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Original Article

Clinical Outcome of Patients with Advanced Biliary Tract Cancer in a Dedicated Phase I Unit

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Abstract

Aims: Advanced biliary tract carcinomas (ABC) are malignancies with limited effective therapies for advanced disease. There is little published evidence of outcomes of ABC patients participating in phase I clinical trials.
Materials and methods: Patient characteristics, treatment details and outcomes of ABC patients treated at a dedicated phase I unit were captured and analysed from case and trial records.
Results: In total, 123 ABC patients were included in the study, of which 48 patients participated in 41 different phase I trials; 75 (61%) did not participate due to rapid disease progression or patient choice. Molecular characterisation of tumours using a targeted panel was conducted in 15 (31%), yielding several potentially actionable mutations, including *BRCA*, *PIK3CA*, *FGFR*, *AKT* and PTEN loss. Of the 39 evaluable patients there was one exceptional responder. Eighteen (46%) other patients achieved stable disease as their best response, with a clinical benefit rate at 4 months of 10%. Treatment was generally well tolerated with grade 3 or 4 adverse events only observed in eight patients (17 %), of which six were drug related and led to trial discontinuation in one (3%), with no toxicity-related deaths.
Conclusion: Carefully selected ABC patients have been found to tolerate experimental phase I clinical trials without excess toxicity. The aggressive nature of this disease warrants consideration of early referral to a phase I unit. Future work will require comprehensive molecular profiling in an attempt to understand the biology underlying the exceptional responders and to match patients in real-time to targeted therapies.

Key words: Biliary tract cancer; developmental therapeutics; drug development; phase I clinical trial

Introduction

Biliary cancers are a heterogeneous group of cancers, with varied definitions and classifications. Most commonly, they include tumours of the gallbladder, extrahepatic ducts, perihilar and intrahepatic ducts and ampullary cancer. Large clinical trials involving systemic therapy for biliary cancer have broad inclusion criteria, including almost all tumours of biliary tract origin [1]. The standard of care for advanced biliary tract cancers (ABC) is systemic therapy, usually with combination chemotherapy, including platinum and gemcitabine [1], but patients invariably progress, with a median survival of less than 1 year [2]. There are currently no standard second-line options [3] and patients are often referred for participation in clinical trials involving various novel agents targeting multiple potential pathways, as well as trials using non-systemic local therapy. Early phase clinical trials investigating these agents are therefore an important option for patients with ABC, but there are limited published data on the impact of experimental drug therapies on the safety and outcome of chemo-refractory ABC to guide recommendations and policy.

In the era of precision medicine, molecular characterisation of tumours has helped to create more efficient clinical trial design and is considered essential in late phase

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trials [4]. However, it is now recognised that identification of these patient subgroups must start in early phase trials, allowing for validation of these results in late phase studies. Increasingly, phase I units throughout the world have started to routinely perform molecular characterisation of tumours and use these results to guide trial allocation for patients [5].

We conducted a retrospective analysis of all patients with ABC treated in the specialist phase I unit in our institution. The aim of this study was to describe the rates of toxicities and treatment-related trial discontinuation in these patients, as well as to describe the anti-tumour activity of these agents. We additionally explored the prognostic role of baseline variables for this group of patients and report on the results of molecular characterisation carried out on ABC tumours.

Materials and Methods

All consecutive patients with ABC treated within phase I clinical trials in the Drug Development Unit at the Royal Marsden National Health Service Foundation Trust, Sutton, UK from March 2002 to March 2016 were included. Patients eligible for phase I participation were $\geq$18 years old and had progressing ABC tumours for which approved treatments were no longer available. Patients were discussed at weekly trial allocation meetings to identify suitable trials based on disease characteristics, tumour molecular characterisation results (if available) and trial slot availability. Patients who received at least one dose of an experimental agent and provided written informed consent for participation in phase I trials as approved by the local Research Ethics Committee were included in this study.

Clinical data that were prospectively collected for each clinical trial were collated. These included patient characteristics, tumour characteristics and laboratory results. For each phase I trial: drug name, class of drug, mechanism, date starting trial, best response, grade of toxicities and date of progression were collected.

Toxicity data were collected as originally recorded in the electronic medical records or the case report forms when required. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for adverse events. Tumour responses were confirmed by a radiologist using Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Molecular Characterisation

From 2011 onwards, patients treated at the Drug Development Unit, Royal Marsden Hospital (RMH) were consented to undergo characterisation of key molecular drivers in the patients' archival tumour tissue. Through the years, various panels of targeted next generation sequencing have been used, for example, from 2013 to mid-2015, 48 genes were tested using the TruSeq panel, and from the end of 2015 to currently, 113 genes were tested using the Generead DNA damage panel. Immunohistochemistry (IHC) for ATM was carried out from 2015. Panels and other additional tests were also dependent on the types of trial and the biomarkers being selected for these trials during that period of time. Of particular note, these panels were not specifically designed to identify mutations peculiar to ABC. The results of these tests, if available, were used to match the molecular aberration identified to a rationally selected experimental trial, if available.

Statistical Methods

Descriptive statistics were used to summarise patient and tumour characteristics. The clinical benefit rate was calculated as the sum of complete response, partial response and proportion of patients with stable disease at 4 months. For patients included in more than one trial, data for progression-free survival (PFS) and overall survival from the first trial therapy were used. Overall survival and PFS were determined using Kaplan–Meier analysis and specified as median survival. Data are presented as survival plots.

Analysis of the effect of potential prognostic factors on survival was undertaken using Cox proportional hazard modelling. Categorisation of numeric variables was based on their deviation from standard reference values. The RMH prognostic was calculated from a model previously described [6]. In brief, the RMH prognostic index uses a composite score of albumin, lactate dehydrogenase and number of metastatic sites to predict survival in phase I trials. Factors identified in univariate models were used to construct an adjusted survival model.

Results

Patient and Tumour Characteristics

Between March 2002 and March 2016, 123 patients with ABC were reviewed for the consideration of phase I clinical trials. Eventually, 48 patients (39% of total) participated in a trial. Of the 75 patients who were reviewed in the clinic but did not participate in a phase I trial, 15 (20%) patients were deemed initially eligible for a study trial, but did not receive any investigational agent due to rapid interim disease progression. Five patients had passed screening for a study, but had deterioration of disease condition and performance status between screening and cycle 1 day 1 and did not receive drug. The average time between the first visit and screening was 3 weeks. Among the other ABC patients reviewed in the unit for the consideration of a phase I study, the most common reasons not to be considered were biliary-related disease leading to abnormal liver function and/or bilirubin that would have qualified as exclusion criteria for trials (21%), poor performance status (18%) and patient's choice (8%).

In total, 48 patients participated in 41 different phase I clinical trials. Eight (17%) entered a second phase I study upon progression on the first study. The primary site of the tumour was the bile duct in 36 (75%); patients had a median of two previous lines of systemic chemotherapy (range

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