Special Session (Mon, 21 Sep, 14:00–15:00)
Metastatic neck nodal carcinoma of unknown primary

34 INVITED

Diagnostic issues and treatment

M. Merlano[1]. [1]*Ospedale S. Croce, Department of Clinical Oncology, Cuneo, Italy*

Neck node metastases from unknown origins account for 5–10% of all neck masses. Although metastases at the upper and middle neck can be easily attributed to head and neck cancers, and those to the lower neck may be attributable to a primary origin below the clavicles, this is not a clear rule and, moreover, many different types of cancer can arise from the head and neck region. Diagnostic procedures include complete physical examination, fiberoptic endoscopy of all head and neck regions and upper oesophagus, biopsies of the suspected regions, CT scan Magnetic resonance. PET-scan may be used as additional investigation, although the research of a primary site in the head and neck cancer areas is hampered by some limitations, in particular the its limited resolution. Some molecular assays have been suggested to identify the potential primary site. These include detection of Epstein-Barr virus (EBV) or Human Papilloma virus (HPV). However, at the moment, molecular assays have a limited role and should be regarded as investigational. The most frequent histology is squamous cell carcinoma (in particular in the upper neck). Adenocarcinoma histology and lower neck involvement, suggests origin in the lung, oesophagus, stomach, or pancreas. In these cases, PET scan may help the identification of the primary site. When the primary origin remains unknown, the therapeutic approaches include surgery and radiotherapy. In case of limited neck node involvement (N1), surgery alone and radiotherapy alone show similar efficacy. In N2 or N3 disease, the combined approach is preferred. Surgical neck dissection, with or without postoperative radiotherapy, or the opposite sequence, is suggested in many cases. However, the extent of radiotherapy remains a matter of debate, and should be weighted against acute and late toxicity and, in particular, the risk of a required re-irradiation whether a primary tumour emerges thereafter. Other approaches (hyperthermia or chemotherapy) must be considered investigational.
Prognosis depends on histology and extension of neck involvement. Patients with limited neck involvement of squamous cell type may show a long disease free survival and cure may be occasionally achieved. The poorest prognosis is observed in patients with adenocarcinoma from unknown origin.

35 INVITED

Metastatic neck nodal carcinoma of unknown primary: which radiotherapy is needed?

V. Gregoire[1]. [1]*UCL Clinique Univ. St. Luc, Department of Radiation Oncology, Brussels, Belgium*

Cervical lymph node metastases of squamous cell carcinoma (SCC) of an unknown primary is a rare disease. One thousand eight hundred ninety patients with SCC of unknown primary of the H&N have been reviewed from 21 series reporting patients treated between 1948 to 1992. Overall survival mainly depended on the stage of the neck. For N1 disease (1997 AJCC/TNM classification), the median value of the reported 5 year survival reached 61% (19–90%); for N2a, N2b and N2c-N3 diseases, median values dropped to 45% (15–87%), 40% (15–63%) and 21% (0–62%), respectively. These figures are consistent with survival data of patients with known primary tumors. All series pooled together, the mean incidence of subsequent primaries in the Head & Neck mucosa did not exceed 13%. When split for different treatment modalities, the incidence reached 21% (13–29%) and 12% (0–48%) for patients treated by surgery alone and radiotherapy alone, respectively. Due to the retrospective nature of the analysis, it is likely that the staging procedure was quite different from one study to another. This probably explains the heterogeneity in the incidence of subsequent primary extending from 0 to 48%. When patients treated by radiotherapy are further divided into those irradiated only on the neck (no attempt to cover the head & neck mucosa) and those treated on the neck and the mucosa, the incidence on subsequent primary reached 13% (5–41%) and 11% (0–48%), respectively. Due to the variety of the radiation techniques used, it is likely that patients intended to be treated only on the ipsilateral neck also received some dose on the ipsilateral mucosa. It is not possible to evaluate the influence of the treatment modality on the survival of these patients from the retrospective analysis. In a retrospective Danish series with more than 200 patients, neither the survival nor the disease-free survival was influenced by the extend of the radiation treatment. On the other hand, extensive radiation treatment was associated with a significant morbidity, mainly xerostomia with its subsequent complications (e.g. taste lost, weight lost, teeth lost, osteoradionecrosis, speech difficulties). The incidence of more than grade 2 xerostomia is estimated in the range of 50 to 60% for extensive H&N irradiation. A reduction by a factor of at least two is expected using a more selective treatment. In conclusion, the review of the literature indicated that the incidence of subsequent primary is rather low and appears to be irrespective of the treatment modality. In particular, no difference could be detected between patients irradiated only on the ipsilateral neck and those irradiated on the neck and the upper aerodigestive tract mucosa.

