

ORIGINAL ARTICLE

Transplant oncology: assessment of response and tolerance to systemic chemotherapy for metastatic colorectal cancer after liver transplantation – a retrospective study

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SUMMARY

Solid organ recipients have a 2–5 fold increased risk of malignancy compared to the general population. Because of the broader indications for transplantation, it is anticipated that an increasing number of organ graft recipients will present with malignancy. There are limited data about responses and tolerance to chemotherapy in solid organ transplanted patients. Twenty-three of 46 colorectal cancer (CRC) patients with nonresectable liver metastases who had undergone liver transplantation (LT) in three different studies were included. All patients had received chemotherapy both prior to LT and after LT, at recurrence of metastatic CRC (mCRC). Adverse reactions (grades 3–4) and clinical and radiological outcome were retrospectively registered. Overall survival was determined from start of palliative chemotherapy after LT. No graft rejection was observed. Chemotherapy for mCRC was overall well-tolerated and there was no increased bone marrow toxicity registered after LT; however, mucositis and diarrhea were more frequent in post-LT chemotherapy. Median overall survival from start of palliative chemotherapy after LT was 13 months. No graft loss was observed when chemotherapy for mCRC was given to LT recipients who had developed nonresectable metastases. Overall, the chemotherapy for mCRC was well-tolerated, induced responses, and long-term survival was obtained in some patients.

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Key words

chemotherapy, colorectal cancer, liver transplant recipients, overall survival

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Introduction

New potent immunosuppressive regimens have reduced the acute rejection rates after transplantation, and advances in surgical skill and critical care medicine have improved 1-year survival across all transplanted organ types. The indication for liver transplantation (LT) has broadened in the last years and LT is today considered

standard of care for patients with end-stage liver failure as well as for selected patients with pretransplantation malignancies like hepatocellular carcinoma [1]. Recurrent and *de novo* malignancies are the second leading causes of late death in solid organ transplant recipients, following age-related cardiovascular disease [2]. Compared to the general population, the overall risk of developing malignancy appears to be three to five times higher in

transplanted patients [3,4]. Systemic chemotherapy will thus likely have to be considered for an increasing number of organ transplant recipients in the future.

Choosing the optimal oncological treatment for patients developing post-transplant metastatic cancer is a substantial clinical challenge. There are limited and diverging data describing tolerability, safety and efficacy of chemotherapy in transplant recipients with malignant disease [5–8].

The aim of the present study was primarily to report the tolerability and clinical response to chemotherapy in liver transplant recipients included in three different clinical trials investigating LT as treatment of nonresectable hepatic metastases from colorectal cancer (CRC). Moreover, since all patients also had received chemotherapy for metastatic CRC (mCRC) prior to LT, data of toxicity related to chemotherapy administered before and after LT were available.

Materials and methods

Patient selection

All patients included in this project were included in one of three studies investigating LT as treatment for patients with nonresectable CRC liver metastases, SECA-I (23 patients; NCT01311453), SECA-II (15 patients; NCT01479608), and RAPID (five patients; NCT02215889). Two patients from the RAPID study included in this report had received a full donor liver graft since this became available, obviating the need for the RAPID procedure. These studies had obtained approval from the Regional Ethics Committee and Institutional Review board (S-05409, 2010/2856, and 2013/580, respectively) and all patients had signed informed consent before inclusion in the study protocols. A total of 43 mCRC patients were included in these three LT studies from 2006 to 2017. Thirty-three patients had relapse of mCRC after LT. Ten patients received chemotherapy directly after relapse. Twenty-three patients underwent metastasectomy or radiofrequency ablation, and 13 of these received subsequent chemotherapy. Thus, in total 23 patients received chemotherapy owing to relapse of the colorectal malignancy after LT and all these patients were included in this study (Fig. 1). Prior to LT, the patients had received one to four lines of chemotherapy for mCRC. No adjuvant chemotherapy had been provided after LT. The immunosuppressive regimen administered after LT has previously been reported [9]; in brief, maintenance immunosuppression after LT was sirolimus (mTOR

