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TITLE: Yttrium-90 trans-arterial radioembolization for chemotherapy-refractory intrahepatic cholangiocarcinoma: a prospective, observational study

RUNNING TITLE: Radioembolization for intrahepatic cholangiocarcinoma

ABSTRACT (243 words)

Purpose: To evaluate the safety and efficacy of yttrium-90 trans-arterial radioembolization (TARE) for the treatment of unresectable, chemotherapy-refractory intrahepatic cholangiocarcinoma (ICC).

Methods: A prospective, observational study was carried out in ten centres between 2013 and 2017. TARE plus standard care was delivered to patients with unresectable, chemotherapy-refractory or chemotherapy-intolerant ICC. Primary outcome was overall survival. Secondary outcomes included safety, progression-free survival (PFS) and liver-specific PFS (LPFS).

Results: 61 patients were treated with TARE. Patients were 53% male, median age was 64 years, 91% had performance status 0/1. 92% had received prior chemotherapy; 59% had no extrahepatic disease. Median follow-up was 13.9 months (95% CIs 9.6-18.1). Overall survival was 8.7 months (95% CIs 5.3-12.1); 37% of patients survived to 12 months. PFS was 2.8 months (95% CIs 2.6-3.1) and LPFS was 3.1 months (95% CIs 1.3-4.8). One severe complication (abdominal pain) occurred at the time of the TARE procedure. Thirty patients experienced a total of 49 adverse events, of which 8% were grade ≥3; most commonly grade 1-2 fatigue and abdominal pain. A total of 77 abnormal laboratory value events were recorded, of which 4% were grade ≥3.

Conclusions: Patients with advanced ICC have limited therapeutic options and a poor prognosis. This prospective study examined the survival of patients with unresectable, chemotherapy-refractory primary ICC treated with TARE in real-world practice. The results demonstrate that this treatment merits further investigation in this patient cohort in a larger study, including collection of patient-reported outcomes.

Key words: bile duct cancer, brachytherapy, selective internal radiotherapy.

Full text

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare primary liver cancer which arises from the epithelial cells of the bile ducts [1]. Surgical resection with clear margins is the only potentially curative approach for patients with ICC, however most cases are too advanced for curative resection and have only palliative chemotherapy and supportive care as options [2]. For patients with advanced and inoperable ICC, cisplatin and gemcitabine has been established as an effective first line systemic treatment [2]. The efficacy of second-line chemotherapy regimens is not supported by randomized controlled trial evidence. Currently active symptom control, including management of biliary tract obstruction and infection and other symptoms arising from tumor progression, is the standard of care for chemotherapy-refractory ICC [3, 4]. A phase III RCT (ABC-06 NCT01926236) is underway comparing FOLFOX chemotherapy to active symptom control which will elucidate the role of second-line chemotherapy in advanced biliary cancer.

Trans-arterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT), is a form of intra-arterial brachytherapy used to treat primary and secondary hepatic tumors. Microspheres containing the beta-emitting radionuclide, yttrium-90 (Y-90), are delivered directly into the tumor via the hepatic artery using a percutaneous transarterial approach [5]. TARE is an established treatment in primary hepatocellular carcinoma (HCC) but the evidence base supporting its use in an ICC population is limited [6,7].

Commissioning through Evaluation (CtE) is a programme where new treatments lacking conclusive evidence but which show promise are commissioned in the NHS (National Health Service) in specialist provider centres in England for a limited period of time and in a specific population [8-10]. In 2013, 10 specialist centres in England were awarded contracts to provide TARE; these centres were required to collect data from all patients treated under CtE arrangements and submit them to an online registry. The hypothesis of this study was

that real-world date can be used to evaluate the impact of TARE on OS, PFS, liver-specific progression free survival (LPFS), and safety.