Special Session (Mon, 21 Sep, 14:00–15:00)
Immunotherapy and vaccination for malignant glioma

36 INVITED

Clinical applications – lessons from pediatrics

S. Van Gool[1], H. Ardon[2], F. Van Calenbergh[2], S. De Vleeschouwer[2]. [1]*U.Z. Gasthuisberg, Dept. of Paediatrics, Leuven, Belgium;* [2]*U.Z. Gasthuisberg, Neurosurgery, Leuven, Belgium*

Background: The prognosis of patients with high grade glioma (HGG) is poor. We investigate a potential role of active specific immunotherapy to improve the prognosis of these patients.
Methods: A cohort comparison trial HGG-IMMUNO-2003 is designed for children and adults to implement immunotherapy with autologous mature dendritic cells loaded with lysate of autologous HGG (DCm-HGG-L) after new resection of the relapsed HGG. By changing per cohort the vaccination schedule and the maturation methodology of the DC, stepwise improvements are aimed.
Results: 125 patients with relapsed HGG were treated with new surgery and DC vaccination in 4 consecutive cohorts. Age did not differ in these 4 cohorts nor did the percentage of total resection versus less than total resection. In this group, 28 patients were younger than 20 y. The median PFS and OS in the latter group were 2.5m resp. 16.6m with a 2 y OS of 34.6%. The median PFS and OS for 97 adults with relapsed HGG were 2.6m resp. 8.7m with a 2 y OS of 16.1%. Looking to the subgroup of 88 patients with relapsed GBM who received DC vaccines, about half of the patients got new total resection of their relapsed GBM. Median PFS of 88 patients was 2.5m, median OS was 8.7m, 2 y OS was 16%. The OS of 15 patients <20 y was 14.6m compared to 8.6m in adults, with a 2 y OS of 30.8% versus 13.6%. Extent of resection resulted in significantly improved PFS and OS as well. In adults with relapsed GBM, the median PFS from cohort A to D were 1.94, 1.67, 3.23 and 2.72% with PFS at 2 y of 4% in cohort C and still 15.3% in cohort D. There were no major side effects, and most of the patients were treated in an ambulatory setting. Quality of life measured with the EORTC QoL questionnaire remained stable during vaccination treatment.
Conclusion: Our work illustrates feasibility and efficacy of immunotherapy for children and adults with HGG without major toxicity. The younger long-term surviving patients illustrate a level 1c medical evidence of clinical efficacy, while the significant shift in PFS of adults treated with immunotherapy in the consecutive cohorts of patients further illustrate level 2b efficacy. The particular organization of care which we developed to perform DC vaccination, made it possible that patients from several countries had access to the treatment.

Special Session (Mon, 21 Sep, 14:00–15:00)
Secondary leukaemia following chemo or radiotherapy

38 INVITED

Molecular pathogenesis and biology of secondary leukaemias

D. Grimwade[1], A.N. Mays[1], N. Osheroff[2], J.A. Byl[2], S.K. Hasan[3], M. Joannides[1], E. Solomon[1], F. Lo-Coco[3], C.A. Felix[4]. [1]*King's College London School of Medicine, Department of Medical and Molecular Genetics, London, United Kingdom;* [2]*Vanderbilt University School of Medicine, Department of Biochemistry, Nashville, USA;* [3]*University of Tor Vergata Rome, Department of Biopathology, Rome, Italy;* [4]*University of Pennsylvania School of Medicine, Department of Pediatrics, Philadelphia, USA*

