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Original Research Article

Protocol for a phase III randomized trial of chemoradiation and systemic chemotherapy vs. systemic chemotherapy alone in patients with unresectable nonmetastatic cholangiocarcinoma

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ABSTRACT

Background: Systemic doublet chemotherapy constitutes the current standard of care for patients with unresectable non-metastatic cholangiocarcinoma. The use of doublet chemotherapy is associated with median survival of 11.7 months. Concurrent chemo-radiation in this cohort is associated with similar overall survival however the impact of combination of chemoradiation and systemic chemotherapy on overall survival has not been investigated. The present phase III randomized study investigates the impact of chemoradiation in addition to systemic chemotherapy on overall survival.

Methods: Patients older than 18 years of age with diagnosis of unresectable non-metastatic cholangiocarcinoma with performance status 0-2and preserved liver function (Child Pugh score up to B7) will be eligible for study participation. The trial is designed such that patients will undergo stratified randomization (extra-hepatic vs. intrahepatic) either into systemic chemotherapy (standard arm) or chemo-radiation and systemic chemotherapy arm (experimental arm). The primary aim of the study is to compare difference in overall survival. The secondary aims of the study will focus on loco regional progression free survival and cause specific survival. The study will also report on the acute and late toxicity, quality of life and resectability rates in both the study arms. To demonstrate 7-month improvement in overall survival from 11 to 18 months a sample size of 142 is needed. Accounting for attrition a total of 155 patients will be accrued. All study subjects will be accrued after written informed consent. The trial is approved by the institutional ethics review board.

This trial is registered with ClinicalTrials.gov as NCT02773485

Keywords: Cholangiocarcinoma, Chemoradiation, Unresectable, Randomized

INTRODUCTION

Surgery is the only potentially curative option for intrahepatic (IHCC) or extra hepatic cholangiocarcinoma (EHCC), however a significant proportion of patients with cholangiocarcinoma present with locally advanced disease and are unresectable at presentation either due to extent of local disease or major vascular encasement.[1] For locally advanced unresectable disease, systemic doublet chemotherapy remains the treatment of choice which leads to median survival of less than a year (11.7 months; ABC-02 trial).[2] Radical radiation with or without chemotherapy and or brachytherapy is associated with equivalent survival.[3] Local failure continues to dominate patterns of failure in patients with resectable and unresectable cholangiocarcinoma treated with surgical or nonsurgical treatments.[4-7] The impact of radiation response in EHCC is best demonstrated in a cohort of patients undergoing neo-adjuvant chemo-radiation prior to liver transplantation wherein 42% patients had complete pathological response in the resected livers.[8] The use of combination of chemo-radiation and brachytherapy with doses > 55 Gy has been associated with median survival of 24 months as compared to doses < 55 Gy wherein median survival was 6 months (p =0.0003). A lengthening of the median survival with increasing radiation dose (4.5 months, 9 months, 18 months and 25 months for < 45 Gy, 45–55, 55–65, 66–70 Gy, respectively) has also been reported.[9] More recently, hypofractionated stereotactic body radiation with sequential systemic chemotherapy is associated with median survival of 35.5 months (4 year survival of 30%).[10]

Several studies have supported the use of radiotherapy in IHCC with median survival ranging from 7-15.3 months with conventional fractionated doses of radiation (45-50 Gy).[11-15] Ibarra et al reported a median survival of 11 months following SBRT of 37.5 Gy/3 fractions.[14] In another study of SBRT for IHCC the use of 32 Gy/6 fractions was associated with median survival of 15 months (6.5-29 months) and infield failure rate of 34%.[15] Overall 67% patients presented with out of radiation field or distant recurrence. Furthermore combination of transarterial chemotherapy with radiation was also associated with improved survival (13.3 vs. 7.8 months).[12,13] While local control could possibly be further intensified by using higher doses of SBRT or integrating chemotherapy with conventional radiation, there is also a need to use systemic chemotherapy to delay death due to systemic metastasis and out of field liver disease.

