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The Tipping Point for Combination Therapy − Cancer Vaccines With Radiation

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Local radiation is an established therapy for human tumours. Radiation may also act synergistically with immunotherapy to enhance immune responses, inhibit immunosuppression, and/or alter the phenotype of tumour cells, thus rendering them more susceptible to immune-mediated killing. As monotherapies, both immunotherapy and radiation may be insufficient to eliminate tumour masses. However, following immunization with a cancer vaccine, the destruction of even a small percentage of tumour cells by radiation could result in cross-priming and presentation of tumour antigens to the immune system, thereby potentiating antitumour responses. This talk will discuss a) mechanisms by which many forms of radiation therapy can induce or augment antitumour immune responses, b) preclinical systems that demonstrate that immunotherapy can be effectively combined with radiation therapy, and c) current clinical trials where standard-of-care radiation therapy is being combined with immunotherapy. Capitalizing on the immunological effects induced by radiation treatment by adding potent antitumour vaccines may lead to synergistic approaches to cancer management that offer feasible, well-tolerated therapeutic options for cancer patients.

Special Session (Sat, 24 Sep, 14:15−15:15)
Monitoring Tumour Response to Therapy − What Do the Images Tell Us?

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PET/CT for Tumour Response Assessment

Abstract not received

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Functional MRI of Therapy Response

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Learning objectives:

1. To approach functional MRI via the depiction of biological information of relevance to cancer
2. To learn the biological basis for commonly available functional MRI techniques such as diffusion MRI, dynamic susceptibility and relaxivity contrast enhanced MRI, and proton spectroscopy. For each techniques to demonstrate how measurements are acquired, the quantification process, and show biological/clinical validation
3. To show the added value of the multiparametric approach for depicting biology, disease characterization and therapy monitoring
4. To show how multiparametric functional MRI can use for medicines development and in the clinic.

Take home points:

1. Multiparametric MRI is potentially important development for non-invasive biological exploration of cancer because of its multidimensional (multispectral, multispatial and temporally resolved) nature
2. Multiparametric MRI can be used for improving tumour characterization as well as for monitoring therapy response
3. Multiparametric MRI allows us to understand how therapies affect tumours and tissue microenvironments
4. Sophisticated, user-friendly software workspaces need to be developed urgently, in order to be able to integrate/cross-correlate data analyses

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Monitoring Effect of Antiangiogenic Treatments by Dynamic Contrast Enhanced Ultrasonography

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New treatments based on antiangiogenic substances are developed in order to destroy tumour vessels and are the object of promising clinical research for cancer treatment. Considering the large number of new targeted drugs under development, there is a great need for early reliable imaging indicators of tumour responses, and identification of a recommended modality of drug administration to guide further steps in the clinical development. The response rate remains the best objective parameter of efficacy of the treatments tested in clinical trials but this parameter is obtained very late in the clinical development, while the effect on the tumour must be determined as soon as possible in order to optimise the schedule and the dose to be recommended for the late clinical development stage. The early functional evaluation of new treatments is a main goal.

At present, technical advances in DCE-US using bolus contrast agent (SonoVue®, Bracco) and perfusion software allow the detection of microvascularization and perfusion for superficial and deep malignant tumours. Thus, it becomes possible to early evaluate the efficiency of antiangiogenic or anti-vascular molecules. Treatment response can be early predicted according to modifications of this vascularization before any volume modification. The acquisition of raw linear data affords the precise quantification (peak intensity, time to peak intensity, sloap of wash-in, and area under the curve. . .) of the perfusion after contrast uptake curves modelization, in particularly using time tracking of region of interest. The results will be focused on GIST, RCC, HCC, and melanoma with different molecules including 117 patients.

Reduction in tumour vascularization can easily be detected in responders after 2 weeks and is correlated with progression-free survival and overall survival in RCC or HCC.

DCE-US is supported by the French National Cancer Institute (INCa), which is currently studying the technique in metastatic breast cancer, melanoma, colon cancer, gastrointestinal stromal tumours and renal cell carcinoma, as well as in primary HCC, to establish the optimal perfusion parameters and timing for quantitative anticancer efficacy assessments. 539 patients with a follow-up of 1 year are included in 19 centers and the preliminary results including 1950 DCE-US demonstrated that AUC could be a robust parameter to predict response.

References

Lassau et al. Metastatic Renal Cell Carcinoma Treated with Sunitinib: Early Evaluation of Treatment Response Using Dynamic Contrast-Enhanced Ultrasonography Clin Cancer Res. 2010

Lassau et al. Advanced Hepatocellular Carcinoma: Early Evaluation of Response to Bevacizumab Therapy at Dynamic Contrast-enhanced US with Quantification–Preliminary Results. Radiology. 2011

Lassau at al. Dynamic contrast-enhanced ultrasonography (DCE-US) and anti-angiogenic treatments. Discov Med. 2011

Scientific Symposium (Sat, 24 Sep, 16:00−18:00)
Optimal Treatment for a 72-Year-Old Patient With Stage III-N2 Non-Small Cell Lung Cancer

64 INVITED

Stage III-N2 Non-Small Cell Lung Cancer − Identifying Patients Subgroups and the Need to Tailor Therapy

Abstract not received

65 INVITED

Evidence to Support Definitive Chemo-Radiotherapy

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Stage III NSCLC is a heterogeneous disease: see www.predictcancer.org. However, phase III trials have mostly included all stage III patients that were in a good general condition with adequate organ function. From a meta-analysis based on individual patient data, it was clear that the concurrent administration of chemotherapy and radiotherapy resulted in a significant improvement of the 5-year survival. Most of these patients had multi-level N2 or N3 disease and had bulky nodes. There is thus level I evidence that if our 72-year old patient is in a good general condition and has adequate organ functions, the first choice treatment is concurrent chemo-radiation.

