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Combined Use of Yttrium 90 Selective Internal Radiotherapy and Chemotherapy in the Treatment of Patients with Inoperable Intrahepatic Cholangiocarcinoma: Single Centre Experience

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Abstract

Purpose: Intrahepatic cholangiocarcinoma is a liver tumour that originates from the intrahepatic biliary tract epithelial cells. It is unclear what the optimal treatment is for locally-advanced unrespectable ICCs without distant organ metastasis. In this study, we evaluated the effect of the TARE and systemic chemotherapy sequential treatment on overall survival, progression-free survival, and quality of life in unrespectable ICC cases monitored at our centre.

Methods and materials: We retrospectively reviewed the medical records of 14 patients who were monitored at our clinic, were diagnosed with ICC, and underwent a combined treatment of SIRT-Y90 and chemotherapy with glass microspheres as the first-line treatment. All patients received cisplatin and gemcitabine as a chemotherapy protocol.

Results: One patient developed grade 3 neuropathy due to chemotherapy, one patient developed hepatic encephalopathy. There was no need for postponement of chemotherapy or dose reduction in the remaining 12 patients. There were no treatment-related fatalities. The most common adverse events were fatigue and abdominal pain.

Keywords: Yttrium 90; Inoperable intrahepatic cholangiocarcinoma; Internal radiotherapy; Chemotherapy

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a liver tumour that originates from the intrahepatic biliary tract epithelial cells, represents 10% of primary liver malignancies with an incidence of 1-2/100,000 in western countries and higher rates in Asian countries [1,2]. While its rate of incidence has increased over the last two decades [3], studies suggest that the cause of this surge is related to the increase in the incidence rate of the hepatitis C virus infection, alcoholic liver diseases, and cirrhosis [4]. The best treatment option for cholangiocarcinoma is marginal negative resection. However, the prognosis is poor because the ICC is often locally advanced and surgical treatment is not possible due to the central location of the tumour. It is unclear what the optimal treatment is for locally-advanced unrespectable ICCs without distant organ metastasis. In an ABC-2 randomized phase III study evaluating systemic chemotherapy in biliary tract cancer cases, including locally advanced unrespectable ICC patients, the median survival time with cisplatin + gemcitabine was 11.7 months [5]. Following the publication of this study, a combined treatment with cisplatin and gemcitabine was found to be superior to treatment with gemcitabine alone for this disease group. In subsequent studies and meta-analyses, survival times through systemic chemotherapy alone were short. Nonsurgical tumour ablation methods, such as radiofrequency ablation (RFA), hepatic intra-arterial chemotherapy (HIAC), trans arterial chemoembolization (TACE), and radio embolization (TARE) are useful for local control of the tumour. The treatment options for unrespectable ICC in the National Comprehensive Cancer Network (NCCN) guidelines are systemic chemotherapy, external beam radiation therapy (EBRT), concurrent fluoropyrimidine, arterially directed loco regional therapies (TARE, TACE), or participation in clinical trials [6]. Yttrium-90 (Y90) radio embolization is a form of selective internal radiotherapy (SIRT), also known as TARE, is a minimally invasive, image-guided procedure carrying millions of small beta-emitting Y90 microspheres to the tumour in the liver via a micro catheter placed into the hepatic artery [7]. Two commercial forms of Y90 labelled spheres are available: glass-based (TheraSphere®, MDS, Nordion, Ottowa, Ontario, Canada) and resin-based (SIR-Sphere®, Sirtex, New South Wales, Australia) microspheres [8]. A retrospective study three on-going prospective studies and one phase I study have/are investigating the outcomes of treatment with the TARE and chemotherapy combination, while there are many retrospective and prospective studies evaluating TARE treatment alone in patients with ICC [9-19]. In this study, we evaluated the effect of the TARE and systemic chemotherapy sequential treatment on overall survival, progression-free survival, and quality of life in unrespectable ICC cases monitored at our centre.