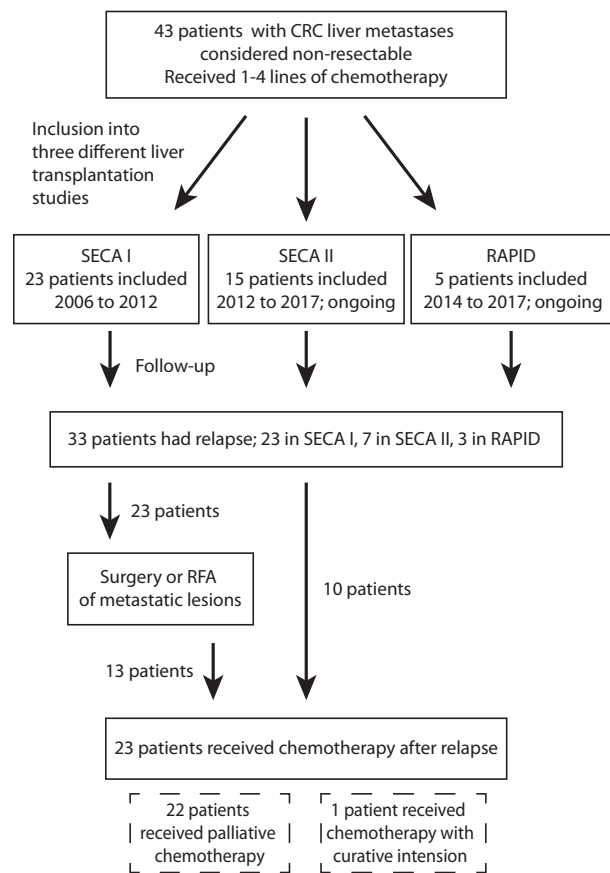


Figure 1 Flowchart of the treatment sequence of colorectal cancer patients starting chemotherapy after liver transplantation.

inhibitor) and mycophenolate mofetil. The patients stopped treatment with mycophenolate mofetil at start of chemotherapy after LT.

All patients in this study had received a full donor liver graft, and they received chemotherapy after LT between 7 January 2009 and 27 July 2016.

Data collection

Data about chemotherapy provided before and after LT, including chemotherapy-related adverse events (AEs) were retrospectively registered from medical records. Response to chemotherapy was collected from radiology reports together with the individual clinical evaluation by the treating oncologist, as noted in the medical records. In short, the responses were classified and interpreted in line with RECIST version 1.1; complete response (CR) was defined as the disappearance of all target lesions, partial response (PR) was defined as a decrease in the sum of the longest target lesion diameter of at least 30%, and progressive disease (PD) was defined as an increase in the sum of target lesion

diameter of at least 20% or the appearance of new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD [10]. Clinical benefit (CB) was defined CR, PR, or SD.

At relapse after LT, surgery, chemotherapy, or other oncological treatment modalities were provided at the discretion of the oncologist responsible for the patients. Adverse events grades 3–5 according to Common Terminology Criteria for Adverse Events [11] were registered. Seven patients received chemotherapy at Oslo University Hospital, 16 patients received their further treatment at nine different hospitals in Norway.

Statistical analysis

Statistical analyses were performed with IBM SPSS version 23, Armonk, NY, USA. Comparison between two groups was calculated using the logrank test and chi-squared test. *P*-values less than 0.05 were considered significant. Survival data from the start of palliative chemotherapy were estimated by using the Kaplan–Meier method. Cutoff date for survival analysis was 24 October 2017.

Results

Patient characteristics

Baseline clinical characteristics at the time of start of chemotherapy after LT and the oncological treatment administered before LT are given in Table 1 and Fig. 1. All patients received chemotherapy after LT owing to relapse of mCRC. Median time from primary diagnosis to LT was 20 months (range 5–40 months), and median time from resection of the primary tumor to LT was 14 months (range 5–40 months). Fourteen patients (64%) had progressive disease at the time of LT. All patients had good performance status (ECOG 0 or 1). Before the start of chemotherapy after LT, only one patient had a reduced bone marrow function (grade 3 thrombocytopenia), and no other grades 3–4 toxicities were reported. Median disease-free survival after LT was 6 months (range 1–33 months) for these patients receiving palliative chemotherapy for mCRC after LT. Median time from LT to start of chemotherapy was 19 months (range 4–90 months), see Fig. S1.

