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Decline in CA19-9 during chemotherapy predicts survival in four independent cohorts of patients with inoperable bile duct cancer

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Abstract ***Background:*** Carbohydrate associated antigen (CA19-9) has been approved by the FDA as a biomarker for monitoring treatment effect in pancreatic cancer. However, the value of serum CA19-9 as a biomarker of response to chemotherapy in bile duct cancer is unclear. The aim of this study was to determine if a decline in CA19-9 (CA19-9 response) during chemotherapy is predictive of survival in patients with inoperable bile duct cancer.
Methods: Consecutive patients with inoperable bile duct cancer treated at a University Hospital were retrospectively included in an investigational cohort (n = 212). Three validation cohorts were established including patients 1) participating in phase I/II trials at a Danish Hospital (n = 71), 2) identified retrospectively in a Canadian cohort (n = 196) and 3) randomized in the ABC-02 trial (n = 410). Patients with a baseline CA19-9 and at least one CA19-9 value measured 10-12 weeks after the start of chemotherapy were included. Multivariate Cox regression analyses were performed.

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Results: Patients meeting the criteria to be included were 54 in the investigational cohort and 34, 68 and 148 in the three validation sets, respectively. Multivariate analysis included radiological response, performance status, bilirubin, gender, site of cancer, extend of disease, CA19-9 at baseline and age. A hazard ratio (HR) of 0.60 (95%CI: 0.44-0.80, $p = 0.0005$) for death in CA19-9 responders was reached in the investigational cohort. The predictive value of CA 19-9 response was confirmed in all three validation cohorts.

Conclusions: CA19-9 response is a robust predictor of survival in patients with inoperable bile duct cancer in four independent data sets.

1. Introduction

Bile duct cancer carries a poor prognosis with a five year survival of 10–40% across all disease stages [1]. A major reason for the poor overall survival is the fact that most patients present with advanced inoperable disease. Recently, the benefit of combination chemotherapy has been established in the ABC-02 trial [2]. However, no tools are available to predict which patients will actually benefit from chemotherapy in terms of improved survival. Despite inconsistent evidence, radiological response is generally used as an indication of benefit from chemotherapy in each individual patient in most solid tumours, and as a surrogate for prolongation of survival [3].

The role of carbohydrate associated antigen 19-9 (CA19-9) as a biomarker in bile duct cancer remains largely undetermined. CA19-9 is a sialylated Lewis blood-group antigen, which is absent in 10% of humans who are Lewis-blood group antigen negative [4]. The protein is expressed in normal biliary, pancreatic, gastric, and colon epithelial cells. CA19-9 blood levels are elevated in patients with carcinoma of the upper gastro-intestinal tract such as gastric, bile duct and pancreatic cancers as well as in cholangitis and cholestasis of non-malignant aetiology [4,5]. The FDA approved CA19-9 for monitoring of disease status in pancreatic cancer in 2002. Baseline elevated CA19-9 in pancreatic cancer is associated with a poor prognosis [6–11]. In inoperable bile duct cancer limited data suggest that pre-treatment CA19-9 level is prognostic of survival, and that decline in CA19-9 during chemotherapy is associated with prolonged overall survival in a subgroup of patients without biliary obstruction [12].

In the process of identifying clinically useful biomarkers, a very important step is to conduct confirmative studies to substantiate the robustness of a candidate biomarker in various data sets [13,14].

Here we test the hypothesis that a reduction in CA19-9 levels during chemotherapy is predictive of overall survival in an investigational cohort and three independent validation cohorts of patients with inoperable bile duct cancer.

2. Materials and methods

2.1. Design

The study was initially designed as a 'prospective-re trospective' study, as defined by Simon et al. [14]. The protocol was prepared prospectively before the collection of data was initiated. Initially it was only planned to test the results from the investigational cohort in one validation cohort. As a result of the addition of two additional validation cohorts (aimed at increasing statistical robustness), the protocol was modified, and response criteria and co-variables were modified to accommodate the availability of data in all cohorts as outlined below.

2.2. Aim

The primary aim of the study was to determine if CA19-9 decline during chemotherapy in inoperable bile duct cancer predicts overall survival. Secondary aims were to evaluate the prognostic value of baseline serum CA19-9 and radiological response.

2.3. Criteria for response

In the original protocol, patients with an elevated pre-treatment CA19-9 measurement of more than 1.5 times the upper limit of normal (ULN = 37 U/ml) were considered evaluable for CA19-9 response defined as a 20% decrease in serum level of CA19-9 after 4 weeks of chemotherapy. However, CA19-9 measurements in validation cohorts 2 and 3 were only available after 10–12 weeks of chemotherapy, and furthermore we were not able to obtain information on ULN for the various assays used in validation cohort 3. Therefore, the protocol was modified: all patients with a baseline measurement of CA19-9 and a measurement after 10–12 weeks