10−23%. Prognosis may be positively influenced by a longer disease free interval of more than 6 months after initial lung resection.
Despite the lack of randomised studies as well as prospective phase II studies the current literature suggests that well selected patents with oligometastatic disease may profit from an individualised treatment including complete resection of the primary tumor as well as the metastases. Not only the indication for surgery is ill defined in the current literature also the role of adjuvant chemotherapy or radiotherapy is unclear despite it is often used in combination with surgery. Improvement in imaging modalities and minimal invasive staging techniques allow more reliably to define the macroscopic tumor extend.

181 INVITED

Which is the best treatment for non-small lung cancer patients with PS 2?

C. Gridelli[1]. [1]*"S.G. Moscati Hospital", UO Oncologia Medica, Avellino, Italy*

Patients with performance status of 2 (PS 2) usually account for a small proportion of patients enrolled in trials of first-line treatment for advanced disease but represent a significantly higher proportion (up to 30–40%) when population-based surveys are conducted. As in other types of cancer, PS has a clear prognostic role in advanced NSCLC. Median overall survival of patients with PS2, whatever the treatment under investigation, is always substantially shorter than that of PS0 or PS1 patients, and rarely exceeds 5 months, with 1-year survival rates <20%, and these unfit patients are at higher risk for severe toxicity.
For this sub-group of patients, there is no treatment widely accepted as standard and oncologists have to choose among several treatment options: best supportive care, single-agent chemotherapy, non-platinum-based combination chemotherapy and platinum-based combination chemotherapy.
It is still unclear if the benefit achieved with cisplatin-based chemotherapy is restricted only to PS0 and PS1 patients, or also applies to PS2 patients. In the meta-analysis published in 1995, although overall results were limited by statistical heterogeneity and evident outcome differences for the different chemotherapy categories, a significant benefit was demonstrated for cisplatin-based trials, and a sub-group analysis confirmed this benefit for both good and poorer PS patients. However, the outcome of 64 PS2 patients enrolled in the clinical trial ECOG 1594 comparing four platinum-based combinations has proven to be very poor. As for the role of carboplatin, the results of the CALGB 9730 study, comparing paclitaxel plus carboplatin versus paclitaxel alone, must be considered. In the sub-group of PS2 patients median survival in the group treated with combination chemotherapy was significantly longer than with paclitaxel alone. In a randomized phase II study carboplatin plus paclitaxel and cisplatin plus gemcitabine, administered at attenuated doses, proved to be feasible in PS 2 patients. After 1995, some advantage of chemotherapy versus supportive care alone has been shown also with many new cytotoxic agents as gemcitabine, vinorelbine, paclitaxel and docetaxel, administered as single agents. These drugs are usually characterised by a good tolerability, with a low incidence of severe adverse events. Most of the studies show some advantage of chemotherapy in terms of overall survival also in the sub-group of PS2 patients, although formal statistical comparisons are precluded by the low absolute number of patients. However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents. An Italian randomised trial compared the combination of gemcitabine and vinorelbine to the two single drugs in patients >70 years of age, and the combination did not show advantage over mono-chemotherapy in terms of overall survival also in the sub-group of PS2 patients. The results of an European Experts Panel on the topic, indicate that single-agent chemotherapy could be the preferred option in the treatment of PS 2 patients, with carboplatin-based or low-dose cisplatin-based doublets representing alternative options. To date randomised trial in USA (carboplatin+ gemcitabine vs gemcitabine) and in Italy (cisplatin+gemcitabine vs gemcitabine) are ongoing. In the near future, the role of targeted agents with better safety profile than chemotherapy as the EGFR-TKI erlotinib, has to be explored in the first-line treatment of advanced NSCLC PS2 patients.

Special Session (Tue, 22 Sep, 17:00−18:00)
Deficient mismatch repair (dMMR) in colorectal cancer

182 INVITED

Defect Mismatch Repair System (dMMR): always genetic and sometimes hereditary

N. Hoogerbrugge[1], M.J.L. Ligtenberg[2], J.H. van Krieken[3]. [1]*University Medical Center St Radboud, Human Genetics, Nijmegen, The Netherlands;* [2]*University Medical Center St Radboud, Human Genetics and Pathology, Nijmegen, The Netherlands;* [3]*University Medical Center St Radboud, Pathology, Nijmegen, The Netherlands*

