322

Pain control

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

Despite the World Health Organisation's validated principles of cancer pain control which can provide cancer pain relief in up to 85-90% of sufferers, we are not generally achieving such control in our practices. Failure to control cancer pain can result from: i. Problems with patient assessment ii. Poor choice of drugs and/or inadequate management of side-effects iii. Difficult cancer pain syndromes e.g. severe neuropathic pain, incident bone pain or paroxysms of pain iv. Lack of non-pharmacological physical and non-physical care When assessing pain, the level of the worst pain experienced in the last 24 hours seems to be the most clinically useful question, rather than average pain. At initial assessment anxiety, depression and general distress must be acknowledged and managed as appropriate.

The use of standard non-opioid or opioid analgesics along with an adjuvant drug according to the pathophysiology of the pain(s) remains the keystone of pharmacological management. However, our pharmacological armamentarium has expanded and this presentation will discuss the role of alternative opioids to morphine and the role of genetic polymorphism. Manoeuvres to minimise opioid side-effects will be presented.

The evidence for newer antidepressants (e.g.venlafaxine) and anticonvulsants (e.g. gabapentin) as adjuvant analgesics and COX-2 drugs will be discussed. These drugs are all positive additions to our armamentarium.

The place of spinal analgesia and implanted devices remains controversial – the clinical usefulness of these procedures in challenging neuropathic and pain and incident pain will be presented with particular reference to the patient who is not actively dying and receiving tumoricidal treatment. Novel preparations such as topical opioids, lignocaine and clonidine will be presented.

Non-pharmacological pain treatments such as TENS and acupuncture can be useful and will be mentioned.

This lecture aims to provide professionals with a range of therapeutic manoeuvres to manage cancer pain.

323

Treatment of advanced bladder cancer

R. De Wit. *Daniel Den Hoed Cancer Center, Interne Oncologie, Rotterdam, The Netherlands*

Following the recognition in the nineteen eighties of the chemosensitivity of urothelial cell cancer, with phase II studies showing activity of cisplatin, methotrexate, adriamycin, vinblastine and 5FU in advanced disease, the next step to the development of effective therapy was to combine the effective agents into 2, 3, and 4 drug combinations. In 1985 investigators from Memorial Sloan Kettering Cancer Center reported on a four drug regimen that was built by combining the two active two-drug regimens studied at Memorial, cisplatin plus doxorubicin and methotrexate plus vinblastine (MVAC). The initial study on 24 patients gave an overall response rate of 71%. Subsequent randomized phase III trials demonstrated the superiority of MVAC compared with single agent cisplatin, and with CISCA, both in terms of response rates and overall survival. Unfortunately, MVAC therapy is associated with significant morbidity. The median age of patients presenting with metastatic urothelial cell cancer is 70 years, and due to smoking as an associated risk factor many patients have pulmonary and/or cardiovascular diseases. Hence, there is need for less toxic agents and chemotherapy combinations in this disease. Moreover, prognostic factor analyses from large randomized trials have demonstrated that patients with impaired performance status, weight loss, and those with visceral metastases rarely benefit from MVAC chemotherapy. The few patients on MVAC who obtain durable responses are those in the good clinical condition category with metastatic nodal disease only. Hence there is need to improve both the efficacy of the chemotherapy as well as the toxicity / benefit ratio. In the past decade, with new agents becoming available, substantial single agent activity has been demonstrated for the taxanes paclitaxel and docetaxel, gemcitabine, and pemetrexed. Initial phase II studies of 2 drug combinations of docetaxel, or paclitaxel, with cisplatin, and gemcitabine with cisplatin (GC) have shown activity in untreated patients, with response rates that are in the same range as can be obtained with MVAC. Based upon the results achieved with two-drug GC combination, from 1996 to 1998 a large multinational phase III trial comparing GC with MVAC was conducted. With a median follow-up of 19 months, overall survival was found to be similar on both arms, GC 13.8 months, MVAC 14.8 months (Hazard Ratio 1.04, 95% CI 0.82 to 1.32, adjusted HR 0.95, 95% CI 0.75 to 1.22). More MVAC patients, compared with GC patients, had neutropenic sepsis (12% versus 1%), and grade 3-4 mucositis (22% versus 1%). Quality of life during treatment was better maintained on GC regarding weight, performance status, and fatigue. Hence, GC provided a similar survival advantage to MVAC with a better safety profile and tolerability. Although the study failed to detect a significant difference in survival, which was the primary endpoint, the favorable risk-benefit ratio justified considering these results for the lesser objective of establishing therapeutical non-inferiority. With the upper bound of the adjusted HR close to 1.2 non-inferiority can be claimed according to regulatory authority guidelines. Therefore GC can be considered a valuable alternative to the MVAC regimen, particularly in the vast majority of elderly patients with metastatic bladder cancer who may have an equal gain of the chemotherapy with the benefit of fewer side effects. Ongoing trials in the EORTC and Spanish Oncology Genito Urinary Group investigate the potential of the incorporation of paclitaxel into the GC-doublet in good performance status patients (PCG), and the substitution of carboplatin for cisplatin in the GC-doublet. In conclusion, the availability of new agents and combinations has expanded the therapeutic options for our patients with advanced bladder cancer.