In unresectable Klatskin's tumors a median survival of 7–12 months can be obtained by chemoradiation.[16-19] In our institution we have observed a median survival of 10 months in patients undergoing chemo-radiation and brachytherapy.[20] Similar median survival has been obtained with external beam radiation or brachytherapy either alone or in combination by other authors.[21-24] Using SBRT alone (45 Gy/3 fractions delivered over 5-8 days) Kopek et al reported median survival of 10.6 months.[25] Most frequent site of failure was outside the primary site. Two other series of SBRT which combined SBRT with systemic chemotherapy have reported median survivals that have not been previously reported even with most aggressive combinations of external radiation, brachy-therapy and chemotherapy. Momm et al reported outcomes of patients treated with 32-56 Gy in fraction size of 3-4 Gy delivered three times a week. Of these 50% received additional systemic chemotherapy.[26] The median overall survival was 33.5 months (6.6-60.4 months). No grade III or higher GI morbidity was observed in this cohort. Polistina et al reported on patients with hilar cholangiocarcinoma treated with SBRT of 30 Gy in 3 fractions delivered in 3 days along with weekly gemcitabine at a dose of 1000 mg/m^2.[10] The median time to progression was 30 months (1-51 months) with a median survival of 35.5 months. Duodenal ulceration secondary to treatment was observed in 10% of patients. Overall 60% developed local progression and 60% developed distant metastasis. The published results using chemoradiation for unresectable EHCC (other than Klatskin's tumors) report a median survival ranging from 10 months to 22 months, with some suggestion of improved outcomes when patients receive systemic chemotherapy and radiation doses >55 Gy.[7,9,27-31]

The results from studies using high dose radiation and systemic chemotherapy suggest that improved outcomes may be expected by combination of both approaches. The current standard of care for unresectable non-metastatic cholangiocarcinoma is systemic doublet chemotherapy. While phase II studies demonstrate benefit of addition of radiation it remains to be confirmed within a prospective randomized study.

Hypothesis

On the basis of available literature we hypothesize that addition of chemo-radiation to systemic chemotherapy will improve overall survival in patients with unresectable non-metastatic cholangiocarcinoma.

Trial design

The study is designed as a phase III open label randomized study to test superiority of combination of chemoradiation and chemotherapy over chemotherapy alone.

METHODS

Research setting

The study will be conducted at Advanced Centre for Treatment Research and Education in Cancer and Tata Memorial Hospital, Tata Memorial Centre, Mumbai, India, which is a not-for- profit academic university hospital.

Study aims

The primary aim of the study will be to compare overall survival between systemic chemotherapy alone (control arm) and chemo-radiation and systemic chemotherapy (experimental arm). The secondary aims of the study will be to compare loco-regional progression free survival, cause specific survival, resectability rates, incidence of acute toxicity and late toxicity and quality of life of the patients between test and control arms.

Study design

All patients with diagnosis of non-metastatic unresectable cholangiocarcinoma who fulfill the study eligibility criteria will be evaluated for study participation. Patients will undergo upfront randomization into one of the study arms. The study stratification will be done according the primary site i.e. intrahepatic vs extrahepatic.

Study eligibility

All patients older than 18 years with tissue diagnosis of adenocarcinoma of the biliary tract and no evidence of peritoneal or distant metastasis or para- aortic nodal disease, with good performance status (0-2) and child pugh class A or B (Score 7), who are deemed unresectable by the hepato-biliary surgical team will be eligible for inclusion in this study. Wherever tissue diagnosis is not feasible in spite of repeated attempts a multidisciplinary consensus on clinic-radiological diagnosis of cholangiocarcinoma (CA 19.9= 100 mg/ml with a radiological evidence of malignant stricture) will be made.

Patients with multicentric intrahepatic cholangio-carcinoma (except adjacent satellite lesions), active cholangitis, unresolved biliary tract obstruction or an expected survival less than 6 months will be excluded from this study. High tumor/liver ratio leading to inability to deliver safe radiation will also serve as exclusion criteria.