Background: Chromosomal translocations leading to the generation of chimaeric oncoproteins play an important role in leukaemogenesis, but mechanisms underlying their formation are largely unclear. Substantial

insights can be gained from investigation of therapy-related acute myeloid leukaemias (t-AMLs), which are becoming an increasing healthcare problem as more patients survive their primary cancers. Exposure to agents targeting DNA topoisomerase II (topoII) predisposes to the development of leukaemias with balanced translocations such as the t(15;17), fusing *PML* and *RARA* genes, in therapy-related acute promyelocytic leukaemia (t-APL) which is a recognised complication of cancer treatment particularly involving mitoxantrone and epirubicin.
Methods: t(15;17) genomic translocation breakpoints in t-APL were characterised by long-range PCR and sequence analysis. The mechanism underlying formation of observed breakpoints was investigated by functional *in vitro* topoII cleavage assays.
Results: We found that in t-APL cases arising in breast cancer patients exposed to mitoxantrone, chromosome 15 breakpoints clustered tightly in an 8bp "hotspot" region within *PML* intron 6, which was shown by functional assay to be a preferred site of mitoxantrone-induced DNA topoisomerase II cleavage (Mistry *et al*, N Engl J Med 2005;352:20−9). However, because cancer patients are typically exposed to multiple cytotoxic drugs often accompanied by radiotherapy, it is difficult to categorically ascribe the causative agent in any given patient with t-AML. Moreover, all previous studies have involved patient populations which could feasibly have been enriched for individuals at particular risk of leukaemia, having already developed one form of cancer. We therefore characterised t(15;17) genomic breakpoints in a cohort of t-APL cases arising in patients treated with mitoxantrone for a non-malignant condition i.e. progressive multiple sclerosis. Significant breakpoint clustering was also observed in this group, with 5 of 12 (42%) chromosome 15 breakpoints involving the "hotspot" within *PML* intron 6. Moreover, one of the chromosome 17 breakpoints occurring within the ~17kb *RARA* intron 2 was found to coincide with that of a previously identified t-APL case arising after mitoxantrone-containing treatment for breast cancer (Mistry *et al*, 2005). Analysis of *PML* and *RARA* genomic breakpoints in functional assays, including the shared *RARA* intron 2 breakpoint at 14444−48, confirmed each to be preferential sites of topoisomerase II-mediated DNA cleavage in the presence of mitoxantrone (Hasan *et al*, Blood 2008;112:3383−90). To investigate mechanisms underlying epirubicin associated t-APL, t(15;17) genomic breakpoints were characterised in 6 cases with prior breast cancer. Breakpoint clustering was again observed in *PML* and *RARA* loci, but *PML* breakpoints were found to fall outside the mitoxantrone-associated hotspot region. Recurrent breakpoints identified in the *PML* and *RARA* loci in epirubicin-related t-APL were shown to be preferential sites of topo II-induced DNA damage, enhanced by epirubicin.
Conclusion: Mitoxantrone and epirubicin exhibit site preference differences for DNA damage induced by topoisomerase II, which may underlie the propensity to develop specific molecularly defined subtypes of t-AML according to the particular chemotherapeutic agent used.

