22 INVITED

Planned neck dissection after chemoradiation for advanced head and neck cancer. Is it always indicated?

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Patients with advanced head and neck squamous cell carcinoma (HNSCC) may benefit from organ preservation treatments based on chemotherapy and radiotherapy (CRT) without compromising survival. This strategy has led to controversial issues concerning the role of neck dissection (ND) following chemoradiation for patients with N2−3 disease. Residual neck disease may be still present in as much as 30 to 50% of patients after completion of CRT. Should ND be proposed to all patients with advanced regional disease at diagnosis regardless whether the response in the neck is partial or complete or only to those with clinical and or radiological evidence of residual lymph node disease, remains controversial. Proponents of planned ND argue that the procedure reduces the regional failure rate and possibly improves the cause-specific survival and that a salvage ND in the event of neck recurrence is unlikely to succeed. Proponents of abstention of ND in case of clinical complete response (CCR) argue that the probability of an isolated recurrence in the neck is low, that no survival benefit has been demonstrated in complete responders and that a systematic planned ND strategy results in overtreatment in more than 70% of patients who have no residual tumor in the neck with increased morbidity.

Today, there are no ongoing prospective trials addressing these specific issues: (1) how often is a CCR achieved after CRT; (2) how accurately does a CCR predict a pathologic complete response (PCR) at neck dissection or the absence of regional relapse if observation is decided; (3) in patients with CCR, does neck dissection yield any additional survival benefit?

The controversy is fuelled by the difficulty to accurately predict a PCR in the neck after CRT because clinical examination, CT and MRI lack sensitivity and specificity. In this respect, the use of PET has gained increasing interest. Recent retrospective studies reported that negative post CRT PET was highly correlated with negative pathologic findings after ND or with the absence of neck relapse (NPV of 97–100%, cut off SUV $\geqslant$3.0). However, these results contrast strongly with those reported elsewhere with NPV varying from 14% to 73%. The differences between these studies can be attributed to many factors like timing of PET after radiation, treatment outcome of the patients (complete response rate assessed by CT and/or MRI), timing of ND, pathology evaluation and quality of PET imaging. A critical point is the timing of PET after radiation. Previous PET studies have demonstrated that best results are obtained when PET is performed 10−12 weeks after radiotherapy. However, some surgeons are still reluctant to perform ND at 12 weeks, fearing a higher rate of postoperative complications. Recently, some authors reported that selective ND was suitable in most post CRT situations and was associated with a low rate of complications.

Since the begin this year, a prospective multicenter registration study is getting under way, sponsored by the GETTEC (French head and neck cooperator study group), to validate the use of PET as a tool able to accurately predict a post CRT complete response and therefore, to select which patients should benefit from post CRT ND. The primary objective should be to assess the NPV of PET in correctly predicting the absence of remaining invaded lymph nodes after CRT. The secondary objectives should assess (1) the suitability of a “no ND” approach in patients considered as complete responders, (2) the ability of PET to correctly predict remaining pathologically invade lymph nodes (PPV) after CRT in patients with a positive PET and who will undergo ND. The results of this prospective study should be of utmost importance to better define whic patients really need post CRT ND.

Special session (Mon, 24 Sep, 13:30−14:30)
What is the optimal treatment of glioblastoma in elderly patients?

23 INVITED

Improving treatment for elderly patients with glioblastoma – is there a role for chemotherapy only?

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The standard treatment of malignant gliomas (WHO grades III and IV) includes tumor resection, involved-field radiotherapy and possibly nitrosourea-based chemotherapy. A modest benefit of adjuvant nitrosourea-based chemotherapy has been confirmed across all age and risk groups. Yet, young age and good Karnofsky performance score are the most potent therapy-independent favorable prognostic factors, and nitrosourea-based chemotherapy is less well tolerated in elderly patients (>65 years). Therefore, the role, if any, of chemotherapy in this patient population has remained controversial. Temozolomide is an alkylating agent which has shown activity in recurrent malignant glioma. The safety profile of temozolomide is superior to that of nitrosoureas, both in terms of cumulative myelotoxicity and pulmonary toxicity. The drug has also been explored in the first-line treatment of glioblastoma, with favorable results, which gave rise to the EORTC 26981 NCIC CE3 trial, which demonstrated a benefit for radiotherapy plus temozolomide chemotherapy compared to radiotherapy alone in the first-line treatment of glioblastoma. Whether elderly patients gained a benefit from that combined modality treatment is at least questionable. The median survival time for elderly malignant glioma patients is in the range of a few months. Radiotherapy is the standard treatment and superior to best supportive care both with respect to progression-free and overall survival. The benefit derived from surgery and radiotherapy is modest, and both treatments are less well tolerated in elderly patients than in the young. The availability of a potentially effective pharmacological agent for malignant glioma, which exhibits a rather favorable safety profile, necessitates a reconsideration of the widespread therapeutic nihilism in the face of malignant glioma in the elderly. However, most elder glioblastoma patients are probably not candidates for combined modality treatment. Therefore, the present studies seek to compare the standard postsurgical treatment of malignant glioma in elderly patients with a Karnofsky performance score >60, involved-field radiotherapy to a dose of 54−60 Gy, with temozolomide alone. In the German Methusalem/NOA-08 trial temozolomide shall be used in a novel one week on/one week off schedule, which allows a dose intensification of up to 2 compared with the standard regime of 150–200 mg/m^2 $\times$ 5 days and which has shown efficacy in recurrent glioblastoma in phase II studies. An EORTC/NCIC approach for an international study initiative looks at radiochemotherapy (with a shortened course of radiotherapy) with temozolomide versus radiotherapy alone in this population.