Lynch syndrome, also called Hereditary NonPolyposis Colorectal Cancer (HNPCC), accounts for about 5% of colorectal cancers and is caused by a germline mutation in one of the mismatch repair (MMR) genes. Colorectal cancer is the most common type of cancer in Lynch syndrome. Also, extra colonic carcinomas occur, i.e. carcinomas of the endometrial, ovaries, small bowel, stomach, sebaceous gland, biliary tract, and upper urinary tract. Typical Lynch syndrome families show an autosomal dominant predisposition of cancers associated with Lynch syndrome, and over 90% of colorectal cancers have a defect in the MMR system (dMMR). Germline mutations have been identified in the MMR genes MLH1, PMS2, MSH2 and MSH6.
Microsatellite instability (MSI) analysis and immunohistochemical (IHC) staining of MMR proteins can detect a defect in the MMR system (dMMR). This defect can be caused either by a germline mutation in the MMR system or by somatic hypermethylation of the promoter region of MLH1. A tumour that shows MSI without staining of MLH1 and PMS2 proteins and with somatic hypermethylation of the MLH1 promoter is characteristic for sporadic cancer, meaning not hereditary.
A disease causing germline mutation can be identified in 60% of patients suspected of Lynch syndrome with an MSI positive tumour (dMMR), 20% show hypermethylation of the MLH1 promoter and therefore do not have a hereditary but a sporadic type of cancer. Interestingly, the remaining 20% of patients, with an unexplained MSI positive tumour, had a less pronounced family history, but were diagnosed at an age comparable to that of proven Lynch syndrome patients.
Differentiation of sporadic CRC from Lynch syndrome-HNPCC is important as surveillance in the latter is more intensive and can reduce mortality from cancer in patients and their close relatives. The finding of a predisposing germline mutation will determine who is (and who is not!) a candidate for participation in surveillance programs. Identification of Lynch syndrome only by family history is insufficient and new strategies are needed to detect more patients at risk for Lynch syndrome.
To improve the identification of Lynch syndrome, we started to implement a new approach called MIPA (MSI indicated by a Pathologist): pathologists select newly diagnosed patients with colorectal cancer for MSI analysis based on one of the following criteria:

1. Colorectal cancer before the age of 50 years;
2. Second colorectal cancer before the age of 70 years;
3. Colorectal cancer and a Lynch associated cancer before the age of 70 years (Endometrial, ovarian, gastric, hepatobiliary, small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)

Next, the treating physician discusses referral to genetic counselling with patients who have a tumour with MSI indicating deficient MMR.
The newly proposed approach, in which pathologists select patients for MSI analyses, is found to be effective, efficient and feasible in daily practice. Deficient MMR is an excellent marker to distinguish sporadic CRC from patients at high risk for Lynch syndrome, but not all patients with dMMR have hereditary cancer. Therefore deficient MMR is always genetic and sometimes hereditary.

183 INVITED

Should patients with dMMR be treated with chemotherapy?

R. Labianca[1], D. Sargent[2]. [1]*Ospedali Riuniti Bergamo, Unit of Medical Oncology, Bergamo, Italy;* [2]*Mayo Clinic, Biomedical Statistics, Rochester MN, USA*

The selection of patients to treat with adjuvant chemotherapy for resected colorectal cancer is of outmost importance, in order to decrease the NNT (Number Needed to Treat), chiefly in stage II individuals, who have a relatively good prognosis after surgery alone. In the last few years, patients with colon cancer demonstrating Microsatellite instability (MSI-H) or defective DNA mismatch repair (dMMR) have been reported to have improved survival and to receive decreased or no benefit from 5-FU based adjuvant therapy as compared to patients with microsatellite-stable (MSS) tumors (Ribic C, JCO 2003).

In the context of a large international collaboration between Europe and USA (ACCENT database) we sought to confirm MMR status as a predictor of benefit from adjuvant therapy in stage II and III colon cancer patients from randomized clinical trials. MSI assay or IHC for MMR proteins were performed on 457 patients not used in previous analyses. All patients had stage II or III disease, and were randomized to 5-FU based therapy (either 5-FU + levamisole or 5-FU + leucovorin, N = 229)) versus no post-surgical treatment (N = 228). The primary endpoint was disease-free survival (DFS). Data were subsequently pooled with data from a previous pooled analysis. Seventy of 457 patients (15%) exhibited dMMR. Adjuvant therapy had a significant beneficial effect on DFS (HR = 0.69, p = 0.03) in patients with pMMR tumors. Patients with dMMR tumors receiving 5-FU had no improvement in DFS (HR = 1.10, p = 0.85) as compared to those randomized to surgery alone. In the pooled dataset of 1027 patients these findings were maintained, and in stage II patients with dMMR tumors treatment was associated with reduced overall survival (HR = 2.95, p = 0.04).
In this experience patient stratification by MMR status provides a more tailored approach to using adjuvant therapy in colon cancer. Therefore, in a patient being considered for 5-FU alone therapy MMR status should be assessed and considered in treatment decision-making.
Although these data are not completely confirmed by the observations in the US trial on 5-FU + CPT-11 (Bertagnolli M et al, JCO 2009) and in PETACC-3 study (Roth A and Tejpar S, ASCO 2009), the MMR determination in the context of clinical research or even in every day practice could become a “must” in the next future, chiefly for stage II patients and with the aim to improve the personalization of cancer treatment.

