can be emphasized and validated by an "high performance" evaluation of QL.

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1499 PUBLICATION

Analgesic efficacy and acceptability of tts – fentanyl (durogesic) in patients with advanced cancer: A prospective examination

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Purpose: The aim of the study was to evaluate prospectively the analgesic efficacy and acceptability of the transdermal fentanyl system (Durogesic) in a sample of patients with cancer-related pain.

Method: Forty-two patients participated in the study: 32 were men and 10 women, mean age was 63 (44–82), and all but 2 had advanced stage (IV) cancer. Patients were administered Durogesic for a period of 8 weeks. Doses were titrated as necessary and ranged from 25 to 225 ig/h. Twenty-eight patients completed the study. Of those who did not complete the 8-week protocol, 9 died due to disease progression, and 5 dropped-out. Data were collected in all phases of the study by structured individual interviews. The analgesic efficacy and evaluation of the transdermal system were analysed by repeated measures analyses of variance.

Results: For pain intensity there was a highly significant effect ($p < 0.001$), indicating a fall on both VAS (Visual Analogue Scale) and EORTC QLQ-C30 scores from baseline to follow-up. Evaluation scores were increasingly positive over time, and the difference was again significant ($p < 0.001$). In addition, 96% of the patients who completed the study found Durogesic easy to use, and reported satisfied or highly satisfied with it. The only observed side-effect was vomiting.

Conclusions: In summary, the transdermal fentanyl system is an acceptable, safe, noninvasive, and highly effective method of managing cancer pain.

1500 PUBLICATION

Cefepime monotherapy as initial treatment for patients with febrile neutropenia

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Introduction: Empirical single-agent antibiotic therapy is a reasonable alternative to combination treatment for the initial management of patients with febrile neutropenia. New cephalosporins have emerged that should be tested in this setting.

Objectives: To evaluate prospectively the efficacy of cefepime monotherapy for neutropenic (<1000 leukocytes/mm3 and/or <500 neutophils/mm3) cancer patients.

Patients and Method: A multicentric, non-randomised trial has been performed. The initial treatment was cefepime, 2 gr e.v./8 h. If fever persisted, sequential antibiotics were added in 72-hour intervals: amikacin, vancomycin/teicoplanin and amphotericin-B. Response was assessed according to EORTC criteria. Sixty episodes of febrile neutropenia have been included to date. There were 42 males (69%) and 18 females (31%), with a median patient age of 61 years (range, 39–78). Median leukocyte count at study entry was 650/mm3 (range, 100–2,400), median neutrophil count of 100/mm3 (0–500), and median duration of neutropenia (<1000 neutrophils/mm3) of 4 days (1–20). Twenty-six episodes (43%) were microbiologically documented (12 gram−, and 8 gram+ bacteraemias, 6 non-bacteraemic infections), 21 (35%) clinically documented, 10 (17%) probable infections, and 3 (5%) doubtful infections.

Results: Fifty-four (90%) episodes were assessed as protocol success, and 5 (8%) as failures (2 deaths, 3 protocol modifications), 1 episode resulting non-evaluable. Cefepime monotherapy controlled 45 episodes (75%), whereas in 15 (25%) another antibiotic step was required (5 amikacin, 3 vancomycin, 2 teicoplanin, and 5 amikacin plus vancomycin/teicoplanin.

Conclusions: Preliminary analysis of this study confirms the efficacy of cefepime as initial empirical monotherapy for febrile neutropenic episodes. Early addition of amikacin and/or vancomycin solves most protocol failures. However, the percentage of cases in which such addition is needed seems lower than required with other monotherapies. This study is ongoing, 100 patients being planned to be recruited.

Melanoma

1501 ORAL

CDKN2A germline mutations in Swedish kindreds with hereditary cutaneous melanomas

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Purpose: Members of Swedish kindreds with hereditary cutaneous melanoma were screened in order to estimate the occurrence of germline CDKN2A mutations.

Methods: Venous blood samples were obtained from 240 affected members belonging to 120 Swedish melanoma prone kindreds, as well as from 65 individuals with multiple cutaneous melanomas, irrespective of family history. DNA was extracted from blood samples, mutation screening was performed by single strand conformation polymorphism (SSCP) analysis of PCR products and mutations were confirmed by nucleotide sequencing.

Results: The same founder mutation in exon 2 of CDKN2A consisting of an insertion of an extra arginine residue in codon 113 (arg113ins) was identified in 8 separate kindreds. Haplotype analysis with multiple microsatellite markers on chromosome 9p showed that the same chromosome segregated with melanoma in all kindreds. One kindred showed an exon 1 codon 48 point mutation resulting in a base substitution of threonine for alanine. Functional analysis of the resulting mutant p16 protein showed a deficiency in in vitro binding to cdk4 and cdk6. A further kindred showed a 24 base pair deletion which included codons 72–79 in exon 2. Finally, one kindred showed base pair −33 G/C point mutation an another a −14 C/T mutation in the 5' noncoding sequence, both of undetermined significance.

Conclusions: CDKN2A germline mutation occur rarely in Swedish kindreds with hereditary cutaneous melanoma. Among families with germline CDKN2A mutations an exon 2 arg113ins founder mutation predominates. The genetic aberration in most kindreds with hereditary melanoma in Sweden remains to be identified.

1502 ORAL

Genetic analysis of N-ras and CDKN2A in sporadic primary melanomas and their metastases

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Purpose: Genetic alterations in the N-ras oncogene and in the CDKN2A suppressor gene have separately been studied in melanoma cell lines, metastases and to some extent in primary tumors. N-ras codon 61 mutations, structural mutations in CDKN2A and evidence for homozygous deletions of this gene have been reported.

Methods: The present study includes 74 primary tumors from 72 patients and 45 metastases from 31 of these patients. Both the N-ras and the CDKN2A gene were, for the first time in parallel, analyzed by PCR/SSCP and nucleotide sequence analysis.

Results: 21 primary tumors (28%) had N-ras codon 61 mutations and 13 CDKN2A mutations were detected in 8 of the primary tumors. Two tumors had both N-ras codon 61 and CDKN2A mutations. The N-ras mutations but not the CDKN2A mutations were present in the corresponding metastases and this may indicate a common occurrence of homozygous deletion of the CDKN2A gene under the progression process.

Conclusions: Alterations in both the N-ras oncogene and the CDKN2A suppressor gene are common in a substantial fraction of melanomas. The N-ras mutations are present in homogeneous expanded cell clones in the primary tumors. CDKN2A mutations present in primaries were in contrast not detected in the corresponding metastases, which indicate homozygous loss of the gene under tumor progression. Homozygous loss of CDKN2A may also occur in primary tumors since in several cases the N-ras exon 2 but not the CDKN2A exons could be amplified successfully.