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BRACHYTHERAPY

A Phase I study of high-dose-rate intraluminal brachytherapy as palliative treatment in extrahepatic biliary tract cancer

Gian Carlo Mattiucci[1], Rosa Autorino[1,*], Andrea Tringali[2], Vincenzo Perri[2], Mario Balducci[1], Francesco Deodato[3], Maria Antonietta Gambacorta[1], Giovanna Mantini[1], Luca Tagliaferri[1], Massimiliano Mutignani[2], Alessio Giuseppe Morganti[3]

[1]*Institute of Radiotherapy, Università Cattolica del Sacro Cuore, Rome, Italy*
[2]*Digestive Endoscopy Unit, Department of Surgery, Catholic University of the Sacred Heart, Rome, Italy*
[3]*Department of Radiation Oncology, Catholic University of the Sacred Heart, Campobasso, Italy*

ABSTRACT

PURPOSE: To determine the recommended dose of endoscopically assisted high-dose-rate intraluminal brachytherapy (HDR-192Ir-ILBT) as a palliative treatment of extrahepatic biliary tract cancer.
METHODS AND MATERIALS: Patients with non-metastatic extrahepatic biliary cancer with age <80 years, unsuitable for surgical resection or radiochemotherapy for comorbidities or Eastern Cooperative Oncology Group (ECOG) ≥2 or patients with age ≥80 years were included. They were undergone to implantation of metal stents by endoscopic retrograde cholangiopancreatography followed by HDR-192Ir-ILBT. The initial dose of HDR-192-Ir-ILBT was 15 Gy. Three levels of dose were planned. At each dose level almost three patients were treated, and if no Grade 3-4 toxicity (considering as dose-limiting toxicity) was recorded, dose escalation was applied with 5 Gy increments until the maximum tolerated dose was established. A high dose Iridium-192 after loading system was used (Nucletron Microselectron HDR).
RESULTS: From May 2007 to January 2010, 18 patients underwent HDR-192Ir-ILBT, with one catheter in 12 patients and two catheters in six patients. Three levels of dose were planned: 15 Gy in three patients, 20 Gy in nine patients, and 25 Gy in six patients with daily dose of 500 cGy per fraction. One patient at Dose Level II experienced acute toxicity (cholangitis) related to brachytherapy procedure, so the cohort was expanded. No patient of Level III had a dose-limiting toxicity and we stopped at this dose level waiting to assess the late toxicity that has not yet appeared at the time of the analysis. Six months and 1 year overall survival was 77% and 59%, respectively, with a median of 12 months.
CONCLUSIONS: The recommended dose was defined as 25 Gy in five fractions. It will be used in a Phase II study to better evaluate tumor and symptom control in patients with extrahepatic biliary tract cancer.

Keywords: Brachytherapy; Colangiocarcinoma; Neoplasm; Metal stents; Endoscopy

Introduction

Extrahepatic cholangiocarcinoma is a rare neoplasm with an unfavorable prognosis (1). At the time of diagnosis, they are most often inoperable and palliative therapy is the only option (2).

Endoscopic biliary drainage with a self-expandable metal endoprothesis has become a favored palliative drainage procedure. However, it is often difficult to achieve long-term biliary patency by stenting alone secondary to high rates of stent occlusion caused by tumor ingrowth or overgrowth (3). So, the high-dose-rate intraluminal brachytherapy (HDR-192Ir-ILBT) could be considered as an effective procedure in preventing tumor ingrowth and prolonging biliary patency. In small and retrospective studies, HDR-192Ir-ILBT plus metallic stenting was considered to be feasible and it may lead to an improved quality of life, moreover in patients with poor performance status (4–6).

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Conflicts of interest: None to declare.
* Corresponding author. Radiotherapy, Pol. A. Gemelli, L.go A. Gemelli, 8, 00168 Rome, Italy. Tel.: +39-320-8652716; fax: +39-06-3015-5339.
E-mail address: rosa_autorino@yahoo.it (R. Autorino).

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The optimal HDR-192Ir-ILBT dose is yet to be determined. There are not studies on biliary carcinoma that evaluated the maximum tolerated dose (MTD) of HDR-192Ir-ILBT combined with metal stent, an important prerequisite for an accurate clinical evaluation in Phase II and III trials.