MATERIALS AND METHODS

Study design and population

This prospective, single-arm, observational, service evaluation study was carried out between December 2013 and February 2017 at 10 sites in England. Sites were selected based on their prior experience of TARE, the number of trained staff in the relevant disciplines on site and their site's ability to serve a geographical population providing equity of access across the whole of England. All patients were de-identified at source. On this basis, following discussion with the Information Commissioner's Office for England, this study was classified as exempt from requiring ethics committee (Institutional Board Review) approval. As such, patient consent was sought using the sites' established processes for interventional procedures.

Adults with unresectable, chemotherapy-refractory or chemotherapy-intolerant, ICC were eligible to take part. Inclusion criteria included: i) histologically confirmed ICC not amenable to curative liver surgical resection; ii) WHO performance status of 0–2; iii) life expectancy > 3 months; iv) evidence of progressive disease by response evaluation criteria for solid tumors (RECIST) criteria during first-line chemotherapy or following first-line chemotherapy, unless the patient has a specific contraindication to chemotherapy; v) adequate hematological and hepatic function as follows: serum bilirubin ≤ 1.5 x ULN; absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L; albumin ≥ 30 g/L; vi) no central nervous system metastases or bone metastases, but patients were permitted to have limited extra-hepatic disease (e.g. lung metastases, multiple lymph nodes or low-volume peritoneal disease) that was agreed at multi-disciplinary team meeting to not be life threatening nor a cause for significant morbidity if the liver malignancy can be controlled with TARE. Exclusion criteria included: evidence of

ascites, portal hypertension or cirrhosis; previous portal vein embolization or chemo-embolization; previous radiotherapy to the upper abdomen.

Patient characteristics and procedural details

There were a total of 61 valid cases entered onto the registry (invalid entries without an eligible diagnosis or procedure date were excluded from the analysis). The number of cases carried out at each of the 10 sites ranged from 1 to 16. Patients were 53% male with a median age of 64 years (Table 1). The majority of patients (91%) had an ECOG performance status of 0 or 1 and 59% did not have extrahepatic metastatic disease. Prior chemotherapy was recorded for 92% of patients which typically consisted of cisplatin and gemcitabine; 5% of patients had not been exposed to chemotherapy due to clinical contra-indications. The median duration from primary diagnosis to TARE was 1.1 years (Table 1).

Thirty one patients (51%) had 1-5 tumors in the liver, 9 patients (15%) had 6-10 tumors, and 13 patients (21%) >10 tumors (Table 2). Thirty nine patients (64%) had bilobar tumors. Median bilirubin prior to TARE was 8.0 µmol/L (IQR 5.3-11.8), and median baseline albumin was 38.0 g/L (IQR 33.5-42.5) (Table 2). Arteries were embolized during the work-up procedure in 21 patients (34%). Thirty two patients (52%) received TARE as a single procedure targeting the whole liver: 16 patients (26%) split administration and 16 patients (26%) single administration. Although the health service did not fund more than one administration of TARE, 12 patients (20%) of patients received more than one session of RE. Forty five RE procedures (74%) were conducted using the resin microspheres, and the remaining procedures were carried out using glass microspheres. The median percentage tumor to liver volume ratio was 17.0 (IQR 8.0-28.5). Forty patients had a hospital stay of 1 night (66%) for the TARE procedure and the others more than one night. Chemotherapy was delivered concomitantly with TARE in 7 patients (12%), and in 9 patients (15%) after TARE and during the follow-up period (Table 2).

Procedures

Each site followed their local process for undertaking TARE procedures. All patients underwent a hepatic arteriogram and a liver-to-lung breakthrough macro-aggregated albumin scan to ensure suitability for and to plan the delivery of TARE. Selective coil embolization of arteries to the stomach, duodenum or other visceral structures was carried out where required. Two brands of CE-marked active implantable medical devices were used to carry out the TARE procedure: Either i) SIR-Spheres (Sirtex Medical Ltd, Australia) resin microspheres; or ii) TheraSphere (Biocompatibles UK Ltd, UK) glass microspheres. Dosing of resin or glass microspheres was carried out as per manufacturer instructions. Administration of concomitant chemotherapy and post-TARE chemotherapy was at the discretion of the treating clinician. Sites were expected to follow patients up every 2 to 3 months after their TARE procedure until progression was detected. Follow-up appointments would usually consist of an abdominal CT scan (plus chest and/or pelvis in patients with extrahepatic disease), and in some cases an MRI or PET scan was also carried out. Adverse events were assessed and recorded throughout the follow-up period.

