Chemotherapy plus percutaneous radiofrequency ablation in patients with inoperable colorectal liver metastases

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Author contributions: Cast J, Breen DJ, Monson JRT and Maraveyas A designed the studies; Sgouros J, Cast J, Garadi KK, Belechri M, Breen DJ, Monson JRT and Maraveyas A performed the research; Sgouros J and Maraveyas A wrote the paper; Cast J, Garadi KK, Belechri M, Breen DJ and Monson JRT reviewed the paper.

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Received: August 15, 2010 Revised: February 10, 2011 Accepted: February 17, 2011 Published online: April 15, 2011

Abstract

AIM: To access the efficacy of chemotherapy plus radiofrequency ablation (RFA) as one line of treatment in inoperable colorectal liver metastases.

METHODS: Eligible patients were included in three Phase II studies. In the first study percutaneous RFA was used first followed by 6 cycles of 5-fluorouracil, leucovorin and irinotecan combination (FOLFIRI) (adjunctive chemotherapy trial). In the other two, chemotherapy (FOLFI RIRI or 5-fluorouracil, leucovorin and oxaliplatin combination) up to 12 cycles was used first with percutaneous RFA offered to responding patients (primary chemotherapy trials).

RESULTS: Thirteen patients were included in the adjunctive chemotherapy trial and 17 in the other two. At inclusion they had 1-4 liver metastases (up to 6.5 cm in size). Two patients died during chemotherapy. All patients in the adjunctive chemotherapy trial and 44% in the primary chemotherapy studies had their metastases ablated. Median PFS and overall survival in the adjunctive study were 13 and 24 mo respectively while in the primary chemotherapy studies they were 10 and 21 mo respectively. Eighty one percent of the patients had tumour relapse in at least one previously ablated lesion.

CONCLUSION: Chemotherapy plus RFA in patients with low volume inoperable colorectal liver metastases seems safe and relatively effective. The high local recurrence rate is of concern.

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Key words: Chemotherapy; Colorectal cancer; Liver metastases; Radiofrequency ablation

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Sgouros J, Cast J, Garadi KK, Belechri M, Breen DJ, Monson JRT, Maraveyas A. Chemotherapy plus percutaneous radiofrequency ablation in patients with inoperable colorectal liver metastases. World J Gastrointest Oncol 2011; 3(4): 60-66 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i4/60.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i4.60

INTRODUCTION

Liver represents the most common site of metastases for patients with colorectal cancer. Fifteen to twenty percent
of patients at initial presentation have synchronous liver metastases and up to 40% will develop metachronous liver metastases despite surgery and adjuvant treatment[9]. Often liver is the sole site of disease recurrence. For these patients the best available treatment, offering the only chance of cure, is surgical resection of the metastases combined with chemotherapy either in the neo-adjuvant or in the adjuvant setting[3]. This group of patients, treated with both modalities seems has a 35% 5-year progression free survival (PFS), a 50% 5-year overall survival and a median survival of around 60 mo[1].

However, not all patients with metastatic disease confined to the liver, even those with low disease burden, are candidates for liver resection. Quite often liver involvement from the metastases is so extensive that safe resection delivering clear resection margins (one of the most important prognostic factors for good final outcome[20]) is not possible. At other times resection is not possible for anatomical reasons or due to patients’ comorbidities.

In patients who cannot have a surgical procedure, systemic therapy (chemotherapy with targeted agents) is the treatment of choice, but it is given with a palliative intent. Median survival in patients with liver only unresectable metastases, treated with the current agents, has not been precisely defined. However, it probably does not differ much from the median survival of patients who have inoperable metastases to other organs or metastases to other organs in addition to inoperable liver metastases (around 20 to 24 mo)[10,16]. In an attempt to improve survival in patients with inoperable colorectal liver metastases, many investigators have used regional therapies such as transarterial chemoembolization, intrahepatic arterial chemotherapy and radiofrequency ablation (RFA)[7,8].

In the latter technique, a probe is inserted intraoperatively, laparoscopically or percutaneously into the target metastases and a monopolar alternating electric current is delivered directly into the target tissue. This causes electrons in the tissue to vibrate back and forth at a high frequency, leading to the production of heat and thereby causing cell death[10].

