Special Session (Tue, 22 Sep, 13:30–14:30)
The management of GIST tumours

123 INVITED

Surgery perspective

P. Hohenberger[1]. [1]*University Hospital Mannheim, Surgical Oncology and thoracic surgery, Mannheim, Germany*

Surgery is the standard treatment for primary, resectable gastrointestinal stromal tumor (GIST). However, surgical resection often is not curative, particularly in cases of large GIST. By 5 years after complete removal of their tumor, half of patients so treated have relapsed. The efficacy of imatinib in the treatment of advanced GIST has aroused interest in the therapeutic potential of multimodality approaches to management that combine surgery with systemic therapy. The approval of imatinib as an adjuvant after GIST resection larger than 3 cm in the US and in patients with significant risk of recurrence in Europe makes it necessary to carefully evaluate the following aspects: 1. The data to be derived from intraaoperative findings as tumor rupture or the necessity of performing a multivisceral resection pose the patient at considerable risk for recurrence. 2. Neoadjuvant treatment of locally advanced GIST has been proven to be well tolerable effective in the RTOG-132 study. The german so-called Apollon trial proved that organ-preserving surgery with very low postoperative morbidity is a major outcome effect of pretreatment and improves patient's QOL 3. In patients with primary GIST who are at high risk for postoperative relapse the Z9001 randomized phase 3 trial comparing imatinib and placebo given for 1 year after primary R0 resection showed significantly shorter time to relapse, but details of tumor pathology and mutation data need to influence the decision whom to treat. 4. The more recent data-driven classification by Miettinen and Lasota is going to replace the Consensus (2002) system and clearly depicts groups of patients with real high risk of recurrence and those in whom – irrespective of tumor size – no adjuvant therapy is indicated. A third group with thorough counseling of the patient can also be defined. 5. Long-term results of surgery in patients with response to imatinib show encouraging results and guide the way towards a phase III study with surgical resection of responsive, residual tumor as the interventional arm versus imatinib alone.

124 INVITED

Gastro-intestinal stromal tumors (GIST): the model for solid tumors treated with tyrosine kinase inhibitors

S. Sleijfer[1]. [1]*Erasmus University Medical Center, Deparment of Medical Oncology, Rotterdam, The Netherlands*

Gastro-intestinal stromal tumors (GIST) are rare tumors from the digestive tract. Despite their rarity, they are of great importance for oncology by being one of the first tumor entities for which a cancer-cell specific therapy became available. Through advances in molecular biology, it was revealed that GIST is driven by mutations in the *c-KIT* and/or *Platelet-derived growth factor receptor A (PDGFRA)* gene yielding receptors that are constitutively activated. Imatinib is a tyrosine kinase inhibitor (TKI) targeting these receptors and its advent has dramatically improved the outcome of advanced GIST patients. Meanwhile other TKIs exhibiting anti-tumor activity against GIST have been identified. Despite the recent introduction of these compounds for GIST patients, major improvements have already been accomplished concerning insight into the mechanism of action, resistance, and patient management issues. In particular insight into resistance has improved. It appears that there are two types of resistance; primary and secondary resistance, the first referring to mechanisms already present before treatment initiation and the latter acquired during therapy. In both primary and secondary resistance, differences in pharmacokinetics between individuals were recently identified to be involved. However, the most important cause underlying primary resistance is the mutational status of *c-KIT* or *PDGFRA*. This mutational status is of clinical relevance given differences in sensitivity to imatinib between the products from these diverse mutations. As a consequence, the initial dose of imatinib is tailored according to the underlying *c-KIT* mutation. Mutations in *c-KIT* and *PDGFRA* are also the main culprit for secondary resistance. Although several of these novel mutated products can be inhibited by other TKIs, progressive GIST almost always harbors numerous variant mutations differing in sensitivity to TKIs. As a result, it is unlikely that all these different products can be inhibited by a single TKI, while combinations of TKIs are hardly tolerable due to toxicity. Consequently, novel ways to treat GIST progressing under TKIs are needed. All together, lessons learned from GIST are widely applicable to other tumor entities rendering GIST the paradigm of solid tumors treated with TKI. This presentation addresses GIST, in particular its treatment, mechanisms accounting for resistance, and potential future perspectives.