Special Session (Tue, 22 Sep, 17:00−18:00)
Case-based: clinical issues in cancer therapy

184 INVITED

Targeted therapies – better awareness of side-effects

A. Margulies[1]. [1]*Universitätsspital Zürich, Klinik und Poliklinik für Onkologie, Zürich, Switzerland*

With the development of the targeted therapies, much attention has been given to the skin toxicities, particularly the skin rash. Rightly so, from the standpoint of the patient. Often nurses and other practitioners are focused on this side effect alone when informing the patient about expected side effects from these drugs.
Increased use of molecularly targeted therapies for an increasing number of cancers, is evident in clinical practice. Also, the regimens employing multiple targeted drugs are increasing whether in larger hospitals, private practices or at home.
Nurses are increasingly involved with these drugs, the tumour entities, all patients and all health economic situations and are therefore challenged to guide the patients throughout these treatments regardless if first, second or third line therapies.
The acne-like rash is one of the most obvious – this meets the eyes of the health professions, the patient the carers. Less obvious, but nonetheless important, are other side effects caused by monocolonal antibodies and the small molecule drugs. An increased awareness of these and reflection on which are relevant for nursing intervention and patient safety is needed. Nurses can support the concordance/adherence and understanding of the patient and carers toward these new therapy options and side effects.

185 INVITED

Controversies in anaemia: making blood transfusion decisions

L. Bishop[1]. [1]*Guy's and St Thomas' Hospital, 10th Floor Guy's Tower, London, United Kingdom*

Background: Clinically defined cancer-related anaemia is common in cancer patients but the impact of mild/moderate anaemia is undetermined, when combined with cancer symptoms and/or the side effects of therapy. Blood transfusion is the standard treatment; however there are significant risks and costs. It is important that the decision to give blood is carefully considered but it is not clear how these decisions are made or who makes these decisions in the clinical setting. It is also unclear as to why blood transfusion decisions are variable. The purpose of this study was to explore the cultural practices in transfusion; and to identify the key elements, which influence clinical decision making in blood transfusion in haemato-oncology and lung cancer patients.
Methods: The assessment and decision making processes for blood transfusion were explored using fieldwork observation, six patient and nine clinician interviews based on ethnographic methodology. Data were analyzed using thematic analysis.
Results: First, the findings suggested that anaemia and transfusion are commonplace in the clinical setting; and because many patients live with anaemia and it may not be viewed as an illness. Second, this study confirmed there is a great deal of uncertainty surrounding the diagnosis and management of this clinical problem; but this uncertainty was acknowledged by both patients and clinicians. Third, clinicians and to some extent patients, are socialized into the practice of the sub-discipline and the decision making was based on the practice within the individual department. Finally it was revealed that the haemoglobin level was used as a distinct fragment of information on which to assess for the presence of anaemia and base the decision to treat with blood transfusion. Conversely it was described that decision making could be improved if there was consistency in patient assessment. The sub-specialisms of haematology and lung cancer used different haemoglobin triggers to describe anaemia for example, the haematology team used haemoglobin of 7−8 g/dl to describe anaemia, however the lung oncology team used a trigger of 9−10 g/dl to describe anaemia and the reasons for this were not clear other than the socialization of practice. Haemoglobin of 8 g/dl was described as being used as a trigger to transfuse and the transfusion trigger did not differ between the sub specialisms.
Conclusion: The management of anaemia is not a priority in this setting however by understanding the complexity of factors for variation in practice in the clinical context, new models transfusion can be developed. It may be that cancer related anaemia should be managed differently from other types of anaemia because it is not a primary diagnosis but a consequence of the cancer and treatment. Patient centred decision making may be a solution to optimize transfusion decisions whereby informed patients make the decisions, similar to the management of other chronic conditions, or as a minimum ensure there is consistency of patient assessment. Furthermore, different collaborative groups could be organized to develop optimal transfusion practices, for example to include nurse-prescribing of blood components.

Wednesday, 23 September 2009

Joint ECCO-ASCO symposium (Wed, 23 Sep, 09:00−11:00)
Controversies in individualised management of prostate cancer

186 INVITED

Bioinformatics and gene discovery in prostate cancer

K.J. Pienta[1], A.M. Chinnaiyan[2]. [1]*University of Michigan, Department of Internal Medicine, Ann Arbor, USA;* [2]*University of Michigan, Department of Pathology, Ann Arbor, USA*

Rearrangements of chromosomes have been demonstrated to play a causal role in haematological malignancies and sarcomas. IThe gene fusions that result from these rearrangements have the potential to serve as diagnostic and prognostic markers of disease as well as therapeutic targets. The development of imatinib, which inhibits the BCR-ABL gene fusion product that defines chronic myeloid leukaemia, is the prototypical example of this type of targeting. Gene fusions involving the prostate-specific gene transmembrane protease, serine 2 (TMPRSS2) and members of the erythroblastosis virus E26 transforming sequence (ETS) family of transcription factors have been identified to be common events in prostate cancer. The most common fusion, TMPRSS2:ERG, is present in approximately 50% of prostate-specific antigen (PSA)-screened prostate cancers and in 15−35% of population-based cohorts. ETS fusions can be detected by FISH in the urine of men with prostate cancer, with a specificity rate of >90% when associated with PSA screening. Furthermore, it appears that there may be an association between ETS fusions and disease aggressiveness. The importance of the family of TMPRSS2:ETS fusions in the biology of prostate cancer, as well as their application to diagnosis, prognosis, and treatment contiues to be delineated.