390 INVITED

Lack of Benefit of Intensified Treatment Strategies in Elderly Patients With Squamous Cell Head and Neck Cancer

Abstract not received

391 INVITED

The Importance of Geriatric Assessment Using the "Frailty Index" Among Patients With Head and Neck Cancer Treated With Radiotherapy: Toxicity and Quality of Life

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Introduction: Elderly cancer patients more often suffer from comorbidity, diminished organ functions with impairment of daily vital functions and cognitive function. Biologic age as such is a poor marker for health risks. Frailty is commonly defined as a state of decreased resilience or vulnerability to stressors. Instruments for comprehensive geriatric assessment, such as the Groningen Frailty Index (GFI) provide information on the functional status of elderly cancer patients, including information on comorbidity, functional status, nutritional status and psychosocial status. The GFI has been developed as a simple screening instrument for frailty and a case finder for elderly patients who would benefit from integrated geriatric care. The GFI score ranges from 0 to 15. The purpose of this study was to determine the influence of the GFI score on acute and late toxicity and quality of life (QOL) among patients curatively treated with radiotherapy of chemoradiation for head and neck cancer.
Material and Methods: The GFI was used among patients with head and neck cancer treated with curative radiotherapy or chemoradiation at the department of Radiation Oncology of the University Medical Center Groningen. All patients were subjected to a standard follow up program, including prospective evaluation of acute and late toxicity, as well as health-related quality (EORTC QLQ-C30 and EORTC QLQ-H&N35). Frailty was defined in case of a GFI > 6. Acute toxicity was measured weekly during radiation and 6 weeks after completion of treatment according to the CTCAE v3.0. Late toxicity was measured every 6 months after radiation. QOL was assessed at similar time points.
Results: The study population was composed of 275 patients, of which 166 (60%) were male. The median GFI was 6. Thirty-nine percent (109 patients) were classified as frail.
At baseline, frail patients experienced significantly more head and neck cancer symptoms and toxicity and performed worse with regard to all functional dimensions of QOL and global quality of life.
Frail patients experienced significantly more acute toxicity, in particular acute xerostomia and sticky saliva, and swallowing dysfunction. After completion, frail patients recovered more slowly. After 12 months late toxicity was similar in both groups. Similar results were found with regard to patient-rated head and neck cancer symptoms and general symptoms. Frail patients scored worse on the general dimensions at baseline and at all time points after completion of treatment.
After correction for baseline scores, these differences partly disappeared.
Conclusions: The GFI is a significant prognostic factor for acute and late toxicity of curative radiotherapy of chemoradiation in head and neck cancer and for worse QOL. As a consequence, frail patients could benefit from more intense and integrated geriatric supportive care during and after treatment.

Scientific Symposium (Tue, 27 Sep, 09:00–11:00)
Managing the Side Effects

392 INVITED

Early and Late Side Effects Related to Surgery

Abstract not received

393 INVITED

Combination of Radiotherapy and Targeted Agents – What Should We Expect?

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The paradigm of combined radiotherapy and Cetuximab in head and neck cancer is assumed to represent the beginning of successfully combining radiotherapy with biologically targeted agents. Based on *in vitro* and *in vivo* studies many agents combined with radiotherapy have the potential to improve tumour control although pre-clinical data demonstrating clear improvement in therapeutic ratio is limited.
Combination of radiotherapy and systemic agents carries the risk of enhancing radiation induced toxicity and this is of particular relevance when treating to doses close to normal tissue tolerance. The increase in both acute and late effects of combined radiation with conventional systemic chemotherapy provides a model for recording the late effects of combination of radiotherapy with targeted agents. Some side effects of combined chemo-radiotherapy were recognised early and others, particularly if unexpected, with delay. The introduction of targeted biological agents with radiation requires phase I studies although the design aimed at assessing agents alone is not generally suitable for side effects of combined treatment which may occur months or years later. The presentation will review the available clinical data on the potential risks of combined radiotherapy and targeted agents and will suggest modern radiotherapy solutions to try and minimise some of these.

394 INVITED

Is It Time to Review the Common Toxicity Criteria in the Era of New Targeted Drugs?