Materials and Methods

We retrospectively reviewed the medical records of 14 patients who were monitored at our own clinic, were diagnosed with ICC between 2014 and 2018, and underwent a combined treatment of SIRT-Y90 and chemotherapy with glass microspheres as the first-line treatment. The ICC diagnoses of all patients included in the study were confirmed histopathologically with core needle biopsy or surgical specimen. All patients were evaluated as being unrespectable by a multidisciplinary tumour council, in which a hepatobiliary surgeon was present. Treatment was planned for patients with adequate liver reserve (Child-Pugh Class A).

For the SIRT-Y90 treatment, we first determined the tumour vascularization via celiac-mesenteric angiography, and applied the Tech-99MMAA test injection selectively. In this angiographic study, a cone beam CT examination was performed for all patients during angiography to confirm tumour selectivity and localization. Immediately afterwards, we evaluated its compatibility with the SIRT-Y90 treatment through a sintigraphic study and determined the dose of 90Y volumetrically. One week later, we performed a Y90 vial injection from this location, on which a test injection was conducted with a second celiac-mesenteric angiography. We did not perform a thorough SIRT-Y90 liver treatment in any of the cases; we adopted a selective/super-selective approach by dividing tumours into lobes and/or segments and, where necessary, performed a second line of SIRT-Y90 treatment on other lobes or segments. Two weeks later, we initiated sequential systemic chemotherapy following checks with blood biochemistry. All patients received cisplatin and gemcitabine as a chemotherapy protocol. cisplatin D1 and D8 25 mg/m^2, gemcitabine D1 and D8 800-1000 mg/m^2 were administered every 21 days.

We evaluated the results from these combined treatments in terms of the patient response to treatment, disease-free survival, and mean survival parameters. Median survival times were analysed using the Kaplan-Meier survival analysis. We evaluated the patient response to treatment and the disease-free survival parameters using blood biochemistry-tumour markers in addition to PET-CT and/or MR examinations two months after the combined treatment and every two months thereafter. For the evaluation criteria, we used tumour metabolic activity (FDG uptake) before treatment for the PET-CT examination, and the tumour contrast uptake (m-RECIST) and decrease in tumour markers for the MR examination. The toxicity was graded using NCI-CTCAE v4.

Results

Fourteen patients who were histologically diagnosed with ICC between 2014 and 2018 were included in the study. Ten of the patients (71.4%) were men and four of the patients (29.6%) were women. The median age was 58 (min: 34, max: 77). Three patients (21.4%) had experienced relapses after primary surgery and the remaining 11 patients (78.6%) were patients with unrespectable locally-advanced tumours upon admission. One of the three patients who had underwent an operation previously received treatment with adjuvant capecitabine, one patient with adjuvant gemcitabine, while one patient had not received the adjuvant treatment. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or below. Seven patients (50%) had a score of PS 0, four patients (28.5%) PS 1, and three patients (21.5%) PS 2. Three (21.5%) patients had Child-Pugh Class A cirrhosis. None of the patients had any signs of disease other than liver disease. There were five (35.8%) patients with a solitary lesion and nine (64.2%) patients with multiple lesions. Sequential chemotherapy treatment with SIRT was initiated as the first-line treatment, with the exception of three patients who initially had surgery. The characteristics of the 14 patients are reported in **Table 1**.

Table 1: Patient Characteristics (n=14).

Gender	10 men (71.4%); 4 women (29.6%)
Age, median (range), y	58 (34-77)
Performance status	
PS0	7 (50%)
PS1	4 (28.5%)
PS2	3 (21.5%)
Cirrhosis	3 (21.5%)
>1 lesion	9 (64.2%)
First-line treatment	11 (78.5%)