Special Session (Tue, 22 Sep, 13:30–14:30)
Palliative cancer care

125 INVITED

Optimal approaches to persistent and chronic pain: new perspectives on an old problem

R. De Wit[1]. [1]*Maastricht University, Department of Nursing Science – Faculty of Health Medicine and Life Sciences, Maastricht, The Netherlands*

Pain is among the most common and distressing symptoms encountered by patients with advanced cancer. The relief of pain is one of the most important clinical tasks of palliative care. The challenge of this task is to achieve effective relief with minimal side effects and to deliver this service to all patients in need of these interventions. Identification of barriers to implementation of effective strategies, determination of strategies to overcome these obstructions, and the monitoring of outcomes for purposes of quality improvement are important aspects.
Although many factors are contributing to the problem of unrelieved pain, patients reluctance to report pain, misconceptions about tolerance, addiction, physical dependency, concerns about side-effects of pain medication, and concerns about the use of pain medication around the clock prevent patients from reporting pain and taking adequate pain medication are important barriers inhibiting adequate management of pain. As the number of cancer patients is growing, there is an urgent need to develop a home monitoring system that makes data immediately available for review by a multidisciplinary pain or palliative team. Systematic approaches to pain management, by means of "disease management" hold the promise of realizing more of the potential benefit of self-monitoring pain, patient adherence to medication (compliance) pain education and instruction by means of teleguidance, improved self-management, and awareness of clinical alerts.

126 INVITED

Advanced disease: managing the complex journey of cancer recurrence towards end-of-life care

P. Larkin[1]. [1]*University College Dublin, Health Sciences Centre Belfield, School of Nursing Midwifery and Health Systems, Dublin, Ireland*

Although the interface between cancer care and palliative care remains evident, the recent revision of the 1990 WHO definition of palliative care to an approach to care beyond malignant disease (WHO 2002) has led to criticism that palliative care is now less clear in its goals and objectives. Similarly, the development of supportive oncology and the interpretation of the use of *palliative* chemotherapy and radiotherapy for symptom management also creates anomalies for patients and families. It is suggested that the term palliative care does not give clear signals to the patient and family about the transition and future consequences of advanced disease (Illhardt 2000).
In this presentation, the impact of this shft will be reflected in relation to the patient and family experience of transition to palliative care services and how a professional re-interpretation of language can confuse and misinform patients about the reality of thier future. The findings of a study into the the transition experiences of patients with advanced cancer will be used as a template to debate the impact of cancer recurrence and the facing of end-of-life on patients and families. A multidisciplinary "total pain" approach will be advocated in order to enable a positive experience of living well until death to occur. Finally, the psychological impact of understanding the finite life wil be addressed and how cancer care practitioners can shape their practice to support patient's at life's end.

Special Session (Tue, 22 Sep, 13:30–14:30)
Synthetic lethality as a novel strategy of cancer therapy

127 INVITED

Hitting cancer where it hurts most: the RNAi strategy to discover synthetic lethal interactions in cancer

R.L. Beijersbergen[1]. [1]*NKI-AvL, Molecular Carcinogenesis, Amsterdam, The Netherlands*