39 INVITED

Secondary leukaemia after breast cancer

F. Lo-Coco[1], S.K. Hasan[1]. [1]*University of Rome Tor Vergata, Biopathology Department, Rome, Italy*

Secondary acute leukemia (sAL) is a well recognised complication of cytotoxic and radiation therapy for breast cancer with an incidence ranging from 0.1 to 1.5% in the reported series. In the archive of the Italian multicenter group for the treatment of hematologic malignancies (GIMEMA), more than 50% of patients with sAL had breast cancer, NHL, or HD as primary tumos. The high number of sAL observed in patients with a previous breast cancer, may be due to the fact that this malignancy is the most frequent neoplasm in women and by the high probability of cure with a consequent prolonged survival. Among treatments for the primary tumor, the association of alkylating agents and topoII inhibitors induced sAL with higher frequency, with cumulative risk at 3 years being 25±10%. According to a prospective Eastern Cooperative Oncology Group (ECOG) study, the use of standard dose cyclophosphamide did not increase the risk of sAL in patients with early stage breast cancer, whereas high doses of cyclophosphamide and doxorubicin were associated with significantly increased sAL development risk as did the combination of fluorouracil-doxorubicin-cyclophosphamide. Notoriously, radiotherapy can further enhance the risk of leukemia, while little is known about the risk of developing t-AL after treatment with novel agents such as monoclonal antibodies, anti-hormone drugs and small molecules. Although the causes predisposing to the development of s-AL are largely unknown, several genetic alterations and cooperating mutations have been identified that may play a role in the pathogenesis of this disease. In this context, individual predisposing factors, including polymorphisms in detoxification and DNA repair enzymes have been identified. As to genetic features of sAL, distinct clinical entities have been described according to the primary treatment, one comprising leukemias arising after alkylating agents which are associated with abnormalities of chromosome arms 5q and/or 7q, and a second group consisting of sAL occurring after topoII-targeting agents that are often associated with 11q23 (*MLL*) or 21q22 (*RUNX1*) or with translocations t(8;21), t(15;17) and with inv(16). The former group is characterized by long latency and poor response to therapy, while the second is associated with relatively short latency, absence of preceeding myelodysplastic features and favourable prognosis. This latter group also includes therapy related acute promyelocytic leukaemia (APL), a subset equally curable as the primary *de novo* disease with retinoic acid-based modern regimens. Survival of patients with s-AL after alkylating agents is extremely poor compared with that of patients with *de novo* AML. Because patients with s-AL have ben often excluded form front-line clinical trial, there is a paucity of prospective treatment data on treatment outcome. In addition, there are no randomized studies comparing standard AL chemotherapy with other treatment approaches. This notwithstanding, there is a general consensus on the view that the treatment most likely to cure t-AML is allogeneic stem cell transplantation. Criteria for therapeutic strategies in patients with s-AL should include the status of the primary cancer, performance status, and cytogenetic characterization of sAL. It is recommended finally that patients with s-AL be enrolled in prospective clinical trials in which therapeutic choices are differentiated according to their genetic features.

40 INVITED

Secondary leukaemia and myolodysplastic syndromes in patients successfully treated for Hodkgin lymphoma: a report from the German Hodgkin Study Group

A. Engert[1]. [1]*Uniklinik Köln, Clinic I Internal Medicine Hematology/Oncology, Köln, Germany*

Treatment-related acute leukaemias (AK) and myelodysplastic syndromes (MDS) occur in patients successfully treated for various malignancies including breast cancer, testicular cancer, non-Hodkgin lymphoma and Hodgkin lymphoma. The prognosis of treatment-related AL and MDS is generally poor. At present, there is no clear treatment strategy for secondary AL/MDS in patients with HL. We thus evaluated the incidence and outcome of sAL/MDS from a total of 5411 patients treated in the trials HD1 – HD9 of the GHSG. After a median observation time of 55 months, the incidence of sAL/MDS was 1%. A total of 46 patients were identified with a median age of 47 years (22 – 79 years). 36 of the secondary malignancies were AL and 10 were MDS. The prognosis of these patients with sAL/MDS was very poor with disease-free survival of 2% and overall survival of 8% after 24 months of observation. An updated analysis with more patients and longer follow-up will be reported.

Special Session (Mon, 21 Sep, 14:00−15:00)
Case-based: linking symptom science to practice

41 INVITED

Symptom management: a case study

C. Miaskowski[1]. [1]*University of California San Francisco, Department of Physiological Nursing – School of Nursing, San Francisco, USA*

Ms. S is a 60 year old woman undergoing treatment for breast cancer. She had a lumpectomy and lymph node dissection and has completed a course of radiation therapy. At the one month follow-up visit, she complains of burning and tingling in her surgical incision and axillary area, persistent fatigue, and sleep disturbance. This presentation will focus on the assessment of this patient's multiple symptoms and the development of an evidence-based intervention plan to manage her symptoms and improve her quality of life.

42 INVITED

Symptom clusters: a case study

E. Ream[1]. [1]*King's College London, The Florence Nightingale School of Nursing and Mid, London, United Kingdom*

A case study will be presented of a patient with complex symptoms, one of which was fatigue. Data relating to this patient will provide the focus for discussions over how symptom clusters should be managed. Participants will discuss various aspects of the process – for example assessment, self-management, multidisciplinary working, and engaging carers.