cancers. We have also shown that combinations of BRAF inhibitors with TNFα 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 nocifensive 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 spina lcord that enhance the pain statWithin 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 nocifensive 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 incontrollable delirium, dyspnoea, pain and/or psychological stress.

Different medications (e.g. haloperidol, propophol) 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.