

cancers. We have also shown that combinations of BRAF inhibitors with TNF α antagonists could provide an effective approach. We have developed mouse models of melanoma that are driven by oncogenic BRAF and the animals get melanoma following activation of BRAF from the endogenous gene, demonstrating that BRAF can be an initiating event in cancer. Finally, we have examined the downstream targets of BRAF and shown that critical to the ability of oncogenic BRAF to induce melanoma is its ability to induce transcription of the melanoma specific transcription factor M-MITF. Oncogenic BRAF regulates M-MITF through transcriptional regulation of the melanocytic factors BRN2 and PAX3. These data explain why BRAF is an addictive oncogene in melanoma.

Symposium (Wed, 26 Sep, 14:45–16:45)

Management and research issues in palliative care

168

INVITED

Neuropharmacology of cancer pain

A. Dickenson. *University College London, Pharmacology, London, United Kingdom*

Until recently, animal models of cancer-induced bone pain were based on the systemic injection of carcinoma cells, resulting in systemically unwell animals with multiple randomly sited bone metastases. This precluded systematic investigation of specific neuronal and pharmacological alterations that occur in cancer-induced bone pain. In 1999, Schwei et al. described a murine model of cancer-induced bone pain that paralleled the clinical condition in terms of pain development and bone destruction, but was confined to the mouse femur. This resulted in progressive bone destruction, elevated osteoclast activity and progressive and distinctive nociceptive behaviours (indicating the triad of ongoing, spontaneous and movement-induced hyperalgesia). In addition, cancer cells induce an inflammatory infiltrate and release growth factors, cytokines, interleukins, chemokines, prostanoids, and endothelins, resulting in a reduction of pH to below 5 and direct deformation of primary afferents. The osteoclast activity that destroys bone correlates with behavioural hypersensitivity suggestive of a neuropathic state. Bone marrow, mineralized bone and the periosteum are innervated by primary afferent fibres and it therefore follows that there would be primary afferent nerve destruction within the cancer laden bone. These peripheral changes, in turn, drive hypersensitivity of spinal cord sensory neurones, many of which project to the parts of the brain involved in the emotional response to pain. In turn, the ability of the painful messages from the spinal cord to impact upon mood, anxiety, the sleep cycle and central autonomic centres can explain some of the co-morbidities commonly observed in patients. Furthermore, these affective areas of the brain appear to drive descending excitations back to the spinal cord that enhance the pain state. Within the spinal cord, a unique neurochemical reorganization within segments of the dorsal horn of the spinal cord receiving nociceptive input from the sarcoma-injected bone has been described and includes an increased expression of the pro-hyperalgesic peptide dynorphin and massive astrocyte hypertrophy. However, changes in certain neurotransmitters as seen in pure neuropathy or inflammation are absent. The progressive nociceptive behaviour, bone destruction and the dorsal horn neurochemical markers all suggest that cancer-induced bone pain is a unique pain state with both elements of neuropathy and inflammation. This talk will consider the efficacy of a number of agents that include opioids and drugs used in neuropathic states based on the current knowledge of cancer induced pain.

169

INVITED

Recent research in opioid treated cancer pain

S. Kaasa. *Norway*

Abstract not received.

170

INVITED

Palliative sedation – its role in refractory symptoms

D. Schrijvers. *Ziekenhuisnetwerk Antwerpen-Middelheim, Department of Oncology, Antwerp, Belgium*

Palliative sedation (PS) is the use of sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in the patients' consciousness. A refractory symptom is defined as a symptom that is uncontrollable despite repeated efforts and various techniques. The appropriate drugs should be carefully titrated to obtain symptom relief. It is advisable to involve a palliative care specialist.

As all other decision at the end-of-life, PS should be discussed with the palliative care patient and his family beforehand and informed consent should be obtained before the initiation of PS. There should be a written procedure how to perform a PS.

PS is the cause of 2.5–8.5% of all deaths in Europe. In palliative care patients, it is used in 4–48% of patients depending on the care setting. The reasons for PS are uncontrollable delirium, dyspnoea, pain and/or psychological stress.