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Targeted therapies exploit molecular features known to be upregulated specifically in neoplastic cells. Hence, it was hoped that by focusing on molecular and cellular changes that act by downregulating or "switching off" processes that are critical to cancer development or progression, targeted therapies may be less harmful to normal cells. Even though most of the targeted therapies produce less toxicity than standard cytotoxic agents, these expectations not always have been met.
The severity of adverse events related to the use of systemic cancer therapies is currently assessed using standard National Cancer Institute Common Toxicity Criteria (CTC). This system was developed primarily as a surveillance tool, at the time when most anticancer agents were administered intermittently, predominantly intravenously, and their toxic effects were transient. Thus, it was mainly designed to identify acute toxicity of a given agent, considering severity and level of necessary intervention. In turn, targeted therapies are typically administered daily, mostly orally and for prolonged periods of time. Although these drugs rarely cause severe toxic effects, subacute toxicity experienced continuously for several months may substantially affect patients' quality of life and activities of daily living. In consequence, this may incur poor compliance, dose reductions or treatment discontinuation. For example, whereas grade 1 or 2 nausea, diarrhea, muscle cramps or fatigue may be acceptable for a couple of days, they may turn out unbearable if become permanent. Similarly, rash severity relying heavily on body surface area coverage fails to account for the location of EGFR-associated rash confined typically to the face an upper trunk. Additionally, with the current recording system, adverse events that persist unabated for several months may remain underreported, and the maximally tolerated doses may be established improperly. Thus, objective assessment of long-term cumulative effects seems to be essential.
There is clearly a need for some modifications of CTC in the era of new targeted drugs. Reporting of adverse events not only should include their grade and attribution, but should also take into account their duration, the impact on patients' quality of life (bother items) and their physical functioning. Proper grading of adverse events should allow their proper management and dose modifications, but may also assist in investigating the relationships between some toxicities and treatment efficacy (for example skin toxicity accompanying anti-EGFR therapies). Although some modifications considering specificity of targeted therapies have already been introduced in the last version of CTC, further amendments are warranted.

395 INVITED

How to Follow up the Acute and the Late Toxicity With New Emerging Therapies?

Z.X. Liao[1]. [1]*University of Texas M.D. Anderson Cancer Center, Radiation Oncology, Houston Texas, USA*

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008 and the cancer deaths are projected to continue to rise to over 11 million in 2030. Cancer therapies typically include local regional (surgery and/or radiotherapy) and systemic, and a combination of local regional and systemic approaches. During past decades, many new therapies have been developed and all cancer therapies developed to date is associated with a spectrum of acute and late normal tissue toxicities and signs and symptoms of varying incidence and severity associated with these toxicities. However, there still issues in methods for reliable diagnosis, follow-up, report, and quantification of acute and late normal tissue toxicities.
Using lung cancer therapies as an example, a review of many of the issues involved in diagnosing, follow-up, reporting acute and late toxicities

from cancer therapies will be presented. The ideal criteria for reporting and grading toxicity should be objective, including biological, imaging, functional, and clinical factors. For late toxicity, the latent time to develop the toxicity should be considered. The importance of predictive and prognostic biomarkers for acute and late toxicities, mechanistic studies, and the design of clinical studies with normal tissue endpoints as a primary outcome will be discussed. A mechanism to use patient and physician reported outcomes as a follow-up tool and an indicator for intervention of treatment related toxicities will also be discussed.

Special Session (Tue, 27 Sep, 11:30−12:30)
Is the Biology of Metastatic Breast Cancer Similar to the Primary Breast Cancer?

396 INVITED

Receptors and HER2/neu Status From Primary to Metastatic Intra Patients Difference?

G. Viale[1]. [1]*European Institute of Oncology University of Milan, Department of Pathology, Milan, Italy*

A great number of studies have invariably shown discordances in hormone receptor (HR) and HER2 status between primary and metastatic breast cancer, endorsing the option to biopsy the metastatic sites to inform the choice of systemic therapy, whenever feasible. Changes in HR and HER2 status have been reported in as many as 30% of the cases, when comparing the primary tumours with either synchronous lymph node metastases or distant recurrences. The reasons for such discordances are still controversial, especially because it is exceedingly difficult to assess whether the changes actually reflect true biological mechanisms or are due to inaccurate assessment of HR and HER2 status. Indeed, the intrinsic error rate of immunohistochemical and in situ hybridisation assays used for the assessment of these markers may well be responsible for an apparent change, because any two measurements of the same variable are expected to yield discordant results unless the method is 100% accurate and perfectly reproducible. Before rendering the final diagnosis of a discordant metastasis, it may be wise to repeat the tests simultaneously on both the primary and recurrent tumour specimens, and also to use a different confirmatory test (e.g., a fluorescence in situ hybridization assay for HER2 or an mRNA based measurement for HR). Though this policy will not completely eliminate false-positive and false-negative results (because of preanalytical variables), it can reduce the technical discordance rate. Plausible biological reasons for a true change in HR or HER2 status include intratumoral heterogeneity in the expression of these markers, and the effects of the systemic interventions in clonal selection. A repeat biopsy of the metastatic site(s) may be justified when there is uncertainty about the true nature of the secondary lesion, and when the disease runs an unusual clinical course. Also, not to deny any patient the possible benefit of a targeted therapy, the repeat biopsy may be justified for patients whose primary tumour had been classified as triple negative and therefore were ineligible for any targeted treatment. A final important caveat against routine repeat measurements of receptor status on all recurrent breast cancers needs to be considered. Intratumoral heterogeneity is feature common to both the primary and the recurrent disease. Different metastatic sites in the same patient may show discordant expression of HR and HER2, so that the biopsy of a single metastasis may not be truly representative of the responsiveness of the disease to different systemic therapies. The decision to perform a repeat biopsy of the metastatic site ultimately must rely on a careful clinical judgement of the possible benefit of such intervention for the individual patients.