Results of the use of RFA in colorectal liver metastases have been reported from many centres with promising outcomes and they have been recently reviewed by Stang et al[9]. Most of the papers reviewed in this article were clinical series where RFA was used as a single modality. Chemotherapy had already failed or it was used upon further progression. There was wide variability in the results with the median local progression time in patients who had only RFA varying between 3.5 and 9 mo, systemic PFS varying between 6 and 13 mo and median overall survival varying between 24 and 59 mo[11]. It seemed reasonable to us to study the combination of systemic chemotherapy with RFA as one line of treatment, trying to determine whether PFS could be increased compared to RFA only. Initially we started two Phase II studies where RFA was given first in one study and in the other chemotherapy first (in both studies we used the 5-fluorouracil, irinotecan combination). As later it became obvious that we had patients that could be treated with RFA and in whom irinotecan had already failed, we started a third study where 5-fluorouracil, oxaliplatin combination was used. Preliminary safety and survival data of the first 10 patients included in our prospective Phase II work have been previously reported[11]. Here we present the mature analysis, the efficacy and the toxicity of the combination of the two treatments with data from all participating patients included. Results of the three studies are presented together as the final accrual was not as had been anticipated.

MATERIALS AND METHODS

Patient selection

The target group for our Phase II work was patients with colorectal cancer with had liver-only metastases which, after discussion at the multidisciplinary team meeting, was deemed inoperable for anatomical reasons or due to comorbidities but was potentially treatable with RFA and chemotherapy. To select patients with a high chance of total ablation, patients were deemed eligible for one of the above studies if they had fewer than seven liver metastases of maximum diameter 5 cm where RFA was given first or 7cm where chemotherapy was delivered first. Protocols were subsequently amended to reduce the maximum diameter of the liver metastases eligible for ablation to 3.5 cm as the injection of hypertonic saline prior to the RFA for large lesions (a method used to increase the necrosis diameter) was abandoned. Other inclusion criteria were adequate liver and renal function and adequate performance status (0 or 1 by WHO performance status scale). Previous chemotherapy was allowed (either adjuvant or for metastatic disease) providing it was ceased four weeks before the trial. In cases where there was prior exposure to irinotecan or oxaliplatin, patients received oxaliplatin or irinotecan respectively. Patients who had prior resection of liver metastases or prior RFA treatment were also eligible. All patients had to sign a consent form prior to the commencement of the treatment.

Treatment plan

As already mentioned, in one study RFA of the liver metastases was done first, followed by chemotherapy (adjunctive chemotherapy study). In the other two studies, chemotherapy was delivered initially with RFA to follow (primary chemotherapy studies). In the adjunctive chemotherapy study and in the first primary chemotherapy study, the chemotherapy regime used was 5-fluorouracil, leucovorin and irinotecan combination (FOLFIRI) forthrightly while in the second primary chemotherapy study the 5-fluorouracil, leucovorin and oxaliplatin combination (FOLFOX) regime was used, again every two weeks. Both regimes were used as per the FOCUS trial through a venous device (Hickman catheter or peripherally inserted central catheter)[12]. In the adjunctive chemotherapy study, chemotherapy was given for six cycles, while in both primary chemotherapy studies patients could receive 12 cycles in total provided they were responding to chemo-
therapy, with radiological assessment every 4 cycles to identify the earliest possible opportunity for RFA.

The percutaneous RFA technique we used has been described before\(^{13}\). It was undertaken using a water-cooled RFA system (Radionics, Burlington, Mass, USA) under ultrasound or computer tomography guidance and under sedation with midazolam and fentanyl. For some larger lesions hypertonic saline was injected prior to the RFA to increase the necrosis diameter. Subjects remained in-patients for 24 h to make sure no acute complications developed and they underwent further imaging 3-5 d later as out-patients to assess total ablation of metastases.

**Evaluation of response**

We determined response to chemotherapy using the response evaluation criteria in solid tumours (RECIST)\(^{14}\). The RFA technique was deemed successful if the post-procedure scan revealed a roughly spherical area of non-enhancement in the area of the treated metastasis. The procedure was also classified as successful even if there was some symmetrical peripheral enhancement (thought to be normal reactive changes following ablation).

**Patient follow up**

Following completion of treatment, patients were followed up at regular intervals. In most cases computer tomography scans of the thorax, abdomen and pelvis as well as the tumour markers CEA and CA19-9 were carried out every three months until progression or death.