Aim of this study was to determine the recommended dose of endoscopically HDR-192Ir-ILBT after metal stenting as a palliative treatment of extrahepatic biliary tract cancer.

Methods and materials

This trial was a prospective Phase I study, conducted at Catholic University at the Department of Radiotherapy.

Study assessment

Dose escalation

Acute toxicity was evaluated according to the Radiation Therapy Oncology Group (RTOG). Dose-limiting toxicity (DLT) was defined as any acute toxicity Grade 3 or 4 treatment-related non-hematologic toxicity or any acute toxicity Grade 3 treatment-related hematologic toxicity requiring a treatment delay of more than 2 weeks or treatment interruption. Three patients were enrolled at each dose level. If no DLT was observed in Level 1, then the increased dose was administered to three new patients. If any of the first three patients experienced a DLT, then the cohort was expanded to a total of new six patients. If the total number of DLT patients at any dose level was two or more, then dose escalation was discontinued and additional patients were enrolled at the lowest dose level. The maximum tolerable dose was defined as the highest dose at which no more than one DLT was observed among the six patients treated. MTD was also the recommended dose for further study. Three levels of dose were planned: 15 Gy in three patients, 20 Gy in nine patients, and 25 Gy in six patients with daily dose of 500 cGy per fraction. At dose level of 25 Gy, we decided to close the trial and consider it as the recommended dose, to better evaluate the late toxicity related to hypofractionated brachytherapy treatments.

Study objectives

The primary end-point was to find MTD and recommended phase two dose for endoscopically assisted HDR-192Ir-ILBT as a palliative treatment of biliary cancer.

Eligibility

Patients with non-metastatic extrahepatic biliary cancer with age <80 years, unsuitable for surgical resection or radiochemotherapy for comorbidities or Eastern Cooperative Oncology Group (ECOG) ≥ 2 or patients with age ≥ 80 years were included. Patients previously undergone to external beam radiation therapy were excluded.

Treatment

Biliary drainage

Transduodenal technique was used. Few days before the brachytherapy treatment, biliary drainage with endoscopic insertion of self-expandable covered or non-covered metal stents (Boston Scientific, Natick, Mass, or NITI-S Tia Wong Medical) was performed (one for distal tumor or two or more for hilar tumors).

The day of the HDR-192Ir-ILBT treatment, one (for distal tumors) or more (for hilar tumors) 10 Fr biliary dilation catheters (SDBC-10, Wilson-Cook, Winston-Salem, NC) was placed through the metal stents above the level of the stricture. Anchoring flaps was ''hand made'' on the tip of the biliary catheters to avoid migration and dislodgement.

Brachytherapy

A 6 Fr intraluminal radiation catheter (Lumencath, Nucletron, AX Veenendaal, Netherlands) was inserted into the biliary drain as a ''carrier'' for the ^{192}Ir source. The dose was prescribed 1 cm from the source axis and a high-dose Iridium-192 remote after loading system was used (''Nucletron—An Elekta Company'') microselectron HDR.

Patient followup and toxicity assessment

After treatment, patients were evaluated by physical examination, complete blood count, blood chemistry, and abdominal ultrasound sonography at 1 month and subsequently every 3 months and by chest X-ray and abdominal CT every 6 months.

Biliary patency was monitored with serial bilirubin levels, alkaline phosphatase levels. The patients underwent to cholangiography if clinical and laboratoristic findings suggested a stent occlusion.

Acute toxicities were assessed using the Common Toxicity Criteria Adverse Event Version 3.0. For late toxicity, RTOG scale was used.

Statistical analysis

Statistical analysis was performed by MedCalc (www.medcalc.be). Overall survival (OS) was calculated using Kaplan—Meier method.

Results

Patient characteristics

From May 2007 to January 2010, biliary drainage with endoscopic insertion of self-expandable metal stents using the transduodenal technique was performed in 18 patients (nine males and nine females). Median age was 79 years (range, 61—86 years). Patients' characteristics are summarized in Table 1. Twelve patients had a common bile duct tumors, 2 a Klatskin I tumor, 1 a Klatskin II, and 3 a Klatskin III tumor (according to Bismuth classification). In two