All patients received cisplatin and gemcitabine as a chemotherapy protocol. Seven patients received one session of TARE treatment, six patients had two sessions, and one patient had three sessions. The average number of chemotherapy sessions after TARE was six (min: two, max: 11 sessions). One patient developed grade 3 neuropathy due to chemotherapy, and the chemotherapy protocol was replaced with capecitabine single agent therapy. One patient developed hepatic encephalopathy after two sessions of chemotherapy, after which the chemotherapy was discontinued. There was no need for postponement of chemotherapy or dose reduction in the remaining 12 patients. There were no treatment-related fatalities. The most common adverse events were fatigue (56%) and abdominal pain (24%). During patient checks in the second month following TARE, a radio logically stable disease (SD) was observed in five patients (35.7%) and partial regression (PR) in nine patients (64.3%). During patient checks in the fourth month, four patients (28.5%) were observed to develop PR, eight patients (57.1%) had SD, and two patients had a progressive disease (PD) (14.4%). One down-staged patient became operable (**Figure 1**).

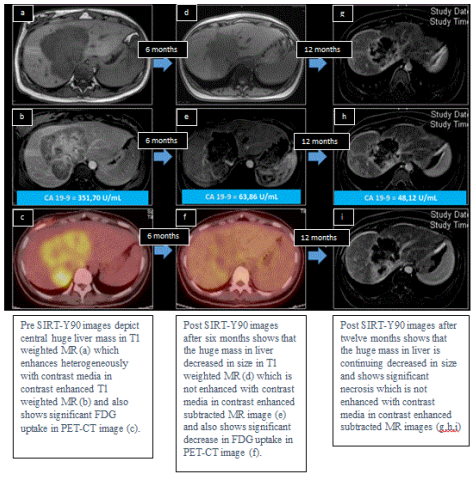

Figure 1: The sixth and twelfth month MR, PET CT images and Ca19-9 values of the patient that became operable after SIRT-Y90 + chemotherapy combined treatment.

The median follow-up time was 21.6 months. Three patients died due to disease progression. The median progression-free survival time was 36.1 months (**Figure 2**).

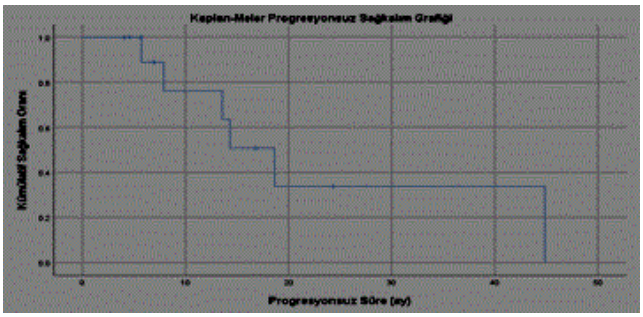

Figure 2: Progression-Free Survival Curve.

The median overall survival time was 49.3 months (**Figure 3**).

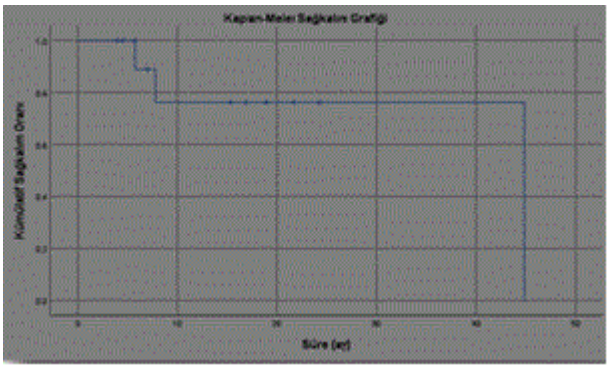

Figure 3: Overall Survival Curve.

Discussion

It is unclear what the optimal treatment is for locally advanced unrespectable ICCs without distant organ metastasis, but the only treatment option shown to deliver benefits through a randomized phase III study is systemic treatment with cisplatin and gemcitabine. In an ABC-2 randomized phase III study evaluating systemic chemotherapy in biliary tract cancer cases, including locally advanced unrespectable ICC patients, the median survival time with cisplatin and gemcitabine was 11.7 months [5]. Following the publication of this study, a combined treatment with cisplatin and gemcitabine became the standard treatment for this disease group, but survival rates are not satisfactory.