24 INVITED

Best palliative care or radiotherapy in patients over 70 years of age: what is the difference? An ANOCEF trial

S. Taillibert. *CHU Pitié Salpetrière, the ANOCEF group, Paris Cedex 13, France*

BACKGROUND: There is no community standard for the treatment of glioblastoma in patients 70 years of age or older. We conducted a randomized trial that compared radiotherapy and supportive care with supportive care alone in such patients. METHODS: Patients 70 years of age or older with a newly diagnosed anaplastic astrocytoma or glioblastoma and a Karnofsky performance score of 70 or higher were randomly assigned to receive supportive care only or supportive care plus radiotherapy (focal radiation in daily fractions of 1.8 Gy given 5 days per week, for a total dose of 50 Gy). The primary end point was overall survival; secondary end points were progression-free survival, tolerance of radiotherapy, health-related quality of life, and cognition. RESULTS: We randomly assigned 85 patients from 10 centers to receive either radiotherapy and supportive care or supportive care alone. The trial was discontinued at the first interim analysis, which showed that with a preset boundary of efficacy, radiotherapy and supportive care were superior to supportive care alone. A final analysis was carried out for the 81 patients with glioblastoma (median age, 73 years; range, 70 to 85). At a median follow-up of 21 weeks, the median survival for the 39 patients who received radiotherapy plus supportive care was 29.1 weeks, as compared with 16.9 weeks for the 42 patients who received supportive care alone. The hazard ratio for death in the radiotherapy group was 0.47 (95% confidence interval, 0.29 to 0.76; P = 0.002). There were no severe adverse events related to radiotherapy. The results of quality-of-life and cognitive evaluations over time did not differ significantly between the treatment

groups. CONCLUSIONS: Radiotherapy results in a modest improvement in survival, without reducing the quality of life or cognition, in elderly patients with glioblastoma.

25 INVITED

Short radiotherapy versus long radiotherapy – should temozolomide be added?

R. Rampling. *UK*

Abstract not received.

Symposium (Mon, 24 Sep, 14:45−16:45)
Stem cells in solid tumours

26 INVITED

Glioma stem cells: from biology to clinics

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Cancer stem cells are the rare population of undifferentiated tumorigenic cells responsible for tumor initiation, maintenance and spreading. Such population should represent the preferential target of effective therapies aimed at eradicating the tumor. The development of technologies that allow the unlimited in vitro expansion of cancer stem cells is a powerful tool for basic and translational research aimed at studying the pathogenic events that drive cancer initiation and progression, while providing crucial information for the development of new antineoplastic compounds. Moreover, the analysis of biological parameters concerning cancer stem cells could be a valuable approach to determine the prognostic value in the clinical setting.
Glioma stem cells have been identified as a subset of CD133+ cells present in the tumor. These cells are resistant to conventional chemotherapeutic drugs and radiotherapy. Moreover, they show a considerable ability to migrate and infiltrate the normal tissues surrounding the tumor. These feautures most likely account for the poor clinical outcome of glioma patients. Thus, the study of glioma stem cells in the clinical setting is a key step to improve the prognostic and therapeutic procedures. We designed a prospective study to determine whether it is possible to identify subgroups of glioblastomas with different intrinsic and prognostic features based on cancer stem cell biology features. We observed that the evaluation of glioma stem cell frequency into the tumor mass, their in vitro growth potential and the expression levels of CD133 together with those of the proliferative marker Ki67 are able to clearly identify the patients at higher risk of disease progression and death.
Thus, although the identification of cancer stem cells from solid tumors is very recent, this research area appears extremely promising and able to foster novel prognostic and therapeutic applications in experimental and clinical oncology.

