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Quality assurance through outcome registration in colorectal cancer: An ECCO initiative for Europe

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In recent years there have been significant improvements in cancer treatment. Besides effective (neo)adjuvant treatment regimes, new surgical techniques made a big contribution to these improvements. Standardised and quality controlled surgical trials seem to have a positive effect that reaches further then the patients and doctors that participated in the study. Good examples are the Dutch TME trial and the Dutch D1-D2 Gastric Cancer Trial. In both trials standardisation and quality of surgical treatments was continuously emphasised by means of masterclasses, supervision and visitation with lasting positive effects.
However, most patients were treated without being enrolled in clinical trials. Furthermore, elderly patients or those with multiple comorbidities are often excluded from trials, leaving little evidence for the treatment of these categories of patients. Therefore, to improve quality of care for the entire patient population, a comprehensive audit could be a more effective instrument. In Europe, several national rectal cancer audit registries have been established of which all showed positive and very economic effects on outcome of surgical care. Despite these laudable efforts there is still a wide variation in treatment outcome between countries, regions and institutions, which calls for a European audit on cancer treatment outcome.
Urged by these arguments, the European Society of Surgical Oncology (ESSO) initiated an international, multidisciplinary, outcome-based quality improvement program which is fully embraced by the European CanCer Organisation (ECCO). Initially, the focus will be on colorectal cancer. In the first period of 2 years the registration will make use of currently existing audit systems for colorectal cancer as in Norway, Sweden, Denmark, the United Kingdom, the Netherlands and Belgium, and start a benchmarking process. The national audit coordinators will provide access to their national databases and will form a multidisciplinary Steering Committee. The second period starts after the development of the European registration system. The data will be continuously used for benchmarking and internal feedback among participants. Afterwards, this experience will be used to extend the audit to other solid malignancies such as breast, gastric and oesophageal cancer.

Scientific Symposium (Mon, 21 Sep, 16:15−18:15)
New drugs and novel therapeutic targets for haematological malignancies

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New drugs and novel therapeutic principles in multiple myeloma

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The outcome of Multiple Myeloma (MM) patients has significantly improved over the last decade, and this has been mainly due to the efficacy of novel drugs, such as Thalidomide, Lenalidomide, and Bortezomib. Nevertheless, most patients relapse and become eventually refractory to all available treatments. Therefore, drugs with novel mechanism of action are urgently needed in order to improve the outcome of these relapsed/refractory MM patients.
Several of these novel targeted anti-myeloma drugs are currently in the preclinical and early clinical steps of development. These drugs interfere with mechanisms which are thought to play a key role for multiple myeloma pathogenesis. They can be classified in five groups according to the cellular structures or mechanism which specifically target: 1. Agents acting through cell surface receptors present in plasma cells (PC) such as activators of cell death receptors, inhibitors of receptors Tyrosine Kinase or monoclonal antibodies against PC antigens. 2. Inhibitors of signalling pathways including Farnesil Transferases, MAPKs, mTOR, or AKT inhibitors. 3. Drugs that interfere with the cell cycle such as CDKs or Aurora Kinase inhibitors. 4. Inhibitors of the unfolded protein response like HSP, Proteasome or aggressome formation inhibitors. 5. Epigenetic agents represented by hypomethylating compounds and deacetylase inhibitors.
Unfortunately, the expectations raised by some of these agents have not been so far confirmed in the clinic, except for two groups of agents that upon used in monotherapy have clearly demonstrated antimyeloma activity in relapsed or refractory myeloma patients: novel proteasome inhibitors such as carfilzomib, and the novel IMID pomalidomide. Moreover these drugs seem to be able to overcome the refractoriness to bortezomib and lenalidomide respectively. Other drugs which have shown promising efficacy, although in combination with the already approved agents, are histone deacetylase inhibitors and inhibitors of the AKT pathway.

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Tyrosine kinase inhibitors in myeloid malignancies

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Even in younger patients it is now emerging that standard chemotherapy with or without the addition of transplantation. There is increasing emphasis in developing risk based approaches. Considerable information about the molecular characteristics of the disease is emerging, which comprises mutations and over-expression of various genes which have brought further prognostic but not yet predictive information.
FLT3 gene mutations occur as internal tandem repeats in 25 to 28% of patients under 60 years and are less frequent in older patients. In addition point mutations in the activation loop of the receptor occur in approximately 7%. The consistent finding is that the ITDs predict that there will be a higher risk of relapse and have become a therapeutic target. Several molecules have demonstrated inhibitory activity in pre-clinical *in vitro* and *in vivo* models. Two, PKC-412 and CEP-701, have entered phase 3 trials in combination with standard chemotherapy. Several unrandomised phase 2 studies mostly in FLT3 ITD patients in relapse suggested that monotherapy produced responses which were limited to clearance of peripheral blasts and in some cases substantial reductions in marrow blasts, but complete remissions were rare. Any responses were of limited duration.
A preliminary randomised comparison of chemotherapy with or without CEP-701 in relapse gave encouragement, but the preliminary result of the subsequent phase 3 trial showed no benefit. Two phase 3 trials in combination with conventional chemotherapy in younger patients are ongoing. It appears that there are two requirements for efficacy. First the blast cells must be sensitive, and second adequate inhibitory levels must be achieved in the plasma.
Another potentially druggable target is *cKIT* mutation which have been reported to occur in about 30% of patients with favourable cytogenetics, and predict an increased risk of relapse combination with chemotherapy. Inhibitors such as PKC-412 or Dasatinib have anti-KIT activity and trials of this approach in this small subset have been initiated. Several other molecular targets will be identified in AML which may be druggable, but it seems likely that the most effective use will be in