Different medications (e.g. haloperidol, propofol) may be used to initiate a PS but midazolam is the treatment of choice. It can be given subcutaneously and should be titrated until the symptoms are controlled. All other medication except drugs for pain control may be stopped. In case of deep sedation, a bladder catheter should be inserted and complications such as pressure sores or eye ulcerations should be prevented by adequate care measures.

After deep PS, the median duration before death occurs is 1–5 days. During this period, it is essential to support the family and also the nursing staff since PS may cause a serious emotional burden.

PS is an essential part of palliative care and may be used in patients with refractory symptoms to improve the quality of life.

171

INVITED

Translational research in malignant bone pain – Impact on clinical practice

M. Fallon. *Western General Hospital, Palliative Care Team, Edinburgh, United Kingdom*

Cancer-induced bone pain (CIBP) is a major clinical problem with up to 85% of patients with bony metastases having pain. The last few years have seen a dramatic transformation in our knowledge of the mechanisms of CIBP and understanding of treatments. This has been largely the result of an appropriate animal model of CIBP and a more functional exchange of information between basic science and the clinic.

We have established a rat model of CIBP and shown that, like other chronic pain states, it relies on spinal NMDA receptor activation. However CIBP appears to be a unique pain state, bringing about a different profile of neurochemical changes in sensory nerves and spinal cord from those in other pain states, involving prominent glial activation.

In addition, the opioid-resistance of movement-associated bone pain may result from the greater sensory nerve activity/recruitment involved causing additional release of afferent transmitters to produce a sensitised state. By identifying the underlying molecular events in CIBP, it may be possible to develop novel and effective analgesics for this challenging clinical problem. Our clinical programme has fed into our basic science programme and vice versa.

Our clinical programme has characterised CIBP in patients attending a Regional Cancer Centre. In this study 50% of patients with CIBP had spontaneous pain. In 50% of cases (including both spontaneous pain or pain on movement) pain resolved in 15 minutes meaning standard oral opioid treatments are often irrelevant, simply leaving the patient drowsy. In addition, the single most important question to be identified to assess pain severity and impact on function was what has been your "worst pain in the last 24 hours".

Exploration of quantitative sensory testing supports peripheral and central sensitisation mechanisms in the clinic which support our basic science findings.

The threads of the clinical characteristics of CIBP, role of opioids and potential role of adjuvants based on basic science data will be woven together in this presentation.

Symposium (Wed, 26 Sep, 14:45–16:45)

New perspectives in melanoma therapy

172

INVITED

New developments in adjuvant therapy in melanoma

A. Eggermont. *Erasmus Medical Center Rotterdam, Daniel den Hoed Cancer Center/Department of Surgical Oncology, Rotterdam, The Netherlands*

The most important recent developments in adjuvant therapy are the outcome of the EORTC 18991 Trial comparing long term adjuvant therapy with Pegylated-IFN (PEG-IFN) versus Observation in stage III melanoma; the outcome of the Hellenic melanoma group trial comparing 4 weeks of iv HDI (high dose IFN) and the analyses of the importance of autoantibodies and S100 in the EORTC 18952 trial and the ECOG adjuvant trials.

EORTC 18991 Trial: Long Term Adjuvant Pegylated Interferon-alpha2b (PEG-IFN) vs Observation in Resected Stage III Melanoma: Final Results of a Randomized Phase 3 Trial by the EORTC Melanoma Group.

Background: EORTC 18991 is the largest adjuvant trial ever conducted in stage III melanoma. It assessed the efficacy and toxicity of long term PEG-IFN vs Observation (Obs.).

Methods and Patients: PEG-IFN (Induction at 6µg/Kg/wk, sc, 8 weeks; followed by Maintenance at 3µg/Kg/wk, sc) for a total treatment duration of 5 years was compared to Obs. in 1256 patients (pts) with stage III melanoma (anyTN1-2M0 without in-transit metastases). Randomization was stratified for nodal involvement N1 (microscopic) vs N2 (palpable nodes), number of nodes, Breslow and ulceration of primary, sex and center. Distant Metastasis-Free Survival (DMFS) was the primary endpoint. Relapse-Free Survival (RFS) was the pre-specified regulatory primary endpoint. Overall survival (OS) was the secondary endpoint. Intent-to-treat analysis was performed.