Chemotherapy after LT

At start of palliative chemotherapy after LT, 10 of 22 patients (45%) had metastases to only one organ, seven

Table 1. Baseline characteristics.

Age, years, median (range)	
At primary diagnosis	53 (42–62)
At start post-LT chemotherapy	58 (45–72)
Primary tumor characteristics, <i>n</i> (%)	
<i>KRAS</i> mutation	9 (39%)
<i>BRAF</i> mutation	0 (0%)
Colon primary	14 (61%)
Rectum primary	9 (39%)
(y)pT1–T2	3 (13%)
(y)pT3–T4	20 (87%)
Treatment prior to primary surgery, <i>n</i> (%)	
Preoperative chemotherapy + CRT	1 (4%)
Preoperative chemotherapy	4 (17%)
Chemotherapy prior to LT, <i>n</i> (%)	
Irinotecan pre-LT	18 (78%)
Oxaliplatin pre-LT	19 (83%)
5-FU pre-LT	23 (100%)
Bevacizumab pre-LT	8 (35%)
EGFR inhibitor pre-LT	6 (26%)
Other treatment prior to LT, <i>n</i> (%)	
Liver resection	3 (13%)
Portal vein embolization	1 (4%)
Liver RFA	1 (4%)

5-FU, 5-fluorouracil; CRT, chemoradiotherapy; LT, liver transplantation; RFA, radiofrequency ablation.

patients (30%) had metastases to two organs and five patients (22%) had metastases to three or more organs. The chemotherapy provided after LT was either combination regimens including 5-fluorouracil/folinic acid with irinotecan or oxaliplatin (Nordic FLIRI or Nordic FLOX [12,13], respectively), or monotherapy of either capecitabine or irinotecan. Nine of 23 patients received chemotherapy combined with an anti-EGFR antibody and six patients received bevacizumab (Tables S1 and S2). Median duration of chemotherapy, from the start of first cycle to the end of last cycle was 11 months (range 0–58 months). Five patients started treatment at a reduced dose; one of these also received the chemotherapy with prolonged intervals. Three of these five patients received dose-reduced chemotherapy prior to LT.

Toxicity

Toxicity of chemotherapy before LT

Before LT, 17 of 23 patients (74%) had one or more grades 3–4 AEs during chemotherapy for mCRC. The majority of AEs was bone marrow toxicity and neuropathy (Table 2). All patients with neuropathy had received an oxaliplatin-based regimen.

Table 2. Chemotherapy-induced grades 3–4 toxicity before and after liver transplantation ($n = 23$).

Toxicity	Pre-LT, n	Post-LT, n
Bone marrow	14	11
Diarrhea	1	8
Nausea	1	2
Skin	2	4
Mucositis	0	5
Lacrimation	0	1
Hand-foot syndrome	1	2
Anaphylaxia	3	1
Neuropathy	4	1
Fatigue	0	1
Proteinurea	0	1
Total	26	37

Toxicity of chemotherapy after LT

After LT, there was no evidence of graft rejection, but 19 of 23 patients (83%) had registered one or more grades 3–4 events related to chemotherapy for mCRC. The majority of these reactions were impaired bone marrow function, diarrhea, or mucositis (Table 2). Five of eight patients who experienced diarrhea had received an irinotecan-based chemotherapy regimen. All patients who had a grades 3–4 mucositis had received a fluoropyrimidine-based regimen. Patients with grade 3 skin toxicity had received an anti-EGFR antibody. Four patients had to stop chemotherapy after 1–2 cycles owing to gastrointestinal toxicity (grade 3 mucositis and diarrhea), and three of them did not receive further chemotherapy. None of the 20 patients with CMV-titers measured regularly after chemotherapy administration after LT had CMV infection. Furthermore, there were no reports of grade 5 toxicity.

Comparing toxicity of chemotherapy before and after LT

There was no significant difference in bone marrow or skin toxicity reported before and after LT (Table 2). Nine patients (39%) experienced grades 3–4 diarrhea or mucositis related to chemotherapy administered after LT. In comparison, only one patient had experienced diarrhea when receiving chemotherapy prior to LT ($P = <0.001$). The sirolimus concentration was similar in patients with grades 3–4 diarrhea, mucositis, and skin toxicity compared to patients without these toxicities (median 9.8 and 10.9 $\mu\text{g/l}$, respectively). No relationship between toxicity related to chemotherapy after LT and the number treatment lines given prior to LT was observed (data not shown).

