The European Palliative Care Research Collaborative. Improved treatment of pain, depression and fatigue through translation research

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Summary description of project objectives
Objective 1 To identify genes and genetic variation relevant for inter-individual variation in opioid responses and genetic variation that may identify patients at particular risk for developing cachexia
Objective 2 To improve classification and assessment of pain, depression and cachexia by computer assisted approaches
Objective 3 To combine the new knowledge of symptoms, genomics and assessment in an internet-based system for implementation of European evidence based guidelines, which will include standardized assessment and individualized treatment plans for pain, depression and cachexia
Objective 4 To establish a long lasting European Collaborative in palliative care cancer research

Contractors involved
1. Norwegian University of Science and Technology, Trondheim, Norway NTNU
2. Bristol Haematology and Oncology Centre, University of Bristol, Bristol, UK UNIVBRIS
3. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy INT
4. King’s College London, London, UK KCL
5. Cantonal Hospital, St. Gallen, Switzerland KSSG
6. RWTH Aachen University, Aachen, Germany RWTH
7. University of Edinburgh, Edinburgh, UK UEDIN
8. Medical University of Graz, Graz, Austria MUG
9. Trollhetta AS, Trondheim, Norway TROLL
10. Bender MedSystems GmbH, Vienna, Austria BMS
11. Verdande Technology AS, Trondheim, Norway VERD
study design

Genetic markers for opioid responses

This work package worked along three lines. The first approach (1) was to select single nucleotide polymorphisms (SNPs) from genes supported by the literature to be candidates for affecting opioid response; the second (2) to identify “new” genes of potential relevance for opioid response by analyzing morphine-induced changes in global gene expression in a neuroblastoma cell line model system, and select SNPs from the most promising candidates; and the third (3) to perform genome-wide SNP genotyping on pools of DNA generated from “poor” and “good” opioid responders. Approaches (1) and (3) were based on the availability of DNA and clinical data from 2294 palliative care cancer patients treated with opioids for pain (European Pharmacogenetic Opioid Study, EPOS).

The work started by extracting and quantifying DNA from the EPOS samples. An SPSS master file with patient demographics and clinical data was generated. Literature reviews were performed to identify genes considered as candidates for affecting opioid response. The 2262 EPOS samples were genotyped using the SNPlex technology (48-plexing) with 191 SNPs from 37 candidate genes, and the genotypes were entered into the EPOS masterfile. Subsequent association and statistical analyses on 123 SNPs covering the 25
most relevant candidate genes were carried out on an explorative sample (2/3 of the EPOS patients), and potentially positive associations were sought replicated in a validation sample (1/3 of the EPOS patients).

DNA pools of “poor” and “good” opioid responders from the EPOS cohort were selected on the basis of criteria defined by an expert group ("poor" responders had high pain intensity scores and a high oral equivalent opioid dose; "good" responders had low pain scores and a low oral equivalent opioid dose). The two pools were genotyped for >1 million SNPs to detect differences between the two groups. SNPs showing different allele frequencies between "good" and "poor" responders were validated by individual genotyping in two independent cohorts and subject to bioinformatic analysis.

Approach (2) was abandoned as three independent gene expression experiments in cell lines after morphine exposure showed only minor changes that could not be replicated.

Genetic markers for cachexia

The work started by a systematic literature review on candidate genes associated with cancer cachexia. DNA was extracted from 855 cachexia samples from Edinburgh, Montreal, and Edmonton, and a phenotype database was composed. DNA was genotyped for candidate genetic markers for cachexia (129 SNPs in 80 genes). 775 samples (discovery cohort) were available for bioinformatic analysis. The results were validated in an independent cohort of 101 patients with cancer cachexia, from St Gallen (validation cohort). In addition, gene group analysis based on functional similarity according to gene
ontology was performed in the discovery cohort.

Biomarkers for pain perception and treatment response

A protocol was developed for a clinical study to explore serum factors as biomarkers for pain treatment. Due to the exploratory nature of the investigation it was decided to start with a limited pilot study, and patients were included at one site only (MUG). The pilot study showed promising results in 20 included patients, and it was decided to continue patient recruitment. A total of 45 patients were included at MUG; 38 were eligible for final analysis. In addition, 20 healthy volunteers were included. Serum samples were analysed for all candidate biomarkers at BMS and biostatistical analysis was performed at MUG.

WP2: Assessment and classification of pain, depression, and cachexia

The three work packages on assessment and classification started by performing systematic literature reviews and expert surveys to identify a set of items to classify and assess each of the three symptoms. Results from a Norwegian multi-centre computerised data collection study on assessment of pain and physical function were used to inform the work. The next step was a large, international empirical study to test the items. Protocol preparation and software development for the computerised assessment tool were done in parallel. The software included a body map for pain localisation. Qualitative patient interviews were conducted to supplement the experts’ views on domains and items.

The large, multi-centre data collection study (EPCRC-CSA, Computerized Symptom...
Assessment of Pain, Depression and Physical Function in Palliative Care) was performed at 16 centres in eight countries and in four languages, yielding a total sample of 1070 patients. The study closed in December 2009. Data has been analysed with respect to optimal items and criteria for the assessment and classification of pain, depression, and cachexia. In addition, data from two other, large data sets (2294 EPOS patients and 1801 patients included in a prospective study at the Mario Negri Centre in Milan) has been analysed to validate domains and items of the proposed pain classification.

Based on the software for the CSA study, Verdande Technology has used case-based reasoning to develop a computerised assessment tool for diagnosis of depression in palliative care.

A clinical study of 50 patients was performed to validate an activity monitoring system for palliative care patients. Data from several studies was combined to study activity monitoring in patients with cancer cachexia.

WP3: Guidelines

The work on the EPCRC guidelines was performed according to a common protocol based on the NICE and SIGN guideline methodology. Systematic literature reviews and expert opinion input through Delphi procedures (including patient representation) complemented each other in the process. In addition, feedback from the general palliative care community was obtained through the EPCRC and EAPC websites and through workshops at the EAPC conferences.

A group of 20 European experts were engaged to do systematic reviews for the pain
guidelines. The 23 resulting reviews were presented and discussed at the 5th Bristol Opioid Conference in February 2010, and form the basis for the recommendations on opioid treatment.

All guideline groups have developed patient summaries of the recommendations.

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