Several studies have shown that intrahepatic tumour treatment with SIRT-Y90 is effective and safe for ICC [14-19]. In a retrospective evaluation by Mouli et al., a total of 92 sessions of Y90 radio embolization were applied to 70 patients with unrespectable ICC [14]. Fatigue (54%) and abdominal pain (28%) were reported as the most common side effects. One patient (2%) developed a treatment-related gastro duodenal ulcer. According to WHO criteria, 11 patients developed a partial response (25%), 33 patients had a stable disease (73%) and one patient had a progressive disease (2%). In five patients, the disease could be brought to a respectable state and resected as R0. In a study by Saxena et al., 25 unrespectable ICC patients who underwent resin-based Y90 radio embolization were evaluated [15]. Partial response was observed in six patients (24%), a stable disease in 11 patients (48%), while five patients developed a progressive disease (20%). The most common clinical toxicity was fatigue (64%) and abdominal pain (40%). In terms of biochemical toxicity, two patients had elevated grade 3 bilirubin (8%) and one patient (4%) had elevated alkaline phosphatase. In a retrospective evaluation by Hoffmann et al., 33 patients were administered resin Y90 radio embolization treatment [16]. The median OS was 22 months after treatment and the median OS was 43.7 months after diagnosis. Grade 3 side effects were rarely observed, and there were no treatment-related deaths. Response rates ranged from 11%-36% and median OS was 9.3-22 months according to the results of these three trials evaluating SIRT-Y90 treatment in unrespectable non-metastatic ICC.

When a combination of systemic therapy and liver-directed therapy is applied for patients with locally advanced unrespectable tutors without distant organ metastasis or patients with limited remote organ metastasis, survival rates may be higher in comparison to either chemotherapy alone or loco regional therapy alone. The reason for a lack of phase III randomized trials confirming this is the relatively rare occurrence of intrahepatic cholangiocarcinoma and the more effective use of local ablative therapies in recent years. In terms of prospective studies, one phase I study was found in which TARE and chemotherapy was administered in combination [13]. In this study, capecitabine, which is known to be a radio sensitizer agent, was administered at a dose of 2000 mg/m^2 in combination with SIRT-Y90 and was sought to determine the maximum tolerated dose of Y90. Sixteen patients were administered capecitabine 2000 mg/m^2 D1-14 every 21 days,

and Y90 was administered in the first week of the second course of treatment. With the phase I study being a trial study to determine the maximum dose, it was concluded that it sheds light on the combined use of chemotherapy and SIRT-Y90 for ICC.

The combination of SIRT and chemotherapy treatment is being evaluated in three on-going prospective trials [10-12]. In a phase II study conducted at the Chinese University of Hong Kong, 30 unrespectable non-metastatic ICC patients have been treated with sequential cisplatin and gemcitabine chemotherapy after SIRT-Y90 resin microsphere therapy [10]. In another prospective study in the US, the combined use of gemcitabine and cisplatin with SIRT-Y90 has been evaluated [11]. In the study on 24 patients, SIRT-Y90 was applied on the third or fourth day of the first combined treatment of cisplatin and gemcitabine chemotherapy. For the first and second courses of treatment, cisplatin 25 mg/m^2 and gemcitabine 300 mg/m^2 were administered every 21 days. The cisplatin dose between courses 3-8 was 25 mg/m^2, while the gemcitabine dose was increased to 1000 mg/m^2 and a total of eight courses of chemotherapy were applied. Meanwhile, a third multicentre phase II prospective MispheC study is being carried out in France [12]. In this study, 41 patients have been treated with cisplatin and gemcitabine in combination with SIRT-Y90. In the three prospective studies whose results have not yet been published, certain criteria have been set for the SIRT and KT combined treatment, such as an ECOG performance score of 0-1, no extra-hepatic diseases other than lymph node metastasis, loco regional and systemic treatment-naive patients (only recurring patients after primary surgery have been included), patients with adequate liver, renal and haematological reserves, and a tumour volume no more than 50% of the normal liver volume.