Response to chemotherapy after LT

Twelve of 17 patients (70%) who were evaluated for response were considered to have CB in first line of chemotherapy, 8 of 14 patients (57%) had CB in second line, and three of seven in third line of treatment. Some patients had CB from even four and five lines of chemotherapy (Table 3). Two patients obtained long-lasting SD (22 and 58 months, respectively) from chemotherapy regimens to which they previously had developed resistance to before LT.

Survival

Median overall survival (OS) from the start of palliative chemotherapy after LT was 13 months (range 1–60 months, Fig. 2). One patient was excluded from the OS analysis since chemotherapy was administered prior to complete resection of a pulmonary metastasis, and therefore, by definition, did not receive palliative chemotherapy; the patient is still alive more than 11 years after LT and 7 years after the start of chemotherapy. Two patients died from other causes than cancer progression; one patient had a sudden cardiac death, and one patient deceased from an intracranial bleeding owing to an accident at home.

Patients who had metastases in the liver graft at the time of initiating palliative chemotherapy had a median survival of 12 months compared to 17 months for patients with extrahepatic involvement ($P = 0.084$). The number of lines of chemotherapy provided prior to LT did not seem to have an impact on OS (data not shown). Three patients discontinued chemotherapy after 1–2 cycles owing to toxicity, two of them lived for 1 month and one lived for 10 months after first cycle of chemotherapy, respectively.

Other treatment modalities after LT

Six patients received radiotherapy after the start of palliative chemotherapy, two of these patients also received stereotactic body radiation therapy (liver metastases) and another patient was treated by stereotactic radiosurgery (brain metastases). Some of the patients received palliative radiation therapy at different time points to different locations. The most frequent cause for palliative radiation therapy after the start of palliative chemotherapy was bone metastases. Other treatment modalities provided to the patients before and after the start of palliative chemotherapy after LT are shown in Table S3.

Table 3. Response to different lines of chemotherapy after liver transplantation.

Treatment line	1st	2nd	3rd	4th	5th
Number of patients in each treatment line, <i>n</i>	23	14	8	5	3
Best response reported, <i>n</i>					
Partial response	7	0	0	1	0
Stable disease	5	8	3	2	1
Progressive disease	5	6	4	2	1
Not assessed for response	6*	0	1	0	1

*Four patients stopped treatment owing to toxicity (grade 3 mucositis, diarrhea, or neutropenia), one patient developed symptoms of bone metastases within 1 week after the first cycle, stopped chemotherapy and died shortly thereafter, and one patient decided to stop chemotherapy after one cycle, and died 7 weeks later owing to intracranial bleeding as a result of an accident at home.

Discussion

This is, to our knowledge, the largest cohort of solid organ transplant recipients studied for tolerance and response to chemotherapy and the only study comparing toxicity and response to chemotherapy before and after transplantation.

Our study showed that chemotherapy administered for mCRC 4–90 months after a liver transplantation was safe and not associated with graft loss. This was also the case in a recent study by Rousseau *et al.* [14] which reported outcome from different malignancies and chemotherapy regimens in both kidney and liver transplanted patients. However, other studies have reported chemotherapy-induced liver graft failure [8]. Graft rejections or graft loss has also been reported in solid organ recipients treated with immune checkpoint inhibitors [15,16].

It has been hypothesized that CRC behaves more aggressively in immunosuppressed transplant recipients

[17] and two studies have reported significantly lower survival of CRC in solid organ recipients compared to the general population [17,18]. A study by Verran *et al.* [19] reported that patients developing mCRC after transplantation had a median OS of only 2 months from time of diagnosis. Furthermore, Martin *et al.* [6] also reported poor outcome from chemotherapy given to liver transplanted patients. However, we have previously shown that CRC patients developing pulmonary metastases after LT do not have an increased growth rate compared to a control group of nontransplanted rectal cancer patients despite ongoing immunosuppressive treatment [9].