Data collection and outcomes

Clinical data were collected by teams at each of the sites and entered into an anonymized online registry. The final dataset was extracted in March 2017 and analyzed by an independent research group, Cedar. Patients had unequal follow-up periods, and those treated most recently were missing some or all follow-up data. Missing data proportions were reported for all outcomes. Patients with a missing diagnosis or missing TARE administration date were excluded from the analysis. Data were only collected on patients who received TARE and no comparator data were available.

OS was defined as the duration from the first TARE procedure until death from any cause. Patients with no date of death recorded were right censored at the date at which they were lost to follow-up. Survival proportions at 3, 6, 12, 24, and 36 months were reported for patients for whom this data were available. Hepatic and extrahepatic tumor response

assessments were carried out locally by a radiologist and recorded in the TARE registry: RECIST criteria were used [11]. PFS was defined as the duration from the first TARE administration to the earliest date of detection of progressive disease (PD; either hepatic or extrahepatic) by CT, MRI, or PET scan, or to the date of death from any cause if progression was not recorded. Patients with no PD recorded were censored at the most recent date of non-progression (complete response (CR) or partial response (PR) or stable disease (SD)). LPFS was defined as the duration from the first RE administration to the date of progression in the liver or death from any cause. Patients with no PD in the liver were censored at the most recent date of non-progression in the liver.

Baseline and procedural parameters were recorded in the registry including hematologic, liver function, and blood biochemistry tests. A search of regimen synonyms was carried out to count the number of patients who received each type of chemotherapy prior to their TARE administration and concomitantly to TARE. Percentage tumor volume to liver volume was recorded for either the whole liver or for right and left lobes separately. Where a whole liver measurement was absent, right and left values were added to produce a proxy for a whole liver measurement. Similarly, prescribed activity (of the Y-90 microspheres) was recorded separately for the whole liver, and for right and left lobes.

Severe “day-of-treatment” complications, post-procedure adverse events (AEs), and abnormal laboratory results were recorded in the registry. Grading criteria were not prescribed and it was assumed that sites used the Common Terminology Criteria for Adverse Events (CTCAE) system. Incidents or complaints related to the radioactive microsphere product used in the procedure were recorded in the registry.

Statistical analysis

Sample size was based on the number of eligible patients projected to be recruited at the participating sites over a 36-month period for this rare cancer. Based on difficulty in enrolling

patients with this rare cancer, a minimum sample size of 60 patients was predetermined to provide NHS England with sufficient pilot data for a commissioning decision. All statistical analyses were conducted in IBM SPSS Statistics version 21.0.0.0 (IBM Corp. Armonk, NY) or R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Descriptive statistics for continuous variables were reported as appropriate. For each statistical comparison, p-value and confidence intervals (CIs) were reported. P-values at <0.05 were considered statistically significant and all tests were two-sided. Median OS, PFS, and LPFS were estimated using Kaplan-Meier analysis. Survival curves were presented with 95% CIs and numbers at risk displayed. The reverse Kaplan-Meier method was used to calculate median follow-up time. On account of the low total sample size, subgroup analyses were not performed since they would lack statistical power.

RESULTS

Survival

Patients were followed up for a median of 13.9 months (95% CIs 9.6-18.1). At the conclusion of the study, 33 (54%) deaths were recorded. A total of 23 (38%) patients were censored at their last recorded follow-up date, and the survival status of 5 patients was not established (missing data). Median OS was 8.7 months (95% CIs 5.3-12.1) (Figure 1). Survival proportions were 89% at 3 months post TARE, 85% at 6 months, 37% at 12 months, and 7% at 24 months.

