

enhancement, biological cooperation, temporal modulation and normal tissue protection are proposed as the five main exploitable mechanisms for rational combination of drugs and radiation in cancer therapy. The large number of novel molecular targeted or cytotoxic agents that are in pre-clinical development will require hypothesis-driven trials to ensure efficient identification of treatments with the most favorable risk:benefit ratio.

In this perspective innovative approaches combining altered fractionation to chemotherapy will be discussed as potential avenues of research to enhance the therapeutic index in the management of locally advanced HNSCC.

130

INVITED

### The impact of the cetuximab trial on the treatment of head and neck carcinoma

K.K. Ang, M.D. Anderson Cancer Center, Radiation Oncology, Houston, USA

Results of numerous phase III clinical trials have demonstrated that, depending on the presence of co-existing illnesses, the preferred treatment for patients with locally advanced head and neck carcinoma (HNC) is one of the established altered fractionation (AF) or concurrent radiotherapy and chemotherapy (CRTC) regimen, or surgery followed by CRTC in the presence of high-risk features. However, both AF and CRTC intensify acute toxicity and CRTC also appears to increase late morbidity relative to the conventional daily radiotherapy. These findings along with advances in cancer biology inspired the search for selective enhancers of tumor response. Motivated by preclinical findings showing a consistent association between high EGFR expression with resistance of HNC to radiation and enhancement of tumor radiation response by EGFR antagonists (e.g., cetuximab or kinase inhibitors), a phase III trial was launched to compare the efficacy of radiotherapy plus cetuximab relative to radiotherapy alone in patients with locally advanced HNC. This trial showed that the addition of cetuximab to radiotherapy significantly improved local-regional control and survival without increasing mucositis or other radiation-related side effects. Cetuximab did induce acneiform rash in most patients and occasionally hypersensitivity reactions.

The cetuximab trial provided thus an important proof of principle that targeting a pertinent signaling pathway can selectively enhance the radiation response of tumors with a given biological feature and established a new treatment option for locally advanced HNC. However, the improvement in the local-regional control rate has been modest (within the range achieved with CRTC) and more than half of patients receiving radiotherapy plus cetuximab still experienced local-regional relapse. Therefore, there is a need to further improve outcome. Ongoing clinical efforts are devoted to address whether the addition of cetuximab to CRTC can yield a better outcome. Preclinical studies are being undertaken to develop rational strategies and assess the relative merits of inhibiting a given signaling pathway at several transduction levels or targeting multiple signaling pathways. Examples of clinical and preclinical studies will be briefly reviewed.

## Scientific Symposium

### Soft tissue sarcoma – no longer one disease?

131

INVITED

#### Soft Tissue Tumors: pathology and genomics

A.P. Dei Tos, Regional Hospital Treviso, Department of Pathology, Treviso, Italy

During the last decade, rapid scientific progress has been made in soft tissue tumor pathology. A significant conceptual advance is certainly represented by the publication of the new WHO classification of bone and soft tissue tumors [1]. Its main strength is represented by the integration of morphology with immunofenotypic, genetic, and prognostic data. Many new entities have been included and several conceptual changes have been introduced, among which the definition of the concept of borderline neoplasia; the settlement of the atypical lipomatous tumour/well differentiated liposarcoma controversy; the reappraisal of the concepts of MFH, hemangiopericytoma and fibrosarcoma. In addition the use of the FNCLCC grading system is advocated because of better discrimination between low and high-grade sarcomas, improved reproducibility [2]. Immunohistochemical characterization becomes a key factor in the diagnostic workup of STS, allowing not only proper classification, but also providing prognostic and/or predictive information. Although traditional morphological and immunohistochemical assessment still represents the mainstay of clinical decision-making, data from genetic studies can improve diagnostic accuracy and help predicting behaviour and response to therapy. Genetic aberrations have been described in

many benign and malignant soft tissue and bone tumours. Of particular importance, a number of sarcomas have consistent specific translocations which have proved diagnostically and prognostically helpful. Mutational analysis is proving particularly relevant in clinicopathological assessment of GIST wherein the type of KIT or PDGFRA genes determines the response to inhibitors of tyrosine kinases [3]. Further advances may be provided by gene expression profiling studies, that may reveal further useful markers for diagnosis and prognosis as well as identify possible targets for molecular therapy [4].

