CTCs retain many molecular characteristics of the primary tumor and its metastases, and can be used to examine the presence of a target or its loss in tumor cells by for example fluorescent in situ hybridization (FISH), sequencing or by immunofluorescence. Analyses of tumor cell specific changes such as mutations or translocations could be useful, allowing a better understanding of mechanisms of resistance or susceptibility to treatment with novel agents. Limitations to these studies, however, may include RNA degradation and contaminating WBC RNA.
Overall, it is envisioned that CTC biomarkers will play an important future role in drug development.

169 INVITED

Genomics in early clinical trials

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It is common to employ gene expression profiling as a predictive marker discovery tool in Phase II clinical trials. However, there are several reasons why this supervised approach to predictor discovery may not yield reliable predictors. The multiple comparison problem, inherent to microarray analysis, leads to a large number of nominally small p-values, many of which are due to chance. Another confounder is that clinically important phenotypic characteristics (e.g. histologic grade, estrogen receptor status of breast cancer) are often associated with coordinated expression of thousands of genes. A simple comparison of transcriptional profiles of breast cancers that respond to preoperative chemotherapy with those that did not will reveal many differentially expressed genes. However, most of these genes will reflect the gene expression differences that underlie the phenotypic differences between the 2 response groups. Since responses are more frequent in high grade, ER-negative cancers compared to low grade and ER-positive tumors, the resulting pharmacogenomic response predictors often represent a predictor of clinical phenotype and may provide only modest added predictive value. The often small gene expression differences that are specific to responders and non-responders are easily masked by the large-scale differences due to any phenotypic imbalance between the response groups and the often small sample size of these discovery studies precludes meaningful adjustment for these confounders. Therefore, candidate predictive marker testing, as opposed to discovery, may be more efficient in conjunction with Phase II clinical trials. Usually, enough is known about the mechanism of action of most new drugs that one could rationally propose at least one or more response predictors. Conceptually, testing a response predictor in a prospective clinical trial is no different from testing a candidate drug in a therapeutic study and a 2-step, Phase II design can easily be adopted for a parallel, multi-arm, simultaneous marker and drug evaluation program.

References

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170 INVITED

Clinical biomarkers and imaging for radiotherapy-induced cell death

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Radiation, like most anti-cancer treatments, achieves its therapeutic effect by inducing different types of cell death in tumors. To evaluate treatment efficacy a variety of routine anatomical imaging modalities is available. However, changes in tumor function (*e.g.,* metabolism, proliferation, hypoxia) often precede these volumetric alterations and may reflect tumor responses to treatment more accurately. Therefore, reliable biomarkers and imaging modalities that could assess treatment responsiveness in an early phase would be very useful to identify responders and/or avoid ineffective, toxic therapies. A better understanding of cell death mechanisms following irradiation is essential for the development of such tools. This has become even more important with the recent introduction in clinical protocols of targeted biological agents that modify the radiation response at different levels.
The currently available assays to detect the most prominent types of radiation-induced cell death (apoptosis, necrosis, mitotic catastrophe, autophagy and senescence) *in vivo* and, if applicable, *in vivo*, will be presented in short. Two examples of non-invasive imaging techniques that allow visualization and quantification of radiation-induced cell death *in vivo* will be discussed in more detail: ^{99m}Tc-Annexin V scintigtaphy (TAVS) and ^{99m}Tc-methoxyisobutylisonitrile (MIBI) SPECT.
In a series 61 patients (NHL n = 27; HNSCC n = 16; NSCLC n = 16; SCLC n = 1; sarcoma n = 1) treated with low dose (2x2 Gy) involved-field radiotherapy (n = 27), cisplatin-based concurrent chemoradiotherapy (n = 16) or cisplatin-based chemotherapy (n = 18), we found a significant correlation between tumor TAVS uptake within 24−48 hours after start of treatment and outcome. More recently, we established a significant correlation between pre-chemotherapy MIBI uptake and tumor size change after 2 cycles of chemotherapy in 11 patients with advanced NSCLC.
The predictive value of these tests might help to design novel (combined modality) strategies and evaluate treatment effects at an early stage. Clearly, additional and more specific methods are needed for accurate patient selection to ensure optimal treatment and limit side effects.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Refining treatment and the cost of the cure − lessons from soft tissue sarcoma in young people

171 INVITED

Stratifying treatment for rhabdomyosarcoma

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All current clinical trials utilise some combination of the best known prognostic factors to stratify treatment intensity for patients with good or poor predicted outcomes. Such an approach is used as much to avoid over treatment of patients with a good chance for cure, as to improve cure rates for patients with less favourable disease.
Experience has confirmed the relevance of a surgical–pathological classification which groups patients according to the extent of the extent of disease remaining after the initial surgical procedure(s) but before beginning chemotherapy.
All groups are currently using the IRSG [Intergroup Rhabdomyosarcoma Study Group] surgical and pathologic grouping system with sometimes light differences.

i. Localized tumour, removed with pathologically clear margins and no regional lymph node involvement
ii. Localized tumour, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both
iii. Localized tumour, with gross residual disease after grossly incomplete removal, or biopsy only
iv. Distant metastases present at diagnosis

However, there is a need for a pre-clinical staging system that did not depend on the surgeon's decision or on pathologic assessment of the specimen. Moreover, the great majority of patients (approximately 75%) have macroscopic residual disease (IRS Clinical Group III) at the primary site at the start of chemotherapy.
The TNM system built by the SIOP [International Society of Pediatric Oncology] and UICC [Union Internationale Contre le Cancer] was validated by many studies. It includes the evaluation of site of the local extension of the disease (T1 Confirmed to anatomic site of origin and T2 Extension to surrounding tissue), the size of the tumour (<5 cm or $\geqslant$5 cm), the regional nodal involvement (N0 Regional nodes not clinically involved, N1 Regional nodes clinically involved by neoplasm) and the presence or absence of metastatic disease (M0 No distant metastasis, M1 Metastasis present).
Last but not least additional prognostic influence of site of the disease, histological subtype and patient age adds to the complexities of treatment stratification.
Recently both IRSG and European Paediatric Soft tissue Sarcoma Group (EpSSG) have reevaluated and updated their staging systems. They take into account additional information to the TNM and IRS staging systems: patient age, histology and tumour site. They are the bases of the risk grouping systems currently used to stratify the chemotherapy as well as the indications of radiation therapy. Concordances and differences between these staging systems will be presented.

172 INVITED

Estimating the total burden of therapy in children treated for rhabdomyosarcoma

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Cure rates of over 70% are currently achieved for patients with non metastatic rhabdomyosarcoma (RMS) but young age at diagnosis (median 5 years) and the divergence of clinical presentation at many different