Progression (either hepatic or extrahepatic) or death was observed in a total of 47 (77%) patients (7 of these died before progression was recorded), 7 (11%) patients were censored at the last imaging date when no progression was recorded, and 7 (11%) patients had no progression status and were excluded from the PFS analysis. Median PFS was 2.8 months (95% CIs 2.6-3.1) (Figure 2). In the LPFS analysis, 46 (75%) patients progressed or died, 8 (13%) were censored, and 7 (11%) were excluded. Median LPFS was 3.1 months (95% CIs

1.3-4.8) (Figure 2). In this cohort, 22 patients had dates recorded for both intra- and extrahepatic progression; in 18 of these patients (82%) these dates were the same, in 2 patients (9%) extrahepatic progression occurred first, and in 2 patients (9%) hepatic progression occurred first.

Safety

One severe complication was recorded at the time of the TARE procedure and associated with the microsphere product which was “severe abdominal pain”. Two patients had “complication” recorded as the cause of death (although this field was poorly completed in the registry); one patient had “tumor lysis syndrome” recorded and died 15 days following RE, and one patient had “portal vein thrombosis and liver decompensation” recorded and died 45 days after TARE.

A total of 30 patients experienced a total of 49 AEs during their follow-up period, of which 4 (8%) were grade 3 or above (Table 3). Two cases of severe fatigue and one case of severe fever were recorded. Relatedness to the TARE intervention was not recorded in the registry. The most common events were mild (grade 1-2) fatigue and abdominal pain. No severe cases of radioembolization-induced liver disease (REILD), gastrointestinal ulceration, radiation pneumonitis, radiation cholecystitis, or radiation pancreatitis were recorded. Sixteen adverse events were recorded under in the “other” category which were in most cases gastrointestinal-related such as diarrhoea, constipation, anorexia, and indigestion/reflux. One grade 3 event was recorded under the “other” category which was diarrhea & abdominal cramping. A total of 77 abnormal laboratory value events were recorded of which 3 were of grade 3 or above (Table 3). Common events were: raised aspartate aminotransferase (17 events), raised alanine aminotransferase (14 events), hypoalbuminemia (12 events), and decreased platelet counts (12 events).

DISCUSSION

Patients with advanced ICC have limited therapeutic options following progression on standard chemotherapy. This study was specifically commissioned to provide real-world evidence within a national health service on the efficacy of TARE in a salvage setting. Registry-based commissioning is an example of 'coverage with evidence development' whereby innovative technologies with uncertainties around effectiveness claims are introduced to the health system conditional on gathering further data [12]. This approach is particularly useful in rare conditions because randomized controlled trials are very challenging to conduct due to ethical considerations and the very long timescales required to get results. This prospective study examined the survival of patients with unresectable, chemotherapy-refractory primary ICC treated with TARE and the results suggest that this treatment is worthy of further evaluation.

A systematic review of second-line chemotherapy in advanced ICC was conducted by Lamarca et al. (2014) [4] which included 25 non-comparative studies of a total of 761 patients. The mean OS was 7.2 months (95% CIs 6.2-8.2) and progression-free survival (PFS) was 3.2 months (95% CIs 2.7-3.7). The authors estimated a 4-month survival in patients treated with best supportive care (BSC) who have progressed following first-line chemotherapy [4]. Previously published pooled estimates of OS in TARE studies are 15.5 months [6] and 13.9 months [7], although many studies were small and had wide confidence intervals around their OS estimates. The median OS of 8.7 months presented in our study is lower than these estimates, which may be explained in part by the pragmatic design of this observational study reflecting more accurately the survival of patients subjected to routine care alongside TARE in a real-world health-service setting. Several studies included in published reviews had a considerable proportion of chemotherapy-naive patients, compared with only 5% of patients in our study presented here. The shorter post-TARE survival may also be explained by the relatively long time from diagnosis to TARE with average 1.1 years.