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JAK-2 and its inhibitors for myeloid neoplasias

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The molecular pathogenesis of *BCR-ABL1*-negative classic MPN, i.e. primary myelofibrosis (PMF), polycythemia vera (PV) and essential thrombocythemia (ET), remained elusive until early 2005 when several groups reported a Janus kinase 2 (*JAK2)* gain-of-function mutation (*JAK2*V617F) in the majority of patients with these diseases. In 2006, an activating thrombopoietin receptor (*MPL)* mutation (*MPL*W515L) was reported in *JAK2*V617F-negative PMF and later in ET. In 2007, other *JAK2* mutations (exon 12 mutations) in *JAK2*V617F-negative patients with PV were described. These discoveries raised the possibility of targeting JAK2 as a therapeutic approach.
TG101348: Summary of abstract presented at the 2009 European Hematology Association meeting. TG101348 was administered orally once daily in 28-day cycles in a phase 1 dose-escalation study. Twenty eight patients were treated in the dose escalation phase, at 8 dose levels from 30 mg to 800 mg daily. At the highest dose level (800 mg), 2 of 6 patients experienced dose-limiting toxicity (asymptomatic grade 3 or 4 amylasemia with grade 4 lipasemia in 1 patient) that was reversible upon holding drug (both patients currently being treated at a lower dose); consequently, the maximum tolerated dose (MTD) was declared at 680 mg. Grade 3/4 thrombocytopenia was seen in 8 patients (29%); grade 3/4 neutropenia was seen in 3 patients (11%). Six (21%) of the 28 study patients have so

far discontinued treatment. A reduction in spleen size was seen in all 22 remaining patients (100%). All 14 patients with leukocytosis at baseline have experienced a marked reduction in their WBC count. Of the 25 *JAK2*V617F-positive patients, 8 (32%) have experienced a greater than 50% reduction in granulocyte mutant allele burden.

INCB018424: Summary of abstract presented at the 2008 American Society of Hematology meeting. INCB018424 (ATP mimetic from Incyte) is a potent, selective inhibitor of JAK 1 and 2. Over 100 patients were enrolled with a mean exposure to drug of >5 months. Twenty percent of patients had received INCB018424 for >9 months. INCB018424 is generally well tolerated with the primary toxicity being dose-dependent grade 3 or 4 reversible thrombocytopenia which occurred in 0%, 18% and 32% of patients dosed with 10 mg BID, 50 mg QD or 25 mg BID. INCB018424 was associated with a rapid reduction of splenomegaly with 50% or greater reduction being observed in 35% of patients dosed with 10 mg BID or 50 mg QD, and 59% of patients dosed with 25 mg BID regimens. Improvements were also seen with constitutional symptoms: night sweats, pruritis and fatigue. There was a dose-dependent weight gain, most pronounced in patients with the lowest body mass index values at baseline. Profound reductions in inflammatory cytokines were observed by the first evaluation at week 2 in virtually all patients, and were maintained during therapy.

CEP-701: Summary of abstract presented at the 2009 European Hematology Association meeting. CEP-701 (ATP mimetic from Cephalon) was studied in *JAK2*V617F-positive MF, in a phase 2 clinical trial, at MD Anderson Cancer Center. Patients were treated with CEP-701 at an initial dose of 80 mg twice daily. A total of 22 patients were treated. Responses were seen in 6 patients (27%) and consisted of reduction in spleen size alone in 3 patients, transfusion independency in two patients, and reduction in spleen size together with improvement in neutrophils and platelets in one patient. Main toxicities were anemia (grades 3−4: 18%), thrombocytopenia (grades 3−4: 18%) and diarrhea (all grades: 68%; grades 3−4: 9%). CEP-701 is currently being evaluated by other centers in the US in *JAK2*V617F-positive MF, PV and ET.

