1495 PUBLICATION

Transdermal Fentanyl for the treatment of chronic cancer pain in patients under home palliative care

A. Gamallo[1], M.A. Monescillo[1], M.A. Pereira[1], J.L. Nuñez[1], S. Hernansanz[1], J. López-Escudero[1], F. Sánchez-Domínguez[1], R. De Pablo[1], P. Satre[1], M. Feyjoo[2]. [1]*Asociación Española Contra el Cancer, Spain;* [2]*The R.W. Pharmaceutical Research Institute*

We report preliminary results of a study aimed to determine patients (pts) and caregivers satisfaction with TTS-fentanyl treatment.

Methods: Pts who were under home palliative care on weak or strong opioids treatment were included. The lowest TTS-fentanyl delivery rate, 25 micrograms/hour was used as the initial dose for strong opioids naive pts. We used the recommended conversion table for non-naive strong opioids pts. Short-acting oral or subcutaneous morphine were supplied as rescue medication. The TTS patch was replaced as a rule every 72 hours. Pain intensity (baseline, days 4, 15, 30 and 45) and satisfaction (baseline, days 15, 30 and 45) were determined by a visual analogue scale going from 0–10 (0: no pain or no satisfied; 10: worst pain ever or very satisfied).

Results: eighty pts were evaluated in this analysis: 36 strong opioid naive and 44 on strong opioids. Fifty-two pts stopped the treatment, 46 because of death, and 6 because other reasons. Number of pts under treatment were 80 at day 4, 58 at day 15, 37 at day 30 and 28 at day 45. Fourteen pts required a dose increase at day 4. Median initial TTS-fentanyl delivery was 25 micrograms/hour (25 micrograms/hour-150 micrograms/hour) and median final delivery was 50 micrograms/hour (25 micrograms/hour-150 micrograms/hour). The mean treatment duration for the 52 pts who stopped the medication was 19 days (4–43). No respiratory depression was observed. The reported side effects were nausea and vomiting (2 pts), diarrhoea (1 pts), anxiety (1 pts) and confusion (2 pts). Comparison of satisfaction at days 15, 30, 45 were statically significant higher ($p < 0.001$) vs. baseline. Comparisons of pain assessments at days 4, 15, 30 and 45 were statically significant ($p < 0.001$) vs. baseline, indicating better pain relief. Mean score in patient's satisfaction changed from 5.2 at baseline to 7.5 at day 45. Caregiver's satisfaction increased in 2.8 points at the end of treatment (5.0 at baseline, 7.8 at day 45). Pain decreased significantly during the 45 days period, mean scores were 5.9, 3.1, 3.0, 2.3, 1.7 and at baseline and days 4, 15, 30 and 45 respectively.

Conclusions: TTS-fentanyl for the treatment of cancer pain in patients under home palliative care is well tolerated and extremely appreciated by patients and caregivers with excellent pain relief.

1496 PUBLICATION

Evidence-based approach to cancer of unknown primary

F. Porzsolt[1], C. Sellenthin[1], H.-J. Schmoll[2], H.-J. Illiger[3]. [1]*University Hospital Ulm, Clinical Economics Group, Ulm;* [2]*University Hospital Halle, Hematology and Oncology, Halle;* [3]*Town Hospital Oldenburg, Wilsede School of Oncology, Oldenburg, Germany*

Purpose: Planning a randomized trial we describe the homogeneity of assumptions in the diagnosis and treatment of cancer of unknown primary (CUP).

Methods: We asked 56 participants (23 m, 31 f, 1 na; 19 with <3 yrs of experience, 29 with 3–10 yrs, 7 with >10 yrs and 1 na) of an educational course on CUP organized by the Wilsede School of Oncology to answer 33 questions (yes/no). These were derived from a review by M. Markman, Clev Clin J Med 1997, 64 (2): 73–75.

Results: In 26/33 statements the responses were homogenous (>80% agreement). In 23/33 there was agreement with the review article. Disagreement (>80%) was found in 3 statements: 1. the most likely primary site found in autopsies is pankreas if the manifestations occurred below the diaphragm, 2. the most likely site is the lung if the manifestation occurred above the diaphragm, 3. Electron Microscopy should be included in the diagnostic evaluation. The responses were heterogenous in 7/33 statements: 1. In 30% of patients the primary is not found in autopsies, 2. The goal of diagnosis in CUP is histologic documentation of cancer, 3. The goal of diagnosis is prevention of immediate harm to the patient (bleeding, obstruction), 4. 1-year survival is 25%, 5. Survival from diagnosis is <6 months, 6. Overall survival rate has changed little over the past 20 yrs, 7. Watchful waiting may be reasonable if the goal is palliation and the tumor is not causing symptoms. There was no correlation with clinical experience, but clinicians with >10 yrs of experience were more likely to accept the statement that survival has changed little in the past 20 yrs.

Conclusion: There is some heterogeneity in the assumptions which could be adressed in randomized trials. We will use these results to design clinical trials and hope that interested physicians will be convinced to participate.

1497 PUBLICATION

Patient selection in perfusional heated chemotherapy in advanced abdominal tumors

M. Pace[1], L. Bandettini[1], D. Brugnola[1], A. Galli[1], R. Gattai[1]. [1]*Clinica Chirurgica I Università di Firenze Florence, Italy*

Introduction: The correct pt. selection is essential for evaluating the efficacy of a therapeutic approach in relation to morbidity, mortality and disease-free and overall survival.

