targeting for radiation oncology depends critically on the appropriateness of tumor models, experimental design and endpoints.

135 INVITED

Combining molecular targeted agents with radiotherapy

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An increased understanding of the signalling pathways that are implicated in cancer progression has led to the identification of a number of tractable targets for therapeutic intervention. Whilst novel agents that inhibit these molecular targets may provide benefit as monotherapy, their use in combination with established modalities warrants examination in an attempt to augment existing treatment outcome. This includes the opportunity to modulate responses to ionising radiation, either through a direct effect on the repair of DNA lesions or via effects on other responses that are known to influence radiosensitivity, such as the rate of tumour cell repopulation or extent of reoxygenation. These complexities present a need for preclinical studies to examine combinations and potentially gain further mechanistic insight into the precise nature of any positive or negative interaction. There are many experimental variables to consider, including the molecular pathology of a given tumour, the selectivity profile of the novel agent, the respective treatment doses and duration of administration, and the relative sequencing of the drug/radiation combinations.
In this presentation, particular reference will be made to preclinical studies that have examined radiation in combination with inhibitors of vascular endothelial growth factor (VEGF) signalling. These have either utilised strategies that sequester VEGF ligand (using antibody or soluble receptor constructs) or used specific tyrosine kinase inhibitors, such as Vandetanib (ZACTIMA^{TM}, ZD6474) and AZD2171, which prevent VEGF receptor activation and intracellular signalling. Blockade of VEGF signalling can reduce tumour vessel perfusion and density, which could potentially increase the hypoxic tumour fraction and limit the effectiveness of ionising radiation. However, studies have shown that concomitant inhibition of VEGF signalling with fractionated radiotherapy can provide better control of tumour xenograft growth when compared to radiotherapy alone.
Ultimately, the translation of preclinical combination strategies to the clinic will benefit from additional biomarker endpoints, to define better the response of pathways to radiation and novel therapies in man.

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Clinical integration of EGFR inhibitors with radiation

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Background: Examine the impact and challenges in integrating molecular targeted therapies, particularly EGFR inhibitors, into cancer treatment.
Materials and Methods: The introduction of molecular targeted therapies in oncology is relatively recent, reflecting several decades of modern molecular biology coming to fruition in the form of smart new anti-cancer drugs. The EGFR inhibitors are highly promising agents in this arena. Increasing numbers of cancer patients are now receiving EGFR inhibitors and many clinical trials are incorporating these agents into future trial design.
Results: The scientific rationale and collective enthusiasm for advancing molecular cancer therapies is very strong. In addition to compelling preclinical results, there are now clinical trial successes that support the concept that we are making true progress. Indeed, the first Phase III trial to identify a survival advantage when combining a molecular targeting agent (anti-EGFR) with radiation has recently emerged in H&N cancer (NEJM 354: 567−78, 2006). Broadly speaking however, there are several challenges worthy of acknowledgement with regard to molecular targeting in oncology. First, there are more negative than positive clinical trials to date. There is a tendency for oncologists to illuminate positive trials and downplay or rationalize inadequacies for negative trials. Second, we may inadvertently over dramatize the impact of positive clinical trials with regard to overall benefits and translatability to global cancer populations. Third, although the toxicity profiles for most molecular targeted therapies appear milder than that of conventional cytotoxic agents, the unique toxicities of molecular therapies are not trivial, particularly for the average performance cancer patient who may be underrepresented in controlled clinical trials. Fourth, many of the new molecular targeted therapies are remarkably expensive. This high cost reflects the manner in which new drugs are discovered, developed and promoted in the current era, and this feature carries implications for who will receive these new cancer drugs in the coming years.
Conclusions: As we make stepwise advances in cancer treatment, it is important for oncologists to exercise rigor in describing the benefits achieved with each new therapy, and to remain actively engaged in promoting the rational and judicious application of new cancer treatments and technologies.

Special session (Wed, 26 Sep, 13:30−14:30)
Treatment of localised gastric cancer. Preoperative versus postoperative adjuvant treatment

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Treatment of localized gastric cancer: pre-operative versus post-operative adjuvant treatment

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Gastric cancer is one of the most common cancers globally, and is one of the top causes of cancer related deaths. Around the world, there is significant variation in the incidence of gastric cancer, being higher in the Far East than in the United States or Western Europe. Surgery is the only potentially curative treatment modality in this disease. However only 20−30% of patients have disease which is localized and operable at the time of diagnosis and many of those who have had complete surgical resections will suffer from disease recurrence of their disease, most likely due to local or distal micrometastatic disease which was undetectable at the time of surgery. With surgery alone patients in randomized trials with operable gastric cancer have a median survival of approximately 25 months and a 5-year survival of between 20−30% [1,2]. Whilst surgical trials in Japan in particular have been able to improve on these outcomes with more extensive surgery and lymph node dissections, these results have not been reproduced in Western patients.
Systemic chemotherapy has recently been shown to improve the survival of these patients, with several trials which have used chemotherapy either perioperatively or post-operatively reporting improvements in survival in favour of adjuvant treatment. The most mature trial results are from the UK NCRI MAGIC trial in which patients treated with 3 cycles of ECF (epirubicin, cisplatin and infused 5-flurouracil, 5FU) chemotherapy before and after surgery had an improved overall and progression-free survival compared to patients treated with surgery alone [1]. The preliminary results of a French (FFCD 9703) in which perioperative treatment consisted of 2−3 cycles of 5FU and cisplatin before and after surgery also suggest a benefit for the treatment strategy [3] – updated results for this trial are expected this year. More recently, a Japanese randomized trial has reported a survival benefit from using the oral agent S-1 as post-operative adjuvant chemotherapy in patients treated with D2 gastrectomies, compared to D2 surgery alone [4]. This presentation will review the available data on the use of adjuvant chemotherapy in resectable gastric cancer, whether given as perioperative or post-operative treatment, and discuss the implications of these results on clinical practice.

References

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138 INVITED

Gastric cancer: multimodal treatment

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Radical surgical dissection of gastric cancer is the basis of cure in this disease. However, because most patients in the Western world present with advanced stages, surgery alone provides long-term survival in only 20−30% of patients. Western series report locoregional failures in about 60% of patients with positive lymph nodes or involvement of the serosa [1,2]. This high relapse rate has initiated a whole spectrum of more aggressive treatments which did not result in favorable survival until the introduction of combined chemoradiation in the adjuvant setting [3].
A few prospective randomized trials, have investigated the role of more extensive lymph node dissection (D2) in comparison with the standard D1 lymph node dissection in which only the perigastric nodes are removed.