Interventions

Once enrolled in the study, positron emission tomography scan (PET scan) and hepatic function assessment scan will be performed prior to randomization. Liver function tests, renal function tests and CA 19.9 should have been performed within 4 weeks of treatment initiation. Stratified randomization (according to location of tumour) will be performed by epidemiology and clinical trial units (ECTU) and the results of randomization will be notified to principal investigator over email. The randomization details will not be masked from patient or principal investigator. Once randomized, patients will be treated according to the allocated arm. The details of treatment within each arm are as follows.

Systemic chemotherapy arm

Those randomized to systemic chemotherapy arm will receive intravenous gemcitabine (1000 mg/m^2 on day 1 and day 8) and cisplatin (25 mg/m^2 on day 1and day 8). In case of treatment related hematological, infective or gastrointestinal toxicity standard modifications to chemotherapy doses will apply. Chemotherapy cycles will be repeated every 3 weeks for 4 cycles, after which patients will undergo repeat CECT/PET scan. If CECT/PET scan shows stable/responding disease then patients will continue to receive same chemotherapy for another 4 cycles. In case of locally progressive/systemic disease on chemotherapy patients may be considered for second line palliative chemotherapy or best supportive care. The use of radical dose chemo-radiation is not allowed on disease progression in the systemic chemotherapy arm. However palliative radiation may be used.

Chemoradiation + systemic chemotherapy arm

The aim of chemoradiation will be to give highest possible safe doses of radiation to the patient. The primary location and extent of the tumour will govern the radiation dose, technique and overall duration of treatment. All patients randomized to experimental arm will undergo radiation planning CT scan in supine position with arms overhead, pelvic immobilization device (knee rest) and 3 fiducial markers placed over the upper abdomen. Intravenous contrast (non-ionic) will be administered at 1 ml/kg. In addition four dimensional computerized tomography scan will be performed to generate internal target volume.

As target volume delineation for cholangiocarcinomas (particularly extrahepatic location) is challenging, the gross tumour volume (GTV) will be delineated with combination of all available imaging. This comprises triphasic contrast enhanced computerized tomography (CECT) and positron emission tomography (PET) or magnetic resonance imaging (MRI) scan (wherever available) for intrahepatic tumour locations and PET/triphasic CECT/magnetic resonance cholangio-pancreatography (MRCP)/percutaneous transhepatic cholangiogram (PTC gram) and cholangioscopy/ cholangiography findings for extrahepatic tumour. The GTV identified with combination of all techniques will comprise the high dose volume. The adjacent areas of suspected microscopic disease will form the clinical target volume (CTV). Organ at risk (OAR) contouring will include liver-GTV, liver-CTV (normal liver), esophagus, stomach, duodenum, kidneys, heart, lungs, bowel and spinal cord. In addition overlying ribs will also be contoured. The study aims at delivering 52.5-60 Gy/25 fractions to the gross disease and 45 Gy/25 fractions to suspected microscopic disease along with weekly Gemcitabine (300 mg/m^2). All care will be taken to restrict organ at risk doses as per standard guidelines.

Special focus will be given to restrict dose to normal liver parenchyma, adjacent gastrointestinal structures to minimize acute and late toxicity. Patients in experimental arm will also receive 6 cycles of systemic chemotherapy.

On treatment evaluation

Toxicity scoring will be performed using common terminology criteria for adverse event (CTCAE) reporting version 4.0. Quality of life (QOL) assessment will be performed using functional assessment of cancer therapy (FACT) QOL assessment scale. Print and electronic database of assessments will be maintained. CTCAE and QOL assessment will be performed at baseline. During treatment, weekly CTCAE will be recorded and then repeated subsequently at every 3 monthly follow up. QOL assessment will be performed at baseline, at mid treatment (week 12 after treatment initiation), post treatment completion and 3 monthly thereafter until last follow up or death.

Response evaluation

Follow up investigations will include liver function tests, CA 19-9 and triphasic CECT scan at 3 monthly interval.

To balance evaluation of treatment response in both arms the first response assessment imaging will be done at 12 weeks from treatment initiation irrespective or arm allocation (after 4 cycles of chemotherapy or 6 weeks after completion of chemoradiation). At first follow up patients will undergo triphasic PET-CECT and will be restaged. Those who have become resectable will be assessed for surgery (hepatectomy or extrahepatic biliary tree excision +/- hepatectomy). Evaluation for resectability will be on the basis of standard guidelines employed outside clinical trial, which includes assessment of local stage, functional liver reserve and general condition of the patient.