In addition to the three I described above, many other anti-JAK2 ATP mimetics or HDAC inhibitors are either being evaluated or soon will be:

1. XL019 (ATP mimetic from Exelixis; completed and not to be pursued further; MF and PV)
2. CYT387 (ATP mimetic from Cytopia; study scheduled to open soon at the Mayo Clinic; MF)
3. AZD1480 (ATP mimetic from AstraZeneca; recruiting in the US and France; MF),
4. SB1518 (ATP mimetic from S*BIO; recruiting in Australia and USA; MF, leukemia and lymphoma).
5. ITF2357 (HIDAC inhibitor from Italfarmaco; phase 2 study completed in Italy; JAK2V617F-positive MF, PV or ET),
6. MK0683 (also known as vorinostat; HDAC inhibitor from Merck; ongoing in Europe; PV and ET)
7. LBH589 (also known as panobinostat; HDAC inhibitor from Novartis; scheduled to open soon in the US; MF)

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HDACs inhibitors for lymphoid neoplasias

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Epigenetic modulation involving the regulation of histone acetylation is proving to be a valid antineoplastic strategy, leading to the first FDA approval of the histone deacetylase inhibitor (HDACi), vorinostat, for cutaneous T-cell lymphoma. Acetylation of nucleosomal histones leads to silencing of tumor suppressor and pro-apoptotic elements of critical importance to lymphocyte regulation; this deacetylation is controlled by histone deacetylase (HDAC) activity. The growing understanding of the role of class II and III deacetylases, which regulate the post translational acetylation of proteins, and their inhibition by various agents will also be reviewed, particularly with regard to lymphoid malignancies. Inhibition of histone and protein deacetylase activity has been shown to affect tumor cell differention, growth arrest, and apoptosis in multiple cell types; we will review several of the pathways, with a focus upon DNA damage response elements, as well as effects of these drugs upon proinflammatory cytokines and the microenvironment.

A review of the pharmacology, preclinical single agent and combination activity of various HDAC inhibitors across the range of lymphoid malignancies, from acute lymphoblastic leukemia through B and T cell lymphomas on to multiple myeloma as well as the potential role of HDAC inhibitors in allogeneic transplant (given the sensitivity of activated lymphoid cells to these agents) will be presented.

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How to select a new drug in paediatric oncology

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How to select a new drug in paediatric oncology

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Each year, 15000 children are diagnosed with cancer in Europe: 75% are cured with current multimodality treatments while 3000 die. Paediatric malignancies are rare diseases representing only 1% of all cancers in human. However, cancer remains the first cause of death by disease over 1 year of age in Europe and new innovative therapies are urgently needed. The paediatric oncology community has been working together during the last 40 years through clinical research networks that achieved major progress in the cure of children with cancer. New safe and effective anticancer drugs need now to be introduced in standard treatments. The European Paediatric Medicines Regulation is currently changing the landscape of paediatric drug development in Europe, and children with cancer may benefit eventually. However, there are some risks and pitfalls that must be anticipated to assure that children with cancer will benefit from the EU regulation.

The development of targeted therapies based on a better knowledge of tumour biology has opened avenues and hope for many refractory cancers in adults such as kidney and liver cancer. Those compounds must be studied in children as well. There are more than 500 new anticancer compounds in clinical development and many more in industry pipelines since oncology became the first area for drug development. Selection and prioritization of compounds to be evaluated in children is the major challenge, within the new frame set up by the EU regulation. Indeed, cancer is rare in children. More than 60 different diseases from rare to extremely rare tumours are observed in the paediatric population. In addition, biology will dissect further paediatric malignancies with regard to therapies as biology has already dissected/fragmented frequent adult cancers in rarer sub-groups that deserve different types of treatment, as illustrated by breast cancer. Understanding biology of the different paediatric cancers, identifying altered pathways and genetic alterations that are functionally involved is crucial and represents the first step to select compounds of interest. Relevant preclinical models of paediatric tumours, either transplantable or transgenic, are needed to validate druggable targets using compounds. Then, extrapolation from adults to children may speed up the initial phases of dose-finding in the paediatric population while innovative study designs are clearly mandatory to evaluate targeted therapies and their biomarkers in rare diseases such as paediatric malignancies. Thus, the choice of anticancer drugs to be evaluated in children should be based on the paediatric needs identified through biology and state of the art for the treatment of each paediatric cancer. A strong and fruitfull partnership in between the Paediatric Oncology Community, the Pharmaceutical Industry and the Regulatory Bodies is mandatory to assure that the best expertise is accessible to establish the more appropriate strategies for new drug developments for children with cancer.

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Phase I and II trial methodology

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The conduct of early clinical trials in paediatrics poses some unique challenges. Balanced against this is a need to continue to develop anti cancer agents in children. In recent years new European legislation has mandated the investigation of all new drugs in children when marketing authorisation is being sought. This is leading to greater numbers of drugs being available to test. In a relatively small pool of patients this in itself poses challenges. The efficient use of children in such studies becomes increasingly important and study design therefore critical.

This talk will look at the methodological techniques that need to be considered when undertaking Phase I/II studies. Whilst many issues are generic, the availability of existing adult trial data does result in the need to modify some design methods and these will be highlighted. The critical importance of study design and selection of appropriate and informative patients will be discussed.

Early clinical trials in children do pose their own challenges, but experience suggests that cooperative networks can deliver these trials in a timely fashion with good quality data and high levels of safety.