In this study, the majority of patients achieved PR or SD during the chemotherapy regimen after LT, with a median OS of 13 months from the start of treatment. Two patients had long-lasting stable disease to a chemotherapy regimen that they had progressed on before LT, and one patient survived for 60 months from start of palliative chemotherapy after LT. Previous studies have reported a median OS of 11–13 months from the start of second-line chemotherapy after progression on first-line treatment [20]. In general, second-line of chemotherapy of mCRC is considered a standard treatment throughout the world. Patients receiving the best supportive care after failing all lines of standard chemotherapy have a median OS of approximately 6 months [21]. Thus, our results suggest that the patients had benefit from palliative chemotherapy when diagnosed with post-transplant metastatic disease.

In our study the incidence of grades 3–4 bone marrow toxicity was similar from chemotherapy provided before and after LT, but chemotherapy-induced grades 3–4 diarrhea (35%) and mucositis (22%) were significantly more frequent after LT. In nontransplanted patients receiving Nordic FLOX, Nordic FLIRI or

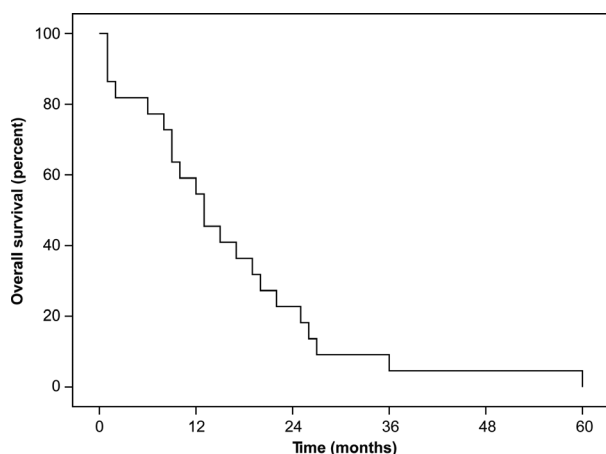


Figure 2 Kaplan–Meier plot. Overall survival from start of palliative chemotherapy after liver transplantation.

FOLFIRI as first-line treatment, 10–15% and 1–2% had been reported with grades 3–4 diarrhea and mucositis, respectively [12,22].

One of the most commonly reported side effects of mTOR inhibitors like sirolimus is mucositis/stomatitis which appears to be dose-dependent [23,24]. None of the patients had diarrhea or mucositis grades 3–4 before starting palliative chemotherapy after LT, but it is reasonable to suggest that a combination of chemotherapy and mTOR inhibitor will increase the risk to develop these side effects, and in particular, the risk of diarrhea in patients receiving irinotecan-based regimens.

Only three of 23 patients (13%) had to stop chemotherapy owing to toxicity in this study compared to five of seven patients (71%) reported by Martin *et al.* [6].

It is of great importance to be aware of the possibility and severity of these side effects, and take appropriate precautions to avoid them since patients who discontinued chemotherapy owing to toxicity had poor outcome. Liver graft recipients generally require less immunosuppression compared to other solid organ transplant recipients [25]. Since we did not observe any graft rejection after administration of chemotherapy, dose reduction of immunosuppressive treatment or even termination of immunosuppressive treatment during chemotherapy may be considered in selected cases. Graft rejection in liver transplanted patients will in most cases be treated successfully with no graft loss.

We acknowledge that the study is limited by the relatively small number of patients and its retrospective approach. However, there are very limited data available on response, side effects and survival in solid-organ transplant recipients receiving chemotherapy for metastatic disease.

In conclusion, liver transplant recipients who develop nonresectable CRC metastases after LT may respond to chemotherapy with acceptable tolerance and obtain extended survival compared to the best supportive care.

Authorship

SD: contributed to the idea. TMS and SD: collected the data. TKG, SD and TMS: did the statistical analysis. TMS, SD, TKG and PDL: participated in writing the article. All the authors reviewed the final article.

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Conflict of interest

The authors have declared no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier plot. Time from liver transplantation to start of chemotherapy.

Table S1. Different chemotherapy regimens administered before and after LT.

Table S2. Chemotherapy regimens given after liver transplantation.

Table S3. Other treatment modalities after liver transplantation ($n=22$).

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