**Statistical analysis**

PFS was measured from inclusion in the study to progression or death (in case death occurred prior to documented progression) and overall survival (OS) from inclusion in the study to death. Statistical comparisons, where needed, were carried out using the Chi-square and Fisher’s exact test. The Kaplan-Meier method was used to calculate progression free and overall survival curves\(^{15}\). The SPSS statistical package was used and a \(P\) value of < 0.05 was considered statistically significant for all analyses. The expected end point of the studies was PFS of 12.5 mo. That was based on data dating from around 2000 (when our trials commenced) indicating median PFS in a study using RFA alone\(^{16}\), and on the hypothesis that chemotherapy would cause an increase of 25% on the PFS achieved with RFA alone. A sample size calculation was not performed.

The protocols received local research ethics committee approval (regulatory numbers 06/00/095, 06/00/096 and 12/02/14) and were run under the Doctors and Dentists Exemption scheme (DDX).

**RESULTS**

**Patient characteristics**

Between September 2000 and August 2004, 13 patients participated in the adjunctive chemotherapy study, 10 patients were included in the primary FOLFIRI study and 8 (5 of whom had already participated in the two previously mentioned studies) in the primary FOLFOX study. Patients’ characteristics are shown in Table 1 and the main point to note is the geriatric nature of this population which reflects the decision-making quandaries (both in terms of co-morbidities, mostly vascular, but also patient preference) in these patients, despite relatively pauci-metastatic disease. Patients participating in the adjunctive chemotherapy study tended to have fewer and smaller liver metastases compared to the patients included in the two primary chemotherapy studies.

**Efficacy in the adjunctive chemotherapy study**

The 13 patients in the adjunctive chemotherapy study had a total of 20 liver metastases (the maximum diameter of 18 lesions was smaller than 3.5 cm) ablated and subsequently received 3-6 (median 6) cycles of FOLFIRI. RFA was well tolerated with mild local pain occurring in some patients. The initial radiological result of metastasis ablation was not satisfactory for 4 lesions (one larger than 3.5 cm) in 4 different patients. In two cases the procedure was repeated and the radiological outcome was then satisfactory (overall good radiological result in 90% of the metastases ablated) (Table 2). Most patients completed the planned course of 6 cycles of chemotherapy with only minor side-effects. As can be seen in Table 3, one patient discontinued chemotherapy early as he developed bacterial endocarditis requiring a prolonged course of antibiotics. Another patient died suddenly during treatment. The cause of death was determined post-mortem as acute cardiomyopathy and was thought to be related to 5-fluorouracil toxicity.

Median PFS and overall survival of these patients were 13 (95% CI: 3.1-22.9) and 24 mo (95% CI: 17-31.1) respectively. For 60% of the patients, the site of initial progression was only in at least one liver lesion previously treated with RFA, for 10% both in RFA-treated lesions and at other sites and for 30% of patients only in other organs.

**Efficacy in the primary chemotherapy studies**

The 17 patients who participated in the two primary chemotherapy studies (one patient participated in both studies) received 2-12 cycles of chemotherapy. Chemotherapy was generally well tolerated. One patient discontinued treatment early due to deterioration of her general condition thought to be related to the chemotherapy (FOLFOX group) and one patient as died due to sepsis while on chemotherapy (FOLFIRI group). As can be seen in Table 3, 22% of patients responded to chemotherapy and in another 55% of patients their disease remained stable. In 8 cases (44%) with a total of 11 liver metastases (7 with maximum diameter \(\leq 3.5\) cm), RFA was carried out subsequently. Ablation was not carried out in patients with progressive disease, in patients with stable disease but with metastases which could not be safely ablated and
in one more patient who withdrew her consent. For 5 lesions (one with diameter > 3.5 cm) the initial radiological result was not satisfactory. Three of them were re-treated (at least two further attempts for each lesion) with a final satisfactory radiological result (overall good radiological result 73%) (Table 2). RFA was well tolerated with mild pain in the right hypochondrium being the most frequent side-effect of the procedure.

Median PFS of participants in the primary chemotherapy studies was 10 mo (95% CI: 7-13). All patients who had RFA, relapsed in at least one ablated lesion and 33.3% of them simultaneously developed extrahepatic progression. Median overall survival was 21 mo (95% CI: 18.3-23.7).

**DISCUSSION**

We have presented here the final results of our three
phase II studies where chemotherapy and RFA were given in a sequential way in patients with small volume inoperable colorectal liver metastases. To the best of our knowledge this is the first full report of a prospectively designed study using both modalities in this patient category.

A limitation of the data presented is the small number of patients included in each study. At the design of these studies, it was anticipated that more patients would participate in each trial but it became apparent that for only a small minority of patients with low volume liver disease a resection would either not be indicated, not possible or would be turned down by the patient. Therefore a summative report was thought the only way lessen this numerical limitation and thereby reach useful clinical conclusions.