	RFS		DMFS		OS	
	Obs.	PEG-IFN	Obs.	PEG-IFN	Obs.	PEG-IFN
Nb. events	368	328	325	304	263	262
4-year rates	39%	46%	45%	48%	56%	57%
Median (yrs)	2.1	2.9	3.0	3.8	NR	NR
HR (95% CI)	0.82 (0.71–0.96)		0.88 (0.75–1.03)		0.98 (0.82–1.16)	
p-value	0.01		0.11		0.78	

HR = Hazard Ratio; NR = Not Reached.

Results: See the table. Median follow-up was 3.8 yrs. Important is much better outcome in Stage III-N1 disease (sentinel node positive patients). In N1-pts (n = 543) the benefit of PEG-IFN seemed more pronounced than in N2-pts (n = 713): RFS (HR 0.73 p = 0.02 and HR 0.86 p = 0.12 for N1 and N2, respectively), DMFS (HR 0.75 p = 0.03 and HR 0.94 p = 0.53) and OS (HR 0.88 p = 0.43 and HR 1.01 p = 0.91).

PEG-IFN treatment relative dose intensity (actual/planned dose while treated) reached median 88% (induction) and 83% (maintenance). 251 pts (31%) stopped PEG-IFN because of toxicity, 9% because of other reasons. Grade 4 toxicities occurred in 9 and 7% in the PEG-IFN and observation group respectively and were disease related rather than treatment related. Grade 3 toxicity(ies) were reported in 21% of PEG-IFN treated patient more frequently than in observation patients and were mostly treatment related including most frequently fatigue (14%), hepatotoxicity (10%) and depression (6%) with ECOG 0–1 Performance Status maintained in 83% of pts during maintenance.

Conclusions: Long term PEG-IFN therapy in stage III melanoma had a significant and sustained impact on RFS, but not on DMFS and OS. Pts with only microscopic nodal involvement (Sentinel Node positive) seemed to have greater benefit in terms of both RFS and DMFS. Similar better effects of adjuvant IFN therapy in pts with lower disease burden are observed in 2 consecutive EORTC trials (18952 and 18991) involving 2644 pts.

Hellenic Melanoma Group trial: Dr H. Gogas and colleagues of the Hellenic melanoma group reported at ASCO on a randomized phase III trial comparing 1 month iv HDI versus the traditional ECOG1684 HDI 1 year schedule: The rationale for this trial was that the ECOG 1684 high dose IFNα regimen was unique for the incorporation of an induction phase of maximally-tolerated dosages of IV therapy for the initial 4 weeks. This is the only trial that has shown prolongation of overall survival and disease-free survival in comparison to observation. Analysis of the hazard curves for DFS and OS in E1684 reveal early and durable separation of the high-dose and observation arms suggesting that the induction phase may represent a critical component of the high-dose regimen. The Hellenic trial consisted of a prospective randomized study of IV induction therapy vs a full year of high-dose IFN with primary endpoints of DFS and OS for stage IIB, IIC and III melanoma patients within 56 days of curative surgery. Patients were randomized to receive IFN alfa-2b 15×10^6 U/m² IV \times 5/7 days weekly \times 4 weeks (arm A) versus the same regimen followed by 10×10^6 U (flat dose) SC 3 times a week for 48 weeks (arm B). The proposed treatment would be considered at least as good as the conventional treatment, if the relapse rate at 3 years from study entry is at most 15% higher in the former arm (power 85%, one-sided test $\alpha = 0.05$, required sample size: 340).

Results: Between 1998 and 2004, 364 patients were enrolled (355 eligible: 178 arm A and 177 arm B). Patients' and tumor characteristics were well balanced between the two arms. At a median follow up of 51 months (95% CI 46–55), the median DFS is 32 months vs 31 months (p = 0.836) and the median OS is 61 months vs 63 months (p = 0.444). Eleven patients discontinued treatment in arm A and 54 in arm B. The discontinuation rate is significantly higher in group B (p < 0.001), possibly due to the longer duration. Reasons for discontinuation were disease progression (69%) and toxicity (19%). Patients in arm B had more grade 3–4 hematologic, constitutional and neurologic toxicity.