## References

- [1] Fletcher CDM, Unni KK, Mertens F (Eds). Pathology and Genetics of Tumors of Soft Tissue and Bone. WHO Classification of Tumours. IARC Press, Lyon, 2002.
- [2] Guillou L, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997; 15, 350–362.
- [3] Corless CL, et al. Biology of gastrointestinal stroma tumors. J Clin Oncol 2004; 22: 3813–3825.
- [4] Segal NH et al. Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. Am J Pathol. 2003;163:691–700.

132

INVITED

### Soft tissue sarcomas: from cytogenetics to genomics and expression profiling

M. Debiec-Rychter, U.Z. Gasthuisberg, Department of Human Genetics, Leuven, Belgium

Soft tissue sarcomas represent a heterogeneous group of tumors with over 50 histotypes. Resolution of this histopathological complexity is being facilitated by data from chromosomal and molecular characterization. Identification of specific translocations and mutations associated with these tumors, which seems to be central to their pathogenesis, has been widely incorporated as diagnostic criteria. Integration of sequencing of the human genome and rapidly evolving microarray technology provide the ability for the analysis of genomic changes and global expression patterns of the variety of sarcoma subtypes, illuminating aberrant signaling pathways that cause the diseases, and determining the biologic behavior and possible therapeutic targets. Distinctive expression profiles have been found in gastrointestinal stromal tumors (GISTs), synovial sarcomas, malignant peripheral nerve sheath tumors, and in subsets of liposarcomas. Subgroups with distinctive expression profiles can be identified also among more pleomorphic tumor types, such as high-grade variants of leiomyosarcomas, fibrosarcomas, pleomorphic undifferentiated sarcomas, and subtypes of liposarcomas. In some sarcoma types, explicit genetic alterations lead to activation of specific tyrosine kinase growth-factors receptors, and these have been successfully treated with drugs that specifically inhibit the activated kinase receptor. The success of imatinib mesylate in treatment of GISTs provides important lessons for development of new therapeutics from targets identified in other sarcomas. The GISTs response to imatinib therapy has been shown to be highly dependent on the presence and the nature of the activating mutations of targeted genes. To date, the molecular mechanisms responsible for the differences in the effect of different mutations on tumor sensitivity to imatinib remain only partially understood. Unstable genomes may lead to the evolution of resistance mechanisms, definition of which may yield identification of other therapeutic targets.

133

INVITED

### Modulating radiotherapy approaches for sarcoma heterogeneity

B. O'Sullivan, Princess Margaret Hospital, Department of Radiation Oncology, Toronto ON, Canada

Contemporary techniques permit very exact radiotherapy delivery to the intended target. This presentation will describe research efforts in this area including on-line cone beam CT imaging with volumetric reconstruction and how these may be applied to soft tissue sarcomas (STS) in the base of skull, paraspinal regions and limb. The latter includes an ongoing clinical trial at our centre designed to delivery very selective radiotherapy volumes to protect tissues with the intent of reducing wound complications. The anatomic, clinical, and technical issues governing this approach will be outlined including a unique method of collaboration between surgical and radiation oncologists tailored to individual patient indications. Myxoid liposarcoma, a distinctive STS having a t(12;16) translocation has an unusual predilection for soft tissue metastases; it is extremely radiosensitive and evidence for this will be presented and the impact this has on management discussed. The role of radiotherapy will also