A 2015 systematic review by Al-Adra et al. (2015) [6] included single-arm studies published up to 2013 and reported a pooled median overall survival (OS) of 15.5 months (range 7-

22.2) [6]. Another review by Boehm et al. [7] presented a pooled OS of 13.9 months (95% CI 9.5-18.3). Recent studies of unresectable ICC patients treated with TARE [13-15] have reported median PFS of 5.6-7.6 months and median OS of 12.0-16.4 months, which is higher than the PFS estimate reported in our study of 2.8 months. An important difference between our study and these reported studies is the proportion of chemotherapy-naïve patients included, which ranged from 28 to 56% in the published studies [13-15]. PFS can provide a consistent measure of what happens to a tumor during therapy, and offers a useful outcome when longer follow-up is impractical. However, caution should be applied because PFS estimates are based on interval-censored data, and the frequency of assessments impacts directly on the result. This is particularly problematic in an observational study with variable follow-up intervals and high levels of missing data. There are also reports that RECIST criteria are an insensitive assessment for TARE-treated tumors and that metabolic-based imaging techniques (e.g. fluoro-deoxy-glucose-PET) may be more sensitive, earlier predictors of response [16]. Routine PET imaging for all patients was not practical in this real-world study.

In this study, severe peri-procedural complications were rare (1 patient), as were severe adverse events during the follow-up period (4 events) and severe toxicities (3 events). The type of these events corresponded to those reported in published papers [13-15], i.e. fatigue, hyperbilirubinemia, AST increase, and ALT increase. The relatedness of safety events to TARE, assessed by the physician, was not recorded in the registry. Direct comparisons of adverse event rates with published studies have not been performed because of differences in the criteria used for reporting, particularly the length of follow-up. It should also be noted that the two types of TARE devices used in the study described here are distinct in their physical properties and administrations. Since 74% of the administrations in this study used the resin microspheres, the results of this study are primarily relevant to this device.

Limitations of this study include the observational design which meant that important confounding factors could not be controlled. The absence of a control group, such as

patients treated with best supportive care, limits the interpretability of the effectiveness of TARE from the results. The observational design using an anonymised registry to collect data meant that missing data and partial patient censoring at time of last follow-up was problematic, as was heterogeneity of patient performance status, tumor burden, type of embolic agent used, criteria used for clinical assessments and embolization techniques. These limitations subtract from the generalisability of the conclusions. Also, details of chemotherapy (agents administered and number of cycles) were not recorded in the registry and external validation of data against routinely collected datasets could not be carried out. Data on health-related quality of life were collected during this study using the EQ-5D-5L tools. However, this tool is insensitive to more nuanced disease-specific symptom changes. Combined with variability in data collection and recording of this outcome measure, meant that reliable conclusions about the impact of TARE on patients' quality of life could not be drawn from this study. Further research using a disease-specific tool is required in this area.

In summary, this prospective study examined the survival of patients with unresectable, chemotherapy-refractory primary ICC treated with TARE. Its pragmatic observational design reflects real-world practice in a national health service providing equity of access across an entire country. The results demonstrate that this treatment merits further investigation in this patient cohort in a larger study, particularly the combination of TARE with systemic chemotherapy. Future studies should include collection of patient-reported outcomes and pre-planned analysis of clinical subgroups.

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Figure 1. Kaplan-Meier curve of overall survival following RE in patients with intrahepatic cholangiocarcinoma.

95% CIs shown shaded; numbers at risk at 3 month intervals displayed.

Figure 2. Kaplan-Meier curve of progression free survival and liver-specific progression free survival in patients with intrahepatic cholangiocarcinoma following RE.

95% CIs shown shaded; numbers at risk at 3 month intervals displayed.