Conclusions: There are no significant differences in OS and DFS between the regimen of 1 month and 1 year treatment tested.

Translational Research projects regarding the prognostic value of the presence/emergence of auto-antibodies during IFN therapy were evaluated in ECOG adjuvant trials and in the EORTC 18952 trials and revealed only a trend or borderline significance for the presence/emergence of auto-antibodies in contrast to the original observation as published in the NEJM by Gogas et al.

Regarding the prognostic value of S-100 determinations in the serum of patients in adjuvant trials of ECOG and in EORTC 18952, a strong independent prognostic value for S-100 determinations was demonstrated. **Conclusions:** PEG-IFN therapy has significant and consistent impact in Stage III-N1 (positive sentinel nodes) disease and only marginal effects in Stage III-N2 (palpable nodes) disease. This outcome is fully consistent with the outcome in EORTC 18952 and thus in 2644 randomized patients. This is an important observation that shows that the biology of N1 disease differs from N2 disease and that IFN-sensitivity differs accordingly. Moreover 4 wks of iv HDI induction therapy was demonstrated in the Hellenic trial as non-inferior (at least as good) as a full year of HDI according to the ECOG1684 regimen. Both trials have therefore important outcomes. Auto-antibodies are of only borderline significance as a prognostic factor, whereas serial S-100 determinations were demonstrated to be of strongly independent significant prognostic value in stage III disease. All these findings will be discussed in the setting of defining new questions and new adjuvant therapy trials in melanoma, such as the EORTC 18071 trial in Stage III-N2 disease comparing adjuvant therapy with anti-CTLA4 vs Observation.

173

INVITED

Immunotherapy approaches to stage IV melanoma

U. Keilholz. Charité-Universitätsmedizin, Department of Medicine III, Berlin, Germany

Melanoma has always been considered to be a partially immunogenic tumor, and because of the lack of chemotherapy efficacy, a variety of immunotheapies have been tested in this disease. This presentation will review the experience with non-specific immunostimulation (IL2-based therapies) and more novel approaches including specific modulation of immune responses, e.g. targeting of CTLA4.

Immunotherapy with IL2 has shown principle efficacy in metastatic melanoma, albeit the objective response rate did not exceed 30% in randomized clinical trials, regardless of the treatment combination used. A constant observation, however, was long-term complete remissions in a small subgroup of patients in all clinical trials with intravenous IL2 schedules. A variety of doses and schedules of IL2 alone have been tested as well as combinations of IL2 with interferons, chemotherapies and histamine dihydrochloride. Unfortunately, none of the combinations used proved to be superior over IL2 alone, and none of the combinations proved to be superior over chemotherapy regimens without IL2. More recently, the dual effect of IL2 on cytotoxic as well as regulatory T cell subsets was partially elucidated providing a potential explanation for the limited clinical efficacy.

Currently, various strategies of modulating regulatory T cell responses are being investigated within early and advanced clinical trials. Most mature are the experiences using antibodies to CTLA4, a molecule expressed on T cells after activation physiologically in order to dampen immune responses and prevent autoimmunity. According to the physiologic role of CTLA4, a variety of very specific autoimmune reactions have been observed in patients receiving anti-CTLA4 antibody treatments, resembling to some extent the clinical picture of chronic graft-versus-host disease. In addition, in all trials with CTLA4 targeting, objective melanoma regression was observed in a subset of patients, often long-lasting. Current strategies investigate the combination of CTLA4 antibodies with vaccines. Furthermore, targeting of a similar immunoregulatory molecule, PD1 is under way in early clinical trials.

The fascination of long lasting remissions in subsets of patients with metastatic melanoma continues to support clinical testing of a variety of immunologic approaches in this disease, which continues to be difficult to treat.

174

INVITED

B-Raf mutations – old and new drugs

K. Flaherty. University of Pennsylvania, Abramson Cancer Center, Philadelphia, USA

Metastatic melanoma remains one of the most treatment-refractory malignancies. Despite decades of clinical trials testing chemotherapy and immunotherapy, a standard first-line treatment for metastatic melanoma has not yet been established. Recent advances in our understanding of the pathophysiology of melanoma have given rise to systemic