Purpose of the Study: To identify valuable parameters for an exact pt. selection by the analysis of 17 pts. suffering from peritoneal carcinomatosis treated by cytoreductive surgery followed by heated perfusional chemotherapy.

Patients and Methods: Out of 36 pts. evaluated for heated chemotherapy (6/96–12/98), in 15 pts. the procedure was not performed due to age > 70 yy, associated diseases or impossibility to obtain minimal residual disease. The procedure was carried out in 21 pts.: for adiuvant purpose in 4 pts. (group A), with serosal invading gastric and colo-rectal cancer, but without carcinomatosis. The residual 17 pts. (group B) suffered from carcinomatosis; the pts. are 6 men and 15 women with mean age 60 yy (range 35–70). At laparotomy, peritoneal cancer index (PCI) according to Sugarbaker was evaluated; the cytoreduction was classified as low, middle and high grade. After radical (group A) or cytoreductive surgery (group B), heated chemotherapy was performed with "closed abdomen" technique, typically with Cisplatinum (25 mg/sm/lt) and Mitomycin C (3 mg/sm/lt) and at a peritoneal temperature ranging 42–43°C.

Results: In group A no morbidity or mortality were observed, and pts. discharge was not delayed. In group B 7 pts. experienced major morbidity requiring relaparotomy for haemorrhage, perforation or anastomosis leakage, with 3 pts. dead because of MOF. The mean PCI was 10.5 (range 3–22) in pts. without complications whilst was 17.1 (12–20) in the 7 above pts.: moreover, cytoreduction was of high grade in all these pts.

Quality of life in follow-up was satisfactory, especially in pts. with preoperative ascites.

Conclusions: The procedure is able to supply encouraging results also in advanced carcinomatosis pts.; relevant morbidity and mortality were observed, possibly related to PCI and consequently to cytoreduction; furthermore, all the pts. with complications had been previously submitted to surgery and/or radio-chemotherapy.

1498 PUBLICATION

Endoscopic palliative laser disobstruction (LD) for endobronchial non resectable or recurrent lung cancer: An evaluation of its impact on the quality of life

G. Mantovani, G. Astara, G. Manca, R. Versace, P. Contu, A. Carai, M. Pisano. *Department of Medical Oncology and Internal Medical Sciences, University of Cagliari, 09124 Cagliari, Italy*

Study Objectives: The objective of this study was that of assessing the impact of LD on the quality of life (QL) of patients with endobronchial obstructions due to non-resectable or recurrent lung cancer.

Design: Evaluation was based on 1) Performance Status (PS) (ECOG Scale), for the "objective" assessment of QL and 2) the EORTC QLQ-C30 version 1.0 ($QLQ\text{-}C30_{(v1)}$) questionnaire for the "subjective" assessment of QL.

Patients: From May 1994 to June 1997, 133 LDs were performed on 89 evaluable patients (M/F 78/11, mean age 62.7/63.7 years, range 42–82/47–73). The QL was evaluated by ECOG PS and $QLQ\text{-}C30_{(v1)}$ at baseline (3 days before LD), t1 (7 days after LD) and t2 (1 month after LD). The objective tumor response was evaluated at t2.

Results: The objective tumor response to LD intervention was: CR in 33 (24.8%) patients, PR in 97 (72.9%) patients, with an ORR of 97.7%. A highly significant decrease in high score (3–4) ECOG PS was registered from baseline to t1 and from t1 to t2. The functioning scales, the global QL scale and the symptom scales/items of $QLQ\text{-}C30_{(v1)}$ showed a highly significant improvement at t1 compared to baseline ($p < 0.001$), whereas only emotional functioning, global QL and the single symptom "fatigue" improved at t2 compared to t1. The results were not related to age, gender, tumor histology, first LD intervention.

A comparison of baseline ECOG PS scale with $QLQ\text{-}C30_{(v1)}$ scale revealed a strong relationship of PS with the symptom "fatigue".

An higher patient clinical response to tumor (CR vs PR) after LD was not consistent with an higher degree of QL improvement during the study.

Conclusions: Our study demonstrates that clinical improvement obtained by an highly effective, although palliative, treatment, such as LD intervention,

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

Work supported by C.N.R., Rome, Contract No. 96.00588.PF39.

1499 PUBLICATION

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

G. Iconomou[1], A. Viha[1], H.P. Kalofonos[1], A. Vagenakis[1]. [1]*University of Patras Medical School, Department of Medicine/Oncology, Patras, Greece*

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

J. Montalar[1], A. Segura[1], C. Bosch[2], A. Galán[3], O. Juan[4], A. Santaballa[1], C. Molins[2]. [1]*Hospital Universitario La Fe;* [2]*Hospital Dr. Peset Aleixandre;* [3]*Hospital de Sagunto,* [4]*Hospital Arnau de Vilanova, Valencia, Spain*

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

J. Hansson[1], A. Platz[1], J. Hashemi[1], U. Stierner[2], U. Ringborg[1]. [1]*Radiumhemmet, Karolinska Hospital, Oncology, Stockholm;* [2]*Sahlgrenska Hospital, Oncology, Gothenburg, Sweden*

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

A. Platz[2], S. Karsberg[2], U. Ringborg[1]. [1]*Radiumhemmet, Karolinska Hospital, Oncology, Stockholm;* [2]*Cancer Centre Karolinska, Karolinska Hospital, Research Laboratory of Radiumhemmet, Stockholm, Sweden*

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.