Treatment was reasonably well tolerated. Apart from mild pain occurring in a few patients and for a few days following the local ablative technique, no other side effects or complications developed in patients treated with subcutaneous RFA.

Chemotherapy was similarly well tolerated although two patients died during treatment (mortality 6.4%) and another two discontinued treatment early due to complications related directly or indirectly to chemotherapy. Mortality for this geriatric population treated with chemotherapy seems to be in line with literature figures[17].

We found that DFS in the adjunctive chemotherapy group was 13 mo and in the primary chemotherapy group 10 mo. We can not conclude that the combination that uses RFA initially is superior to the combination using chemotherapy initially as patients in the primary chemotherapy studies had larger liver metastases and also almost 50% of the patients were unable to receive RFA treatment.

The primary end point of 12.5 mo median DFS in our patients was met only in the adjunctive chemotherapy study. Patients who participated in the two primary chemotherapy studies had a shorter median DFS, probably attributable to the fact they had higher tumour burden and less than 50% were able to have RFA in addition to chemotherapy. The suggestion that the combination of the two treatment modalities is superior to chemotherapy only seems to be supported by the final results of the CLOCC study where systemic therapy with FOLFOX plus or minus bevacizumab was compared to the same systemic therapy plus RFA in patients with colorectal cancer and fewer than nine liver metastases[18]. The results of this EORTC multicenter study showed that patients treated with chemotherapy and RFA had longer median DFS than patients treated only with chemotherapy (16.8 mo vs 9.9 mo).

Of concern is the high recurrence rate (81.25%) at the ablated lesions which did not seem to be related to the size of the metastases. More worrying is the fact that local recurrence was documented in all patients who had RFA once their metastases were down-sized with primary chemotherapy. This recurrence rate is higher than those reported in previously published studies although great variation exists. For example, in two studies where laparoscopic RFA was used, the recurrence rate of the lesions ablated ranged between 6.7% and 28%[21,22] while in two other studies where patients had the procedure percutaneously, local recurrence rate was approximately 50%[23,24]. In a meta-analysis published after our studies were closed, Muller et al[23] showed that the two most important factors predicting low recurrence rates in primary or metastatic liver tumours treated with RFA are the surgical approach for placing the electrodes and lesions smaller than 3 cm. Neither of these criteria was met in our current studies and this possibly played a part in the high local recurrence rate. It seems that the chemotherapy used in the current trials did not affect the high local recurrence rate.

In conclusion the combination of RFA with chemotherapy in patients with low volume inoperable colorectal liver metastases can be safely delivered and seems to be relatively effective. The CLOCC study may perhaps answer the question of whether the combination is better than chemotherapy only. It would also very interesting if the combination treatment were to be compared with RFA as sole treatment treatment in different arms of a Phase III trial. For such a study only patients with metastases smaller than 3 cm should be included.
ACKNOWLEDGMENTS

The authors thank the patients for participating in these studies and the staff of the Hull Cancer Unit Trials office for their support and hard work. Also Aventis for an unrestricted grant.

COMMENTS

Background
Chemotherapy and radiofrequency ablation are used in the treatment of colorectal liver metastases. Usually radiofrequency ablation is used once chemotherapy has failed. Limited data exist regarding the use of both treatment modalities as a single line of treatment.

Research frontiers
There is one randomised study by EORTC comparing chemotherapy plus Radiofrequency ablation (RFA) to chemotherapy only but so far results have been published in an abstract form.

Innovations and breakthroughs
The current article is the first paper with results of the efficacy and tolerability of the combination of chemotherapy and RFA collected prospectively.

Applications
The results of this paper show that the combination of chemotherapy and RFA in patients with colorectal liver metastases is safe. Confirmatory studies are needed for establishing its efficacy.

Terminology
RFA is a technique where a probe is inserted into the target metastases and a monopolar alternating electric current is delivered directly into the target tissue. This causes electrons in the tissue to vibrate back and forth at a high frequency, leading to the production of heat and thereby causing cell death.

Peer review
The patient number is rather low, and the study population in this pooled analysis is heterogeneous. However, these trials were conducted well, each patient gave written informed consent and local research ethics committee approval was also obtained. Adequate statistical methods were applied and of note, the authors also discussed the main limitations of their analysis within the discussion section appropriately. The obtained data are presented adequately and the results are discussed within the current scientific standard of CRC research.

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