The search for novel therapeutic agents in cancer relies on the identification and validation of new molecular targets. Ideally, inhibition of such targets would have detrimental effects in tumor cells where normal cells would not be affected. Tumor cells have acquired multiple mutations associated with different properties of malignant transformation. However, gain of these

mutations can also result in increased susceptibility to specific changes and situations. The concept that a particular mutation has deleterious consequences under specific conditions is known as synthetic lethality. Two genes are defined as synthetic lethal when cells die if they have both genes mutated but can survive if either gene alone is mutated. The approach of exploring synthetic lethal gene-gene interactions is attractive because it turns a hallmark of cancer cells, specific mutations, into a weakness that can be explored therapeutically. The development and application of the RNAi technology in mammalian cells has enabled us to systematically examine the consequence of inactivation of large numbers of individual genes in human (tumor) cell lines with defined tumor specific genetic alterations. This lecture will focus on the use of large collections of synthetic siRNAs in a screening model based on primary human cells with defined genetic alterations for the discovery of specific synthetic lethal interactions.

128 INVITED

Investigation of RAS and PI 3-kinase signaling networks in cancer using synthetic lethal screens

J. Downward[1]. [1]*London Research Institute, Signal Transduction Laboratory, London, United Kingdom*

The RAS oncogene is very frequently activated in human tumours and, as a result, the signaling pathways it controls have been well studied. However, effective targeting of these pathways as a therapeutic approach to cancer has remained elusive.
In order to find novel targets in RAS signaling pathways, we have undertaken a number of studies using large-scale RNA interference libraries. One has been a screen for genes that cause apoptosis in RAS oncogene addicted cells. In this way a number of pathways have been identified that are important for survival of RAS transformed, but not normal, cells. Some of these have not previously been implicated in RAS signaling. Further investigation indicates that some of these hits reflect true RAS oncogene addiction while others represent acute synthetic lethality of target knockdown with RAS signal. Targeting both mechanisms, synthetic lethality and oncogene addiction, together may provide optimal differential killing of cancer cells relative to normal cells.
An example of the potential power of blocking RAS signaling has been provided recently when we introduced point mutations into the gene encoding the phosphatidylinositol 3-kinase p110α, which block its ability to interact with activated RAS. Mice homozygous for the p110α mutation show a very dramatically reduced rate of cancer incidence in two models of RAS oncogene driven tumour formation. Failure of RAS to engage PI 3-kinase results in elevated rates of apoptosis in tumour precursor lesions and consequent failure of tumours to develop. Targeting this interaction may have clear therapeutic potential.

Special Session (Tue, 22 Sep, 13:30−14:30)
Breast cancer in the elderly

130 INVITED

Breast cancer in the elderly: a medical perspective

H. Wildiers[1]. [1]*U.Z. Gasthuisberg, Department of General Medical Oncology – Multidisciplinary Breast Centre, Leuven, Belgium*

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer mortality in women worldwide. The elderly comprise a large part of the breast cancer population, and there are important specific considerations for this population. From the medical perspective, mainly the use of chemotherapy is challenging since toxicity increases with age and efficacy in terms of overall survival effect might decrease.
Certainly in the adjuvant setting, the balance between benefits and harm from chemotherapy can be delicate, and careful assessment of the patient including some form of geriatric assessment are crucial. Treatment with adjuvant chemotherapy should not be an age-based decision but instead take into account individual patients' estimated absolute benefit, life expectancy, treatment tolerance, and preference. Recent studies indicate that adjuvant chemotherapy is mainly beneficial for older people with hormone insensitive tumors and nodal involvement, while the benefit is much less clear for those with highly hormone sensitive tumors. However, there remains considerable uncertainty remains regarding the subgroups of older women most likely to benefit.
Also concerning the choice of chemotherapy, specific regimens/aspects can be considered. Anthracyclines are usually preferred over CMF in elderly patients with breast cancer. A recent phase III study showed that a 'soft' chemotherapy regimen like oral capecibatine is clearly inferior to classical AC/CMF in this population. Taxane regimens such as TC are a valuable alternative to anthracyclines without intrinsic cardiotoxicity.
In metastatic disease, quality of life is more important than quantity of life, certainly for older individuals. Preference is often given to chemotherapeutic agents with 'safer' profiles such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine, and vinorelbine.
Targeted therapies such as trastuzumab and bevacizumab have been shown to be useful in the treatment of breast cancer. The risk of side effects increases with age however, and certainly for antiangiogenic compounds, the balance between benefits and risks/costs should be carefully weighed.

