Cancer Treatment Reviews 50 (2016) 148–154

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Selective internal radiation therapy for liver metastases from colorectal cancer

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ARTICLE INFO

Article history:
Received 18 March 2016
Received in revised form 2 September 2016
Accepted 3 September 2016

Keywords:
Yttrium spheres
Colorectal cancer
Survival
Review

ABSTRACT

Liver metastases are often the dominant site of metastatic disease in colorectal cancer. Selective internal radiation therapy (SIRT) involves embolising radiolabeled spheres (SIR-Spheres) into the arterial supply of the liver. This review assesses the effectiveness and toxicity of SIRT in the treatment of metastatic colorectal cancer liver metastasis when given alone or with systemic or regional hepatic artery chemotherapy. We reviewed only randomised controlled trials comparing SIRT and chemotherapy (systemic and/or regional) with chemotherapy alone, or comparing SIRT alone with best supportive care. Only four randomized trials were identified. Due to heterogeneity of the patients and treatments received it was not possible to perform a formal meta-analysis, therefore this is a descriptive analysis only. All studies included patients with either liver only or liver dominant metastatic colorectal cancer. Two trials compared SIRT alone and SIRT with chemotherapy first line. The first with only 21 patients revealed a significant improvement in PFS and median survival with SIRT. The larger second study SIRFLOX of 530 patients comparing SIRT and current standard first line FOLFOX chemotherapy (+/− bevacizumab) with standard FOLFOX +/− bevacizumab alone. There was no improvement in overall PFS with addition of SIRT. In chemotherapy refractory patients SIRT and systemic chemotherapy (fluorouracil) improved progression free survival but not overall survival. A final study (63 patients) compared SIRT and regional chemotherapy (floxuridine) with regional chemotherapy alone in first line showed no significant difference in progression free survival and median survival. There remains a lack of evidence that SIRT improves survival or quality of life in patients with metastatic colorectal cancer. The overall survival results from SIRFLOX combined with FOXFIRE and FOXFIRE Global are awaited.

Introduction

Colorectal cancer is the third leading cause of cancer death in the United States and Europe [1,2]. The liver is often the dominant site of metastatic disease and is a significant clinical problem. While resection of liver metastases results in five year survival rates of 30–40% [3] and offers the potential for cure, fewer than 20% of patients with metastatic disease are suitable for resection at diagnosis [4]. Chemotherapy plus or minus biological agents can also result in significant tumour down-staging allowing for subsequent resection of liver metastases. For these patients five year survival of 33% can be achieved. A proportion of patients with initially unresectable liver disease become suitable for resection following systemic chemotherapy (12.5–40%) [5–7]. So although liver resection can achieve long term survival, most patients have extra-hepatic disease or are unresectable due to tumour size and number, location, or inadequate residual liver. For patients with unresectable disease, the 5 year survival remains just over 10% and hence exploration of targeted treatments for liver only or liver dominant disease is potentially important [8]. In an attempt to improve upon the long term outcome for those patients who do not have resectable disease and to achieve better control of liver metastases, multiple loco-regional strategies have been trialed, including radio-frequency ablation, intra-arterial chemotherapy and selective internal radiation therapy (SIRT).

Normal liver parenchyma has a poor tolerance to radiation, limiting the ability to use external beam radiotherapy. SIRT involves embolising radiolabeled spheres into the arterial supply of the liver. Tumours within the liver receive their blood supply almost entirely from the hepatic artery whereas the normal liver

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http://dx.doi.org/10.1016/j.ctrv.2016.09.007
0305-7372/

is supplied mainly from the portal vein. Therefore, infusion of radiolabeled microspheres into the arterial system results in delivery of effective doses of radiation to the tumour without causing intolerable toxicity to the normal liver [9,10].

Yttrium-90 is a high energy beta particle emitting radioisotope that can be incorporated into glass or resin microspheres. There is one commercially available product for use in colorectal cancer liver metastases. This is the SIRSphere (SIRTex Medical, Sydney, Australia), which is a resin microsphere with an average diameter of 32 μm ± 10 μm embedded with Yttrium-90. Prior to administration an angiogram is performed to ensure that the arterial anatomy is favourable to proceed. Macroaggregate albumin labelled with Technetium 99 m (99mTc-MAA) is then injected into the hepatic artery to determine the degree of shunting from the liver to the lung or gastrointestinal tract. Arterial shunting of greater than 20% is a contraindication to proceeding because of the risk of radiation pneumonitis and gastric/duodenal ulceration. Other recognised toxicities includes abdominal pain, fever, lethargy, fatigue and a transient rise in liver function tests [10,11].

SIR-Spheres received FDA approval for the treatment of hepatic metastases secondary to colorectal cancer in 2002 following a trial of 74 patients by Gray et al. [12]. Patients with non-resectable liver metastases from colorectal cancer where randomised to hepatic artery chemotherapy with floxuridine with or without the addition of SIRT. This study included patients receiving first line treatment and 10 patients who had received prior palliative chemotherapy. Response rate and time to progression of disease within the liver were significantly improved with the addition of SIRT (response rate 18% vs 44% and PFS 9.7 months vs 15.9 months respectively) but there was no improvement in overall survival. Non-randomised trials of SIRT have shown significant activity in the treatment of liver metastases from colorectal cancer both in combination with chemotherapy and when given alone, in both first line treatment and in the treatment of chemotherapy refractory disease [13–18]. When the appropriate pre-treatment assessments are performed, SIRT has been shown to have tolerable toxicity.