324

Germ cell tumours

H.J. Schmoll. *Martin Luther Universität, Medizinische Fakultät-Z. für Innere Medizin I, Halle, Germany*

Germ cell cancer is a rare malignant disease; however, it is the most frequent tumor type in young men in the age from 18 - 35 years. Due to high efficacy of platinum-based chemotherapy the cure rate is excellent, with the exception of advanded cases with poor prognostic features where the cure rate is only 50%. Because of the high efficacy of chemotherapy the treatment strategy is changed over the years from mainly surgical and radiotherapeutic procedures to either surveillance strategies or chemotherapeutic management. Such a strategy is able to reduce as much as possible the amount of treatment load as well as late toxicity, and therefore improve the quality of life. However, high quality of management as well as expertise is necessary to give the optimal treatment to the patient and maintain the high level of cure. Therefore, patients should be treated within centers with a large experience, and international developed guidelines must be followed, e.g. the ESMO- and the recently published international Consensus Conference-Guidelines of the European Germ Cell Cancer Consensus Group (www.hodentumor.de). This is a comprehensive Guideline regarding the diagnostic and supportive measurements including fertility issues, organ preserving surgery, carcinoma in situ as well as recommendations for treatment of early stage seminoma and nonseminoma as well as advanced stages. It is of importance that many centers as possible participate in the current international protocols (EORTC) to improve the treatment in intermediate prognosis-patients (PEB x 4 vs. Taxol/PEB x 4) and poor prognosis-patients (PEB x 4 vs. PEI, followed by 3 cycles high dose PEI plus stem cells). The aim of these studies is to improve the cure rate also of these patients who have still an intermediate or poor prognosis by standard treatments.

325

Drug interactions with neoplastic agents

J.H. Beijnen, J.H.M. Schellens. *Slotervaart Hospital/Netherlands Cancer, department of Pharmacy and pharmacology, Amsterdam, The Netherlands*

Multiple drug therapy is common practice in patients with disseminated malignancies. Apart from cytotoxic agents they usually receive supportive pharmacotherapeutic care including pain medication, antiemetics, antidepressants, antibacterials etc. Herbal medicines may be ingested without awareness of the physician. There is, however, a considerable potential for pharmacokinetic drug-drug interactions when agents are administered concomitantly and metabolised via the same cytochrome P450 pathway or transported via the same carrier pathway. Drug interactions may also result of enzyme induction. Pharmacodynamic drug interactions can emerge when drugs interfere with each other in binding to their biological target. These may lead to loss in efficacy and the occurrence of side effects, and should thus be prevented. An example of a wanted drug-drug interaction is the combined administration of a P-glycoprotein blocker such as cyclosporin A and paclitaxel to boost its oral uptake from the gastrointestinal tract (J Clin Oncol 2000;18:2468-75). Preclinical, both in vivo and in vitro research may be helpful to predict any clinical drug-drug interaction (Toxicol Appl Pharmacol. 2003;189:233-46). The combined use of drugs is surrounded by pitfalls. Profound knowledge, awareness and recognition of drug interactions are essential in the optimisation of pharmaceutical care of the patient with cancer. Careful evaluation of potential drug-drug interactions during the early stage of development of a drug candidate is advised.