27 INVITED

ALDH1 is a marker of normal and cancer breast stem cells and a predictor of poor clinical outcome

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Application of stem cell biology to breast cancer research has been limited by the lack of simple assays for identification and isolation of normal and malignant stem cells. We show that stem/progenitor cells in normal breast epithelium and breast tumors have increased aldehyde dehydrogenase activity. Furthermore, immunostaining using ALDH1 antibody identifies normal and malignant stem/ progenitor cells in situ. In a series of 577 breast carcinomas on tissue microarrays, expression of ALDH1 was an independent predictor of poor prognosis. These findings provide support for the “cancer stem cell hypothesis” and offer an important new tool for the study of normal and malignant breast stem cells. Moreover, In situ detection of the cancer stem cell population using ALDH1 would be an important step in developing new diagnostic and prognostic methods for breast cancer.

28 INVITED

Wnt/beta catenin signaling in intestinal and mammary cancer stemness

R. Fodde. *Erasmus MC, Department of Pathological AnatomyJosephine Nefkens Instituut, Rotterdam, The Netherlands*

Breast and colon cancers are generally thought to arise from normal epithelial cells through a stepwise accumulation of genetic alterations in oncogenes and tumor suppressor genes. However, this genetic model does not take into account other essential characteristics of human cancers, namely their vast intratumor cellular heterogeneity and the role played by a minority of cells, the cancer stem cells (CSCs), in determining invasion into surrounding tissues and distant organ sites. The Wnt/β-catenin signal transduction pathway is known to play a central role in self-renewal and differentiation during embryonic development and in the maintenance of many stem cell niches in adulthood. To study how different dosages of Wnt signaling activation may trigger multi-organ tumorigenesis, we have generated several hypomorphic alleles of the Apc tumor suppressor gene by gene targeting. Notably, while both in man and mouse Apc mutations result in intestinal cancer, we have generated specific allelic variants associated with tumor susceptibility in organs other than the GI tract, namely in the mammary gland, skin and liver. Notably, in cancers resulting from Apc mutations intracellular β-catenin accumulation, the earmark of canonical Wnt signaling activation, is found to be heterogeneous within the tumor mass. Here, I will present experimental data indicating that intracellular β-catenin accumulation earmarks cancer stem cells capable of self-renewal and differentiation. The results also indicate that the specific Wnt signaling dosages encoded by different Apc mutations differentially affects homeostasis of adult stem cell compartments and triggers tumor initiation, progression, and metastasis in a organ-specific fashion.

29 INVITED

Prostate cancer stem cells: new therapeutic targets?

N.J. Maitland, A.T. Collins. *YCR Cancer Research Unit University of York, Department of Biology, York, United Kingdom*

Background: Prostate cancer is characterised by not only its heterogeneity of appearance, which can compromise diagnosis of the course of the disease, but also by its heterogeneity of response to most conventional therapies. This heterogeneity is also apparent in the genetic constitution of the tumours where, unlike many of the more common tumours, there remains an inconsistency in the types of genetic lesions and phenotypes observed. Such heterogeneity is characteristic of a stem cell mechanism of cancer differentiation, in contrast to a stochastic mechanism, where all cells are clonal, rapidly dividing, and have a common appearance. At present most therapies for prostate cancers are based on a stochastic mechanism and, as a result, it is probably not surprising that tumour recurrence from a therapy resistant fraction occurs so frequently.
Materials and Methods: We have sought to examine the cancer stem cell hypothesis by fractionation and primary culture of human prostate tumours. Short term cultures in non-differentiating conditions have allowed us to purify sufficient material to carry out microarray expression analysis (using the Affymetrix platform) on the different cell populations present within various grade of human prostate cancers, and non-malignant control cultures derived as described by Collins et al, 2005 Cancer Res. 65: 10946.
Results: The cultured “cancer stem cells” have a unique phenotype which marks them apart from both their non-malignant equivalents (cultured from benign prostatic tissues) and also from their more differentiated, but still basal, amplifying progeny. There is also an association with patient outcome, as the Gleason 4 pattern tumours are distinguishable from Gleason pattern 3 (and below) based on the stem cell phenotype. Clinical outcome has been clearly associated to the relative prevalence of Gleason pattern 4 histology. The phenotype most closely associated with prostate cancers, androgen receptor-expressing and PSA/PAP secretion, is not present within the stem cell population. However, both in vitro and in vivo, stem cells can be manipulated to generate three dimensional structures and also tumours in an orthotopic xenograft which will regenerate the androgen sensitive phenotype.
Conclusions: Detailed knowledge of the phenotype of the cancer stem cells should allow us to design stem cell-specific therapies. These therapies are likely to be carried out in parallel or immediately after the destruction of the mass of tumour cells which surround, and interact with, the cancer stem cell. The availability of both cultures and of a robust in vivo model using cells from individual patients should allow us to design the optimum therapies in the future. Ultimately, it is only the destruction of the cancer stem cells and a resultant abrogation of tumour recurrence which will provide the proof of the cancer stem cell hypothesis for prostate cancer. Deletion of prostate cancer stem cells offers a real hope for curative rather than palliative long term therapy.