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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