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

135 INVITED

Combining molecular targeted agents with radiotherapy

S.R. Wedge[1], K.J. Williams[2], I.J. Stratford[2]. *[1]AstraZeneca, Cancer Bioscience, Cheshire, United Kingdom; [2]University of Manchester, Dept. of Pharmacy, Manchester, United Kingdom*

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.

136 INVITED

Clinical integration of EGFR inhibitors with radiation

P. Harari. *University of Wisconsin, Dept of Human Oncology, Madison, USA*

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

137 INVITED

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

D. Cunningham. *The Royal Marsden Hospital, Medicine, Sutton, United Kingdom*

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

[1] Cunningham D, Allum WH, Stenning SP, et al. N Engl J Med 2006; 355(1): 11−20.
[2] Macdonald JS, Smalley SR, Benedetti J, et al. N Engl J Med 2001; 345(10): 725−30.
[3] Ychou M, Pignon JP, Lasser P, et al. J Clin Oncol (Meeting Abstracts) 2006; 24(18 suppl): 4026−.
[4] Sasako M, Yamaguchi T, Kinoshita T, et al. Program and Proceedings of the 2007 Gastrointestinal Cancers Symposium, Orlando, Florida.

138 INVITED

Gastric cancer: multimodal treatment

C.J.H. van de Velde. *Leiden University Medical Centre, Department of Surgery, Leiden, The Netherlands*

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.

In the Dutch Gastric Cancer Group trial 711 patients that were treated with curative intent were randomized between D1 and D2 lymph node dissection. After a median follow up of 11 years there was no survival difference (30% vs. 35%; $p = 0.53$). Morbidity (25% vs. 43%; $p < 0.001$) and mortality (4% vs. 10%; $p = 0.004$) however, were significantly higher in the D2 group [4]. In the British MRC trial 400 gastric cancer patients were also prospectively randomized between D1 and D2 lymph node dissection [5]. Five year survival was 35% in the D1 and 33% in the D2 group; morbidity was 28% and 46% respectively, mortality was 6.5% for D1 and 13% in D2. Since these two trials were published a lot of debate has been generated about two topics. First of all, since subgroup analyses have indicated a trend for better survival in N2 patients after a D2 dissection, the question has risen whether there is a role for D2 resections in this subset of patients. Furthermore, there is considerable debate about the role of routine splenectomy and resection of the pancreatic tail in order to facilitate a D2 resection. It is hypothesized that in performing a D1 dissection without splenectomy and resection of the pancreatic tail, together with dissection of at least 15 (N1 and N2) nodes, a so-called D1 over (D1+) resection, can result in better outcome [6,7].

In 2005 final results of the MAGIC-study on perioperative chemotherapy have been presented [8]. In this large multicenter study patients were randomized between surgery only and 3 cycles preoperative ECF (epirubicin, cisplatin, 5-FU) followed by surgery and then another 3 cycles of ECF chemotherapy. This regimen resulted in a 10% higher resectability rate and a significant survival benefit of 13% (23% vs. 36% at 5 years). It should be noted that 80% underwent surgical resection, and that 66% of the patients commenced the postoperative chemotherapy and 42% completed the entire treatment. In addition, 50% of patients who completed preoperative chemotherapy and surgery, also completed postoperative treatment. The main reason (70% of the patients) for not starting postoperative chemotherapy was disease progression or patient choice (Cunningham, ASCO GI 2006). Despite this disappointing number of patients undergoing systemic treatment, perioperative chemotherapy with ECF may be considered as a new standard of treatment in operable gastric cancer.

In a Cochrane review of randomized trials in advanced gastric cancer highest survival rates were achieved with anthracyclines, cisplatin and 5-FU, both independently and in combination (Cochrane Library, 2005). Within these combinations ECF proved to be tolerated best. However, the use of continuous infusional 5-FU is considered cumbersome, because it requires the implantation of central venous catheter devices and the use of portable infusion pumps, which are associated with complications such as thrombosis and wound infection. Capecitabine, a prodrug and oral analogue of 5-FU, is believed to mimic continuous infusion of 5-FU and has demonstrated to be at least equally effective in tumor control and to be less toxic than intravenous 5-FU in patients with stage III and IV colon cancer.