Statistical consideration

Primary end-point

The calculation of study sample size is towards the primary end-points of overall survival. The standard of care treatment is associated with median survival of 11 months. The addition of high dose radiation will increase median survival to 18 months. Assuming 4 years of sample accrual and 3 years for subsequent follow up using a two-sided alpha of 0.05 and power of 0.80 a total of 71 patients will be needed in each arm. Accounting for attrition a total of 155 patients need to be randomized in the study. In order to achieve this, a total of 400 patients are planned to be screened in this study. A stratified analysis will be done for intrahepatic and extrahepatic location. No interim analyses are planned. However interim audit or analyses may be suggested by institutional data and safety monitoring subcommittee.

Data collection

All trial data will be maintained by the principal investigator of the study at ACTREC, Tata Memorial Centre at Mumbai, India.

Secondary end-points

The loco-regional treatment response, distant disease spread and cause of death will be reported in order to determine secondary endpoints of local control and cause-specific survival for these patients. In addition resectability rate, QOL and toxicities will be reported.

Quality control

Informed consent

Informed consent will be obtained by principal investigator or personnel designated by the principal investigator. Patient will be given appropriate time to decide regarding study participation. Study does not involve minors, pregnant mothers, and neonates. After serving informed consent patient will be asked to describe the study procedure, benefits and risks involved to ensure comprehension.

Treatment execution

The contouring and treatment execution will be done directly under the supervision of principal and co-principal investigators and any deviations and violations from the proposed plan will be reported to data and safety monitoring subcommittee. Serious Adverse Events will necessitate reporting as per standard procedures. Hospital or trial funds will cover for the cost of medical management of radiation related side effects or injury. Toxicity arising out of systemic chemotherapy or patients developing cholangitis will not be considered trial related injury or a related SAE. Compensation will be paid as per prevailing rules for investigator initiated trials at Tata Memorial Centre. The trial will be monitored at a regular interval by the institutional data and safety monitoring board and its report will be submitted to the ethics committee and institutional review board.

Withdrawals

Subjects may withdraw from the study at any point of time.

Data analysis plan

The primary analysis of overall survival will be calculated using Kaplan Meir survival analysis. The loco-regional relapse free survival and cause –specific survival analysis will also utilize Kaplan Meir survival analysis while toxicity and quality of life will use a categorized group comparison between two arms for specific domains.

DISCUSSION

The current standard of care for non-metastatic unresectable cholangiocarcinomas is doublet-based chemotherapy (cisplatin + gemcitabine) which yields a modest survival of 11.7 months. However, increasing phase II evidence is being generated in favour of combined modality chemoradiation. An analysis of patients with unresectable non-metastatic cholangiocarcinoma from the National Cancer Database in the USA (n=1636), revealed a significant benefit for combined modality treatment with 2-year survival rates of 26% compared with 20% for the cohort treated with chemotherapy alone.[32] A dose-response has also been demonstrated for IHCC in a retrospective analysis from MD Anderson cancer centre. The 3-year OS rate for patients receiving BED greater than 80.5 Gy was 73% versus 38% for those receiving lower doses (P = 0.017); BED as a continuous variable significantly affected local control (P = 0.009) and overall survival (P = 0.004).[33] Further recently published outcomes of phase II trials exploring benefit with chemoradiation from Italy report that in patients receiving concurrent chemoradiation, median OS was 14 months, and patients who had dose escalation using a brachytherapy boost had a median OS of 21 months.[34] These results suggest that combined chemoradiation and systemic chemotherapy may be superior to chemotherapy alone. As there is paucity of level I evidence the present phase III trial is designed with an aim to test incremental benefit of local radiation.

Implications for research

This study proposes to test the role of chemoradiation in cholangiocarcinoma for improving overall survival. There have been minimal incremental gains with available additional chemotherapeutic agents. In a disease with such dismal outcomes even a modest improvement in survival may allow redefinition of standard of care.

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