be discussed for certain unusual diseases with characteristic anatomic presentations. Angiosarcoma of the scalp, a disease with unique technical challenges due to its extensive nature in proximity to the brain, and locally extensive dermatofibrosarcoma protuberans often need special radiotherapy approaches. In addition certain diseases are more likely to develop lymph node metastasis and the radiotherapy approach to these and patients with established lymph node will be discussed. Rhabdomyosarcoma is often exquisitely sensitive to chemotherapy and radiotherapy and may have extensive lymph node involvement and primary disease. Protocols that exploit the interaction between systemic treatments will also be highlighted. Potential molecular opportunities will be also discussed. For example, beta-catenin is a potent regulator of the Wnt pathway involved in wound healing and fibromatosis patients have globally elevated beta-catenin levels that may confer a wound healing by protecting against the adverse effects of pre-operative radiotherapy. The mdm2 gene (an E3 ubiquitin ligase that targets p53 for proteasomal degradation) is amplified and over-expressed in 1/3 of STS. In vitro and in vivo pre-clinical models have demonstrated the effectiveness of the combination of radiation and proteasomal inhibitors in a broad range of histologic sub-types and it is possible that this may augment radiotherapy in STS with suitable expression profiles.

134

INVITED

#### Medical management of soft tissue sarcomas

I. Judson. Royal Marsden Hospital, Sarcoma Unit, London, United Kingdom

Soft tissue sarcomas (STS) are known to be relatively insensitive to chemotherapy and single agent doxorubicin remains the treatment of choice for many subtypes, even after decades of searching for improved therapy. Combination chemotherapy with doxorubicin plus ifosfamide is commonly used but there is little or no evidence in favour of the combination for palliation of advanced disease, in contrast to adjuvant or neoadjuvant therapy indications and this question remains the subject of a multinational randomised trial (EORTC).

Individual subtypes are now identified that appear to respond favourably to a variety of other chemotherapy agents: angiosarcoma – taxanes; leiomyosarcoma – gemcitabine + docetaxel; leiomyosarcoma & liposarcoma – ET-743 (trabectedin). As yet the molecular basis for this apparent selectivity is unknown.

Gastrointestinal stromal tumour (GIST), which is driven by activating mutations in *KIT*, or less commonly *PDGFRA*, is of course amenable to therapy with the receptor tyrosine kinase inhibitor imatinib (Gleevec). The majority of patients experience partial response or disease stabilisation with relatively little serious toxicity, accompanied by marked symptomatic improvement and prolonged survival. Tumours with the most common exon 11 *KIT* mutation are most sensitive to imatinib and the responses are more durable than in the case of exon 9 mutant tumours. It is now known that treatment needs to be continuous, that a higher dose of the drug is beneficial in the treatment of exon 9 mutant tumours and that resistance will develop after a number of years, necessitating exploration of treatment with alternative tyrosine kinase inhibitors, e.g. SU11248, AMG706. Research is ongoing into the role of imatinib as adjuvant therapy for completely resected tumours.

The success of imatinib in treating (GIST) has raised expectations that other sarcomas will become treatable by the new generation of molecularly targeted therapies. Although inhibitors of EGFR are being investigated in synovial sarcoma and malignant peripheral nerve sheath tumour there are few other striking examples, other than dermatofibrosarcoma protuberans (DFSP), which is activated by a translocation that results in overexpression of PDGFB. Imatinib is effective here via inhibition of PDGFR. It is hoped that further investigations into the molecular biology of STS will lead to a similar improvement in the treatment of other diseases.

135

INVITED

#### Surgery adapted to lab data – the way to a tailored approach

P. Hohenberger. University Hospital Mannheim, University of Heidelberg, Head, Section of Surgical Oncology and Thoracic Surgery, Mannheim, Germany

Despite the recent advances of developing a molecular profile of sarcomas or to detect the decisive mutation for sarcoma progression, surgery is the mainstay of treatment of primary, non-metastatic sarcomas.

However, the era of identifying molecular targets also yields important results for surgical decision making.

Dermatofibrosarcoma protuberans (DFSP) represents a disease often recurring locally due to inadequate margins of safety and being not suitable for radiotherapy. The detection of PDGFRa ligands that can be blocked with imatinib leads the way to successful treatment of formerly irresectable cases.

In GIST, mutation analysis of tumors responding to imatinib therapy is the decisive element to decide on resectional treatment in responding patients. Depending on the mutation present, patients with long-lasting responses to be expected can be separated from those with presumably only short term tumor control. In patients with multifocal progression parallel to tumor sites with long-lasting response, mutation analysis guide the way whether a radical surgical approach needs to be pursued or whether different drugs (other types of tyrosine kinase inhibitors) should be used for continuing treatment.

