Park[2], T. Sauer[2], R. Kåresen[2]. [1]*The Norwegian Radiumhospital, Tumor Biology, Oslo, Norway;* [2]*Ullevål Hospital, Pathology, Oslo, Norway*

The sensitivity and accuracy of methods for tumour cell detection in sentinel lymph nodes and bone marrow from breast cancer patients is debatable. In a large collaborative study on samples obtained at time of primary surgery we have examined the presence of tumour cells by immunobead selection (IMS) and characterization, in many cases followed by molecular studies on a pure population of cancer cells specifically isolated by the CellPick system (MMI). The sentinel lymph nodes were cut in half, one half was disaggregated and used for IMS with an anti-EpCam antibody, and the other half for immunohistochemical (IHC) identification with an anti-cytokeratin antibody applied to ten sections of each node. The IMS method showed by far the highest sensitivity, but there was only a minimal overlap in results between the two methods. Verification of the cells identified with IMS as tumour cells was obtained by simultaneous binding of non-magnetic fluorescent beads coated with antibodies recognizing known breast cancer markers (Muc1, erbB2, EGFR, B7-H3). Surprisingly, such validated tumour cell positive samples were equally distributed between the IHC positive and negative groups. The results suggest important methodological problems inherent to both IMS and IHC detection approaches. To further investigate this, we used qRT-PCR and arrayCGH on the IMS selected cells followed by specific isolation of 5−20 bead-confirmed tumour cells. qRT-PCR targeting mammaglobin, AGR2, TFF1, and SBEM mRNA were positive with at least one marker in 50% of 60 IMS EpCam positive samples studied, but was negative in cells isolated from bone marrow. ArrayCGH