Special Session (Tue, 22 Sep, 13:30−14:30)
Individualisation of treatment based on pharmacokinetics and pharmacogenomics

131 INVITED

Population-based PK/PD modelling

S. Kaestner[1]. [1]*Plymouth hospitals NHS Trust, Medicines Managment Team, Plymouth, United Kingdom*

Cancer chemotherapy drugs are characterised by narrow therapeutic windows and significant intra- and inter-patient variability in therapeutic and toxic effects. In an attempt to reduce this variability most chemotherapy doses are traditionally individualised according to patient body surface area, but for many drugs this approach appears to have limited benefit. In addition, subsequent dose reductions or delays are usually made in response to excessive toxicity, while it is less common to increase doses for patients who tolerate treatment well to avoid the risk of under-dosing and suboptimal therapeutic effects.
The pharmacokinetics (PK) and pharmacodynamics (PD) of chemotherapy drugs and their metabolites may be influenced by various intrinsic and extrinsic factors, such as for example gender, age, body size measures, nutritional status, renal/hepatic function, disease, tumour characteristics, drug resistance, enzyme functions, genetics, concomitant medications, smoking and diet. It is therefore complicated to select a dose with maximal anti-tumour effects and acceptable levels of toxicity, but it is clear that an understanding of the sources of variability is crucial to the optimal individualisation of therapy. In population-based PK/PD modelling the potential contributions of these different factors to the intra- and interpatient variability in PK/PD are studied in large groups of patients. Statistical models can then be used to develop optimised prospective dosing strategies for specific populations, subpopulations, or individual patients based on the most relevant variables. Population PK and so called Bayesian models have been successfully developed and applied prospectively for various cytotoxic drugs, including paclitaxel and carboplatin. However, the clinical application of the approach may be limited by the lack of relationships between PK and PD for many chemotherapy drugs. Additionally, the difficulties in measuring the clinical effects of chemotherapy drugs most commonly results in the use of toxicity as the PD measure, and its use as a surrogate for clinical effect may not be appropriate in all settings. The clinical feasibility of PK/PD modelling therefore needs to be carefully assessed in each case.

132 INVITED

Individualisation of cancer treatment by pharmacogenetics

H.J. Guchelaar[1]. [1]*Leiden University Medical Center, Dept. Clinical Pharmacy & Toxicology, Leiden, The Netherlands*

Although in recent years, chemotherapeutic options for treatment of cancer have expanded, overall benefit – both with respect to efficacy and toxicity – could be improved. Pharmacogenetics studies the association between heritable functional variants in DNA (genotype) with outcome of therapy (phenotype). In recent years, pharmacogenetics in oncology has become an increasing field of research. Pharmacogenetics in oncology will ideally allow oncologists to individualise therapy based on a genetic test result. Severe toxicity and clinically significant underdosing may be avoided, whereas predicted non-responders can be offered alternative therapy.
In this presentation an overview of pharmacogenetics in oncology will be given including: thiopurine *S*-methyltransferase (TPMT) enzyme activity and 6-mercaptopurine (6MP) in treatment of acute lymphoblastic leukaemia (ALL); dihydropyrimidine dehydrogenase (DPD) enzyme activity and 5-fluorouracil (5FU) or capecitabine; uridine diphosphate glucuronosyl transferase (UGT) activity and SN-38 (active metabolite of irinotecan); glutathione S-transferase (GST) and platinum-based drugs or irinotecan; excision repair cross complementing group 1 (ERCC1) and platinum-containing compounds; cytochrome P450 2D6 (CYP2D6) enzyme and tamoxifen in treatment of breast cancer; methylene tetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS) and 5FU.