397 INVITED

Genomic Data on Metastatic Disease

Abstract not received

398 INVITED

Should a Biopsy Be Done in Each Patient With a Suspicion of Metastatic Relapse?

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Modern management techniques with a strong focus on adjuvant therapies have markedly reduced the risk of breast cancer recurrence. At the time of clinical or radiological suspected relapse, patients are frequently managed based on the site of relapse, the relapse-free interval, previous adjuvant therapies and the expression in the primary tumour of relevant prognostic and therapy predictive factors.

The percentage and intensity of oestrogen receptor expression together with HER2/neu status, non-amplified or amplified in the primary tumour, frequently serves the basis for management also in the metastatic disease. Previously, mostly small respective studies had revealed a lack of stability and reliable frequency both for ER and HER2/neu. Recently two prospective studies have, essentially, confirmed the presence of lack of stability for these therapy predictive markers in the comparison between the primary tumour and the corresponding relapse. In addition to this, biopsy confirmation will also discover whether the radiological lesion actually represents another primary cancer or metastatic disease from another primary tumour or even a benign lesion. The frequencies are likely to be quite/very low although for the individual patient the management may be dramatically different.
Standard radiological investigation even including CT PET scan evaluating metabolism in a tumour lesion versus the surrounding area will, of course, not be discriminative for different types of malignant lesions.
The lecture will describe an update of prospective and retrospective data on this topic and give pros and cons for biopsy verification of metastatic lesions.

Special Session (Tue, 27 Sep, 11:30−12:30)
Strategies of Prolonged Multimodality Treatment in Advanced Patients

399 INVITED

Intermittent Treatment

Abstract not received

400 INVITED

Strategies of Prolonged Multimodal Treatment on Metastatic Colorectal Carcinoma (mCRC): Maintenance Treatment With Targeted Agents

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CRC is one of the most prevalent cancers that accounts for a great number of research projects (5% of NCI budget on 2010). Common questions like the duration of treatment for metastatic patients still remains a matter of debate. Currently, this population is usually treated with chemotherapy until progression or unacceptable toxicity, in an approach that comes from the firsts studies conducted with 5-FU s/a. Nevertheless, the long-term toxicity resulting from the incorporation of new cytotoxic agents makes almost impossible to follow this strategy. Some clinical trials have been conducted to explore maintenance strategies in mCRC. Targeted agents have been incorporated in the treatment of mCRC and they have shown an improvement of efficacy with mild increase of toxicity in selected patients. The next question with these agents is whether they can contribute to improve maintenance strategies and therefore increase progression-free survival.
Anti-VEGF treatment: CONCEPT and MACRO trials suggest that maintenance treatment with Bevacizumab is feasible, but some questions regarding the correct schedules of treatment administration remain still to be answered. Currently there are 7 trials ongoing exploring different schedules with bevacizumab as part of maintenance therapy in mCRC. Mature results of CAIRO 3 and NCT 00973609 are highly awaited. For the time being, maintenance therapy with bevacizumab may be recommended as a treatment option in selected patients, although questions on cost-efficacy and patient's selection remain still unanswered. Further studies on predictive biomarkers are highly recommended.
Anti-EGFR treatment: Anti-EGFR drugs have shown s/a activity. In this field of treatment we have well-defined predictive biomarkers − KRAS mutation status − and some others that are not fully validated (like BRAF, NRAS, PIK3CA mutation status, PTEN loss, quadruple wild-type signature, and others). Nevertheless, the available studies have not explored the concept of maintenance treatment under the knowledge of predictive biomarkers, and therefore the results of COIN and NORDIC are not useful to answer this approach. Currently, there are at least 3 active clinical trials exploring combinations of chemotherapy with cetuximab or panitumumab to explore the maintenance concept. As an example, the MACRO 2 study is evaluating the feasibility and efficacy of s/a cetuximab in this setting.
Future perspectives: Further improvement in molecular biology knowledge will help to define mechanisms of primary and secondary resistance to conventional cytotoxics and targeted agents and hopefully will translate in the identification and validation of predictive biomarkers that help us to better select the treatment options in mCRC. Theoretically this approach would also help to define which patients would derive benefit from this maintenance approach and the best treatment options.