The establishing of a molecular profile of sarcoma subtypes (e.g. synovial sarcoma and EGFR expression, angiosarcoma and integrin expression, liposarcoma and expression of PPRy ligands or certain fusion proteins) show the way to a tailored approach. There is also little scope for further improvement in survival with surgical treatment of chondrosarcoma. Inhibition of PTHLH signalling or bcl-2 antisense therapy could be future options for tumor control. Locally advanced or recurrent tumors not amenable to surgery with adequate clear margins may be controlled with extensive surgical and multimodality procedures. Hopefully in the future, progression arrest could also be achieved by individualized targeted therapy.

Diagnosis of sarcoma is no longer histological and immunohistological alone with accurate subgroup classification but provides important information for subsequent treatment decisions. Thus, a molecular staging of sarcomas should accompany TNM/AJCC staging in the future.

### Scientific Symposium

#### Non-myeloablative transplantation in solid tumours

136 Abstract not received

137

INVITED

#### Complications of therapy, supportive care

D. Blaise<sup>1</sup>, J. Bay<sup>2</sup>, P. Viens<sup>1</sup>. <sup>1</sup>Institut Paoli Calmettes, Unité de Transplantation et de Thérapie Cellulaire, Marseille, France; <sup>2</sup>Centre Jean Perrin, Unité de Transplantation, Clermont Ferrand, France

The graft versus leukemia (GVL) effect has been shown to be a major component of the anti-leukemic efficacy of allo stem cell transplantation (ASCT). In patients suffering from refractory solid malignancies, only anecdotal evidence of a "graft-versus-tumor" (GVT) effect had been reported thus far. Since the initial report suggesting some clinical and biological clues supporting a GVT effect, at least in breast cancer, the overall experience of ASCT in patients with solid tumors (ST) remained scarce. In 2001, 6413 ASCT were reported to the European Group for Blood and Marrow Transplantation (EBMT) registry, but only 149 (2%) were performed in patients with ST. On the other hand, the benefit of immunotherapeutic approaches for selected ST is now widely documented in a non-allogeneic setting, indicating that some immune effectors are able to induce tumor regression. In the allogeneic setting, the importance of minor HLA antigen mismatch was shown to be an important determinant of immune tumor control. Based on the initial case reports, we started in 1996 to investigate the potential of ASCT in patients with advanced metastatic ST. Our main objective was to investigate the feasibility of ASCT defined as a procedure being acceptable for both patients and the medical oncology community. Our initial experience combined with that of others confirmed that standard dose myeloablative ASCT is associated with a GVT effect, but also a prohibitive transplant related toxicity rate. The introduction of reduced intensity preparative regimens that could mediate a potent GVT effect in patients with hematological malignancies offered an attractive tool for investigation in patients with ST. Based on these encouraging results, we investigated ASCT for ST with an anti-thymocyte globulin (ATG)-based reduced intensity conditioning regimen (RIC). Fifty seven patients, of whom 39 had a progressive disease (PD) at time of ASCT, received a RIC ASCT combining fludarabine, anti-thymocyte globulin (ATG) and busulfan. Patients were analyzed in terms of engraftment, transplant related mortality (TRM), disease response and outcome. In this setting, RIC was associated with rapid engraftment and low overall TRM (9%; 95%CI: 1–16). The cumulative incidence of objective responses (OR) reached 14% (95%CI: 6–30) with this being significantly higher in patients without PD [44% (95%CI: 21–67) vs. 0;  $P < 0.0001$ ] at time of ASCT. Achievement of OR translated into a significantly better overall survival (OS). In multivariate analysis, OS was significantly influenced by disease status at time of ASCT (odds ratio, 4.88;  $P < 0.001$ ) and chronic GVHD occurrence (odds ratio, 2.86;  $P < 0.01$ ). Overall, these results showed that OR can occur after RIC ASCT for resistant ST with a relatively low TRM and potential benefit especially in patients with slowly progressive disease. Further studies are warranted in patients with less advanced ST.