The purpose of this review is to summarise randomised controlled trial evidence for the use of SIRT in the management of advanced colorectal cancer. We previously published a Cochrane review in 2009 [19] and this updated review includes subsequently published studies.

Methods

We performed an electronic search of MEDLINE (OVID 1966 to 2016) and EMBASE (from 1980 to 2016) using search strategies in Appendix 1. The proceedings of relevant oncology meetings (ASCO from 1985 until 2015, and ASCO GI from 2004 until 2016) and bibliographies of references and reviews were also searched. Articles published in any language were considered for inclusion. The titles and abstracts of every record retrieved were screened independently by two reviewers (AT,TP). The full text article of all potentially eligible trials were then reviewed.

We included all randomised controlled trials that included patients with unresectable liver metastases from colorectal cancer assessing the use of SIRT either alone or in combination with systemic chemotherapy, regional chemotherapy or both. The primary endpoint of interest was progression free survival and secondary endpoints; overall survival, tumour response, toxicity/adverse events, quality of life and rate of hepatic resection.

Individual patient data was obtained where possible and hazard ratio determined for time to event data. Analysis was performed in order to analyse patients with and without extra-hepatic metastatic disease separately where possible.

Results

Following the planned search 4 randomised controlled studies were identified. The characteristics of the 4 studies, including primary and secondary endpoints are summarized in Table 1 and results are summarized in Table 2. Two studies compared SIRT and systemic chemotherapy with systemic chemotherapy alone in first line treatment. The first study [20] (van Hazel 2004) compared SIRT and fluorouracil and leucovorin (5FU/LV) with 5FU/LV alone in 21 patients. It showed an improvement in PFS in patients randomized to 5FU/LV and SIRT compared with 5FU/LV alone as first line therapy with a PFS of 11.5 months in the SIRT and chemotherapy group compared with 4.6 months in the chemotherapy alone group ($p = 0.004$). Survival was also improved (median survival 29.4 months versus 11.8 months, $p = 0.008$), and response rate increased (73% versus 0). The benefit in PFS persisted in the 15 patients without extra-hepatic metastases (HR 0.23 (CI 0.06–0.96)).

The second study [21] (van Hazel 2016), SIRFLOX, an international, multi-centered, open label RCT compared SIRT and mFOLFOX ± bevacizumab with mFOLFOX and bevacizumab as first line treatment in 530 chemo-naïve mCRC patients with liver metastases plus or minus limited extrahepatic metastasis (fewer than 5 lung nodules of ⩽1 cm diameter or a single nodule of ⩽1.7 cm diameter, and/or lymph node involvement with a single anatomic area of <2 cm diameter). Extrahepatic disease had a predefined limit of 40%. 530 patients were randomized from Oct 2006 to April 2013 to either mFOLFOX ± bevacizumab or mFOLFOX ± bevacizumab + SIRT with a median follow up of 36.1 months. The primary end point was progression free survival at any site as assessed by independent centralized radiology review and secondary end points summarized in Table 1. Patient characteristics were well balanced and median age was 63 years. Extra hepatic metastasis was present in 40% of cases in both arms. Interestingly 90% of patients had synchronous metastases at the time of diagnosis and 45% had their primary tumour in situ. 18 (7%) patients could not have SIRT after randomization and 3 (1%) did not receive any study treatment due to compromised performance status, serious adverse events or disease progression before study treatment. PFS at any site was similar in both arms (median PFS control 10.2 months vs SIRT 10.7 months; HR 0.93; 95% CI; 0.77–1.12, $P = 0.43$). There was also no difference in overall response rate at any site 68.0% vs 76.4% in control and SIRT arm respectively ($P = 0.113$). Overall response rate in the liver was improved with the addition of SIRT 68.8% vs 78.7%; $P = 0.042$ but there was no improvement in liver resection rate after treatment (13.7% vs 14.2%, $p = 0.857$). Planned subgroup analysis of patients with liver only metastatic disease did not show any improvement in progression free survival ($n = 318$, HR 0.9 (0.70–1.15)). Overall survival data is expected to be presented in 2017 as a combined analysis with the FOXFIRE and FOXFIRE Global studies to give enough statistical power to detect meaningful impact of SIRT.

Beyond first line, a single study randomized 44 patients to SIRT and systemic chemotherapy (fluorouracil) or systemic chemotherapy alone in the treatment of chemotherapy refractory metastatic colorectal cancer (third line treatment) with liver only disease [22] (Hendlisz 2010). The median progression free survival was 4.5 months in the SIRT and chemotherapy group compared with 2.1 months in the chemotherapy alone group ($p = 0.03$). There was no significant benefit in survival with the addition of SIRT ($p = 0.8$, median survival chemo + SIRT: 10 months vs. chemo: 7.3 months), however 10 patients in the chemotherapy alone arm subsequently received SIRT monotherapy. The objective response rate was not significantly improved with the addition of SIRT and remained low (chemo + SIRT: 10% vs chemo: 0%, $p = 0.22$), although one patient in the SIRT arm subsequently underwent surgical resection of metastases.