In 2001, with the introduction of postoperative combined chemoradiotherapy for the first time a substantial improvement in survival and locoregional control has been described. In the SWOG/ Intergroup 0116 trial 556 patients were prospectively randomized between surgery only and surgery plus postoperative chemoradiotherapy. Radiotherapy consisted of 45 Gy in 25 fractions in five weeks. The chemotherapy regimen consisted of three cycles of 5-fluorouracil and leucovorin according to the Mayo regimen perioperatively and two shortened courses during radiotherapy. An impressive increase in median overall survival was obtained in the chemoradiotherapy group; 36 months versus 27 months in the surgery only group. Furthermore relapse free survival was prolonged from 19 months in the surgery only arm to 30 months in the chemoradiotherapy arm. It was thus shown that in gastric cancer too, the advantage in combining modalities is the ability to address both locoregional and systemic disease simultaneously. This postoperative chemoradiotherapy regimen has become standard treatment in the USA; nevertheless this study has been criticized because of suboptimal surgery, concerns about toxicity, an outdated chemotherapy regimen and suboptimal radiotherapy techniques. Indeed, 54% of all patients underwent a D0 lymph node dissection, which in it self could be one factor in undermining survival.

Taken the abovementioned pivotal MAGIC and SWOG/Intergroup studies together, the important question that needs to be answered is whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients that receive neoadjuvant chemotherapy followed by a D1+ gastric resection. We therefore conduct a prospective randomized multicenter phase III trial addressing this important question. To ascertain patient compliance and improve patient selection/ treatment tailoring, we plan to incorporate validated prognostic and predictive tests, such as Maruyama Index and nomogram for gastric cancer. In the chemoradiotherapy arm state-of-the-art 3D-conformal or Intensity-Modulated RadioTherapy (IMRT) should be a minimal requirement in order to limit normal tissue toxicity, in particular kidney damage. The chemotherapy schedule in both arms should be effective and safe. The combination of epirubicin, cisplatin and capecitabine fulfils these requirements. An optimized chemoradiotherapy schedule with radiosensitizing drugs during the entire radiotherapy treatment has been established with daily cisplatin and capecitabine in our phase I−II study.

- A phase III study which randomizes between preoperative chemotherapy (3 courses of epirubicin, cisplatin and capecitabine (ECC)) and D1+ gastric surgery followed by postoperative chemotherapy (another 3 courses of ECC) or chemoradiotherapy. Chemoradiotherapy consists of 45 Gy radiotherapy in 25 fractions with concurrent capecitabine and cisplatin (protocol available upon request).

References

[1] Gunderson LL, Sosin H: Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 8: 1−11, 1982.
[2] Landry J, Tepper JE, Wood WC, et al.: Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys 19: 1357–1362, 1990.
[3] Jansen E, Boot H, Verheij M, et al.: Optimal locoregional treatment in gastric cancer. J Clin Oncol 23: 4509–4517, 2005.
[4] Hartgrink HH, van de Velde CJ, Putter H, et al.: Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 22: 2069–2077, 2004.
[5] Cuschieri A, Weeden S, Fielding J, et al.: Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 79: 1522–1530, 1999.
[6] van de Velde CJ, Peeters KC: The gastric cancer treatment controversy. J Clin Oncol 21: 2234–2236, 2003.
[7] Petrelli NJ: The debate is over; it's time to move on. J Clin Oncol 22: 2041–2042, 2004.
[8] Hallissey MT, Dunn JA, Ward LC, et al.: The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 343: 1309–1312, 1994.

Special session (Wed, 26 Sep, 13:30−14:30)
New developments in clinical functional imaging

139 INVITED

Angiogenesis imaging

M. Neeman. *The Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel*

Background: Angiogenesis, the growth of new blood vessels, plays an important role in reproduction and wound healing as well as in tumor progression. Non invasive imaging of angiogenesis can help in preclinical drug discovery and development and can also provide biomarkers during clinical monitoring of targeted antiangiogenic therapy.
Materials and Methods: Over the last years multiple approaches for imaging angiogenesis were developed for the various imaging modalities, providing structural, functional and molecular markers of the process.
Results: Imaging angiogenesis includes nowadays a large family of methods providing structural information on blood volume, vessel diameter and tortuosity. Functional information revealed by imaging includes blood flow and perfusion, vessel permeability and vasoreactivity. Lastly molecular imaging allows to probe changes in the composition and enzymatic activity in the extracellular matrix, expression of specific cell surface markers on endothelial cells, and imaging methods for following the recruitment of vascular and perivascular precursor cells as well as in vivo detection of gene expression.
Conclusions: Over the last decade multiple imaging approaches were developed to detect angiogenesis, thus complementing the efforts for therapeuric intervention. Clinical translation of these imaging approached could help tailor antiangiogenic therapy and provide early mechanism based markers for response.

140 INVITED

Two-photon imaging of tumour invasion

P. Friedl. *University of Würzburg, Rudolf Virchow Center for Exp. Biomedicine and Department of Dermatology, Wurzburg, Germany*

Multiphoton microscopy has defined standards for 3D fluorescence and higher harmonic generation analysis of cells and tissue structures in vitro and in vivo. Compared to single-photon excited confocal microscopy, two-photon microscopy utilizes near-infrared (NIR) excitation generating twice to multi-fold enhanced tissue penetration, reduced light scattering and