Patients with resectable N2 disease were randomized between surgery and definitive chemo-radiation after induction concurrent chemo-radiation in the Lung Intergroup Trial 0139. 75% of the patients had single nodal station NSCLC. There was no difference in survival between the two arms. Although the study has often been criticised because of the high rate of pneumonectomies and toxic deaths in the surgery arm, the overall median survival as well as the 5-year survival, about 24 months and 25%, respectively, is at least as good as single-institutional surgical series that reported on an intention to treat basis. Indeed, a major caveat in surgical series is beside patient selection that often only patients that indeed went on to surgery are reported, which is mostly only 70−80% of the initial population that initiated therapy. In the same trial, a hypothesis-generating non-planned subgroup analysis was performed of patients that were treated with concurrent chemo-radiation (45 Gy) followed by

lobectomy. As expected, the median survival increased to 34 months and the 5-year survival to 36%, but this is analogous as what has been achieved with concurrent chemotherapy and radiotherapy without surgery in patients with single nodal station N2 disease. Patients with small volume disease (<50 ml) may even have better survival rates with systemic treatment concurrently with radiotherapy.
Apart from emotion and "believes", there are no data to support surgery in patients with T4 and/ or N2/N3 disease over chemo-radiation.
As most patients still die of their cancer, due to both distant and local relapses, there is much room for improvement at all sites. This includes better treatment options for the old and/ or frail patient, characterisation of the tumour by fine needle biopsies, circulating tumour cells and imaging, tailoring systemic treatment and radiotherapy according to these characteristics, taking into account intra-tumour heterogeneity, including stem cells, for e.g. selective boosting of these areas, heterogeneity within organs at risk and the role of prophylactic cranial irradiation (PCI) to decrease the incidence of brain metastases.

66 INVITED

Evidence to Support Use of Planned Surgery

P. De Leyn[1]. [1]*De Leyn, Thoracic Surgery, Leuven, Belgium*

There remains controversy on the role of surgical multimodality treatment for stage IIIA-N2 disease due to the lack of fully convincing randomized trials and the diversity of phase II studies. The main reason for this controversy can be explained by the fact that N2-disease is a very heterogeneous entity and compasses a broad spectrum of metastatic LN involvement. The two randomized trials failed to show a survival benefit for the surgical treated cohort. In the Intergroup trial, potentially resectable N2-disease was included. In the EORTC study, patients with irresectable N2-disease were included. In this study, induction chemotherapy did not convert unresectable disease into resectable disease as illustrated by the 50% incomplete resection rate in the surgery arm − and, not unexpectedly, did not result in better outcome compared with radiotherapy. However, in the Intergroup trial disease free survival was significantly higher in the surgical cohort and the 5-year survival was doubled (36%) compared to the radiotherapy arm when pneumonectomy could be avoided. Moreover, both trials observed substantial long- term survival in patients with mediastinal downstaging. Prediction of complete resection and downstaging seems to be essential in the setting of combined surgical multimodality. Therefore, careful baseline stage is very important. Patients with stage IIIA should be evaluated by a multidisciplinary team including an experienced thoracic surgeon in thoracic oncology. The thoracic surgeon has to assess baseline resectability. Bulky, extracapsular and/or multilevel disease are contraindicating surgical multimodality treatments. After induction treatment, restaging should be performed. Mainly patients with evidence of response in the primary tumour and LNs with benefit from surgical exploration. PET-CT and invasive mediastinal techniques are indicated. Patients should be carefully reassessed including new pulmonary function tests with diffusion capacity. (Mainly) right pneumonectomy should be avoided and the bronchial stump should be protected by viable tissue. In experienced centers, mortality after induction therapy can be as low as to 2 to 3% with very acceptable morbidity.
We believe that in experienced centers, selected patients with N2-disease may benefit from surgical multimodality treatment.
In this patient we would prove N2 disease by N2 disease. After induction chemotherapy, mediastinoscopy could be performed and histological response evaluated. IN case of downstaging to N0 or single level disease, resection by upper lobectomy would be the best option for her.