The most helpful study to date on combined therapy is a retrospective study by Edeline et al. in which 24 patients were analysed [9]. In this study, 24 patients with unrespectable ICC were treated with glass microspheres SIRT-Y90, 10 (42%) of the patients received concurrent chemotherapy, 13 (54%) received induction chemotherapy before SIRT-Y90, while one (4%) patient received sequential chemotherapy after SIRT-Y90. Survival results from the combined treatment of SIRT-Y90 and chemotherapy were compared with results from similar patients being treated with cisplatin and gemcitabine alone in the ABC-2 study. There were no side effects in four (17%) patients undergoing the SIRT-Y90 and chemotherapy combined treatment, while grade 1 side effects were observed in 12 (50%) patients, grade 2 side effects in seven (29%) patients, and a grade 3 side effect – hepatic dysfunction-was reported in one (4%) patient. Compared with chemotherapy alone, the median hazard ratio of 0.42 for the OS SIRT + chemotherapy was significantly better (p=0.026). Progression-free survival was found to be 4.5 months longer (p=0.001) and 17 down-staged (46%) patients became operable. The present study has concluded that a combined treatment of SIRT-Y90 and chemotherapy is a promising strategy to treat ICC as a first-line treatment.

We have analysed the safety and the contribution to survival of cisplatin and gemcitabine, a standard combination of chemotherapy administered sequentially with SIRT-Y90, in 14 patients with unrespectable non-metastatic ICC. We administered the combined chemotherapy treatment not concurrently but sequentially, two weeks after the SIRT-Y90 treatment. Of the two currently on-going prospective studies in the literature, one uses concurrent chemotherapy while the other uses sequential chemotherapy. As sequential administration reduces the chemotherapy doses by up to 10%, the patient's systemic treatment is continued without disruption.

When the safety of the combined treatment of SIRT and chemotherapy is examined, no treatment-related fatalities were observed; in terms of grade 3 side effects, one patient developed neuropathy and another patient developed hepatic insufficiency (14% in total), in which case the treatments were changed. Grade 1-2 side effects, limited abdominal pain and fatigue, were seen at a rate of 24% and 56%, respectively. While there is no conclusive data for reliability due to the low number of patients, we can say that we applied the SIRT-Y90 and chemotherapy combined treatment safely at our centre and managed side effects easily, when evaluated together with other retrospective studies.

We have one patient who became operable after being down-staged. Eleven patients became operable after being down-staged in a study by Edeline et al. [9] and five patients in a study by Mouli et al. [14]. We think that the combination of SIRT-Y90 and chemotherapy is a good strategy for a patient who can tolerate it, when it is considered that the only course of treatment in this disease is marginal negative resection. In Mouli et al.'s study, SIRT-Y90 alone was used as a treatment strategy and five down-staged patients were able to be treated; however, there is no evidence of which choice is better because there is no study comparing SIRT-Y90 against the combined treatment of SIRT-Y90 and chemotherapy.

In the trial conducted by Edeline et al. [9], the combination therapy was compared with the chemotherapy sessions in the ABC-2 trial, and the combined treatment of SIRT-Y90 and chemotherapy bimodality therapy was found to have a greater contribution to survival rates than chemotherapy alone. We make no comparisons in our study, but we see that the survival times of the 14 cases we reviewed is much longer than the median survival times reported by other studies on locally advanced unrespectable ICC. The median progression-free survival time of 36.1 months and the median overall survival time of 49.3 months are considerably longer than the reported survival times in the literature. Although, the lower number of patients suggests that these longer survival times may depend not only on the success of the treatment, but also on patient selection.

The limitations of the study are its retrospective nature, lack of a comparative aspect, and the insufficient number of cases to reach a clear conclusion. We support the results of the retrospective study conducted by Edeline et al. with another case series and find it beneficial in terms of a supplementary comparative prospective study in this regard.

In conclusion, we believe that the combined use of SIRT-Y90 and chemotherapy is a promising strategy in locally advanced unrespectable ICC, a disease with limited treatment options.

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