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Stage III-N2 Non-Small Cell Lung Cancer − Choice of Chemotherapy Schemes

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Surgical resection alone in stage IIIAN2 non-small cell lung cancer (NSCLC) is associated with poor outcome. In those patients with bulky ipsilateral mediastinal lymph nodes visible on a computed tomography imaging of the chest, only 18% complete resection has been achieved with a 9% 3-year survival despite complete surgical removal. The rationale of neoadjuvant chemotherapy lies in the eradication of micrometastatic disease, which is often present when ipsilateral mediastinal or subcarinal lymph nodes are involved. One of the earliest neoadjuvant combination chemotherapy programs was developed at MSKCC. Stage IIIA patients with clinical N2 disease were given mitomycin, vinca alkaloids and high-dose cisplatin (MVP). In a group of 136 patients, the objective major response rate to MVP chemotherapy was 77%. Overall, 65% of patients underwent complete resection; 14% had pathologic complete response at surgery. Overall, median survival was 19 months and the 3-year survival for completely resected patients was 41%. In a similar study using the same MVP chemotherapy program prior to surgery, the Toronto investigators reported a 69% response rate, a 49% complete resection rate, and a median survival of 19 months for all 35 patients included. These two studies demonstrated what appeared to be improved median survival time and prolonged 3-year survival when compared to historical controls.
Two subsequent randomized trials suggested that neoadjuvant therapy in stage IIIA disease improved survival. These trials established neoadjuvant chemotherapy followed by surgery as one reasonable means of treating stage IIIA NSCLC.
There has been some controversy about whether carboplatin can be used in neoadjuvant treatment. Based on two meta-analyses in stage IV disease, it was suggested that cisplatin should be used in fit patients with PS 0−1 who have adequate organ function. Another point for discussion was the optimal cisplatin dose to be used in the neoadjuvant setting. The Spanish Lung Cancer Group (SLCG) conducted a randomized trial to address whether higher neoadjuvant cisplatin doses result in improved survival and increased pathologic complete response. Patients with stage IIIA clinically enlarged and biopsy-proven N2 lesions were randomly assigned to receive either high-dose cisplatin (HDCP) (100 mg/m^2) or moderate-dose cisplatin (MDCP) (50 mg/m^2) in combination with ifosfamide and mitomycin. Eighty-three patients were randomized: 46 received HDCP, and 37 MDCP. Radiographic response rate was 59% for HDCP patients, and 30% for MDCP patients ($P = 0.01$). Thoracotomy was performed in 71 patients (86%), 58 of whom had resectable disease. Complete resection rate was 61% in the HDCP group, and 51% in the MDCP group ($P = 0.5$). Pathologic complete response was observed in one patient who received MDCP. Median survival in the HDCP and MDCP groups was 13, and 11 months, respectively ($P = 0.3$). Although, higher radiographic response rate was observed in patients who received HDCP, this study failed to show any significant improvement in either overall survival or pathologic complete response.
Third generation drugs have been analyzed in the neoadjuvant setting. The EORTC carried out a phase II trial in patients with stage IIIAN2 using cisplatin/gemcitabine followed by surgery or radiotherapy. Results showed that this was a well tolerated combination achieving a 70% response rate. A multicenter phase II trial evaluated neoadjuvant chemotherapy with cisplatin/docetaxel followed by surgery in 90 patients with stage IIIAN2 disease. The overall response rate was 66%. Pathologic complete response was observed in 19% of patients who underwent surgery. This phase II trial showed that cisplatin/docetaxel was effective and well tolerated in stage IIIAN2 NSCLC.
The SLCG conducted a phase II trial in patients with stage III disease analyzing a triplet combination as a neoadjuvant treatment (cisplatin/gemcitabine/docetaxel). The survival results obtained in this study were very similar to those reported with doublet combinations. Since this trial, a cisplatin doublet has remained the standard approach in the neoadjuvant setting.
In stage IV disease, randomized studies that have compared platinum-based doublets using third-generation drugs among themselves showed no differences in survival and gave no evidence for a single "standard" doublet for the treatment of metastatic NSCLC. A phase III randomized trial comparing cisplatin/pemetrexed *vs* cisplatin/gemcitabine showed no difference in outcome between the two combinations with a lower haematological toxicity profile for the pemetrexed-based regimen. A pre-planned subgroup analysis showed a survival advantage for cisplatin/pemetrexed as compared with cisplatin/gemcitabine in non-squamous histology (11.8 *vs* 10.4 months, respectively; $P = 0.005$) while a survival advantage for the gemcitabine-based combination was observed in squamous histology. These results may be translated to the neoadjuvant setting although no randomized trials focusing on these two combinations have been performed in stage III disease.
In summary, stage IIIA patients have systemic disease requiring a multimodality management approach. Different cisplatin-doublets using third generation agents have been included in the neodjuvant setting and are now the gold standard. Combined modality treatment in locally advanced NSCLC continues to evolve and is a subject of ongoing research. Improving the outcome for patients with stage IIIA NSCLC requires the close cooperation of surgeons, radiation oncologists and medical oncologists. One challenge for present research is to integrate new active agents into the neoadjuvant setting. A further aim is to use molecular biological markers to identify patients for more individualized treatment.

References

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[2] Burkes RL, Ginsberg RJ, Shepherd FA, et al. Induction chemotherapy with mitomycin, vindesin, and cisplatin for stage III unresectable non-