Surgical Oncology 25 (2016) 298–307

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

The influence of chemotherapy-associated sinusoidal dilatation on short-term outcome after partial hepatectomy for colorectal liver metastases: A systematic review with meta-analysis

Kim M.C. van Mierlo [a, 1], Junfang Zhao [a, 1], Jos Kleijnen [b, c], Sander S. Rensen [a], Frank G. Schaap [a], Cornelis H.C. Dejong [a, d], Steven W.M. Olde Damink [a, e, *]

[a] Department of Surgery, Maastricht University Medical Centre & NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Universiteitssingel 40, 6229 ER, Maastricht, The Netherlands
[b] Kleijnen Systematic Reviews Ltd, York, United Kingdom
[c] CAPHRI School for Public Health and Primary Care, Maastricht University, Universiteitssingel 40, 6229 ER, Maastricht, The Netherlands
[d] GROW School for Oncology and Developmental Biology, Maastricht University, Universiteitssingel 40, 6229 ER, Maastricht, The Netherlands
[e] Department of HPB Surgery & Liver Transplantation, Institute for Liver and Digestive Health, Royal Free Hospital, University College London, London, United Kingdom

ARTICLE INFO

Article history:
Received 31 March 2016
Accepted 30 May 2016

Keywords:
Sinusoidal dilatation
Sinusoidal obstruction syndrome
SOS
Partial hepatectomy
Postoperative liver failure
Chemotherapy-associated liver injury

ABSTRACT

Summary background data: Hepatic sinusoidal dilatation (SD) is a histopathological entity that occurs in up to 75% of patients undergoing oxaliplatin-based chemotherapy for colorectal liver metastases (CRLM).
Objective: To study the influence of SD on outcome after partial hepatectomy in patients with CRLM.
Methods: Medline, Embase, CENTRAL, LILACS and CINAHL were searched for studies published between 01.01.2004 and 09.06.2015 with keywords: "sinusoidal obstruction syndrome", "hepatic veno-occlusive disease", and "Stuart-Bras syndrome". Studies comprising adults who underwent partial hepatectomy for CRLM with grading of SD and registration of postoperative morbidity and/or mortality were included. Risk of bias and quality of studies were evaluated with the Quality In Prognosis Studies Instrument (QUIPS) and modified GRADE framework.
Results: Search strategies produced 2007 hits from which 23 and 13 articles were extracted for qualitative and quantitative analyses, respectively. Meta-analysis on the influence of SD grade 2–3 *vs.* SD grade 0–1 on postoperative overall morbidity showed an odds ratio (OR) of 1.26 [95% CI 0.74, 2.15]($p = 0.40$), an OR of 1.03 [0.15, 6.89]($p = 0.98$) for liver failure, an OR of 1.21 [0.23, 6.35]($p = 0.82$) for overall mortality, and an OR of 3.52 [0.31, 39.91]($p = 0.31$) for liver-related morbidity. QUIPS showed a low to high risk of bias for studies, and GRADE showed very low quality of evidence per outcome.
Conclusions: No significant effect of SD grade 2–3 on short-term outcome after partial hepatectomy was found. However, the data on which this conclusion was based were not very robust and therefore no solid conclusions could be drawn.

1. Introduction

Sinusoidal dilatation (SD) is a common manifestation of hepatotoxicity that occurs in patients with colorectal liver metastases (CRLM) after administration of oxaliplatin-based chemotherapy [1–3]. Regimens based on the platinum containing agent oxaliplatin are used extensively as neo-adjuvant therapy to downsize initially irresectable CRLM, with convincing response rates and survival outcomes [4–6]. However, liver injury is demonstrated in over 75% of patients [1,3].

SD is part of a broad range of liver injuries due to specific drugs,

* Corresponding author. Department of Surgery, Maastricht University Medical Centre & NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Universiteitssingel 40, 6229 ER, Maastricht, The Netherlands
E-mail addresses: k.vanmierlo@maastrichtuniversity.nl (K.M.C. van Mierlo), junfang.zhao@maastrichtuniversity.nl (J. Zhao), jos@systematic-reviews.com (J. Kleijnen), s.rensen@maastrichtuniversity.nl (S.S. Rensen), frank.schaap@maastrichtuniversity.nl (F.G. Schaap), chc.dejong@mumc.nl (C.H.C. Dejong), steven.oldedamink@maastrichtuniversity.nl (S.W.M. Olde Damink).
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.suronc.2016.05.030
0960-7404/

in conjunction with sinusoidal obstruction syndrome (SOS). SOS is macroscopically identified as 'blue liver' and microscopically characterized by injury of the sinusoidal endothelial cells (SECs), parenchymal lesions (e.g. SD and peliosis), venular lesions, and fibrosis. Various pathogenic factors have been described to contribute to these histopathological changes [7]. Key features of oxaliplatin-induced toxicity are its reaction with reduced glutathione and F-actin depolymerization, which results in rounding up and subsequent dehiscence of SECs and obstruction of sinusoidal blood flow leading to SD and erythrocyte extravasation [1,8–12]. Activation of hepatic stellate cells (HSC) results in neodisposition of collagen bundles in the perisinusoidal space which, in combination with subendothelial fibroblast activation in the terminal hepatic vein, leads to fibrotic venular occlusion. In the last stage of SOS, dense perivenular fibrosis is observed and hepatic vein lumina can no longer be identified [13].

The grading system of Rubbia-Brandt et al. classifies all histological features of SOS including SD, and is routinely used for stipulating severity [1,2]. In most studies, SD functions as the standard for liver damage. Reversibility of sinusoidal injury is discussed widely, and although human and animal models show ceasing of pathological features at repeated hepatic resection [2,14], other studies show persistence or progression of lesions even after cessation of chemotherapy [15].

Clinical importance of SD is reflected in the development of hepatomegaly, ascites, splenomegaly, thrombocytopenia, portal hypertension, and systemic elevation of liver enzymes [16–19]. With regard to liver surgery, a diminished preoperative functional reserve, (transient) postoperative liver failure, higher morbidity rates and longer hospital stay, as well as impairment of postoperative liver regeneration have been reported [20,21]. Numerous studies have shown a negative influence of SD on postoperative outcome [20,22,23], yet others could not reproduce this [24–29]. This systematic review with meta-analysis aimed to determine the influence of SD on short-term outcome after partial hepatectomy in patients with CRLM.

2. Methods

2.1. Criteria for considering studies for this review

An extensive study protocol can be found in Appendix 1 (Supplementary data). This review was conducted and reported in compliance with the PRISMA and MOOSE guidelines, and followed the Cochrane protocol for prognostic factor reviews [30–32]. Studies were considered eligible for inclusion in this review when they met the following criteria: (I) studies comprising adults (≥18 years old) with CRLM, (II) who underwent minor or major partial hepatectomy, (III) with postoperative histological grading of SD in liver tissue distant from the tumour according to the scoring system of Rubbia-Brandt, (IV) and with registration of overall morbidity, liver-related morbidity, liver failure, or overall mortality (≤90 days or in-hospital) after liver resection. Case reports, comments/editorials, published abstracts, and reviews were rejected, in addition to records not covering the subject or including non-adults (<18 years old). Cohort studies including patients who underwent liver surgery for malignancies other than CRLM were included albeit that this group comprised less than 30% of the total study population. No distinction was made between first and repeated resections, and studies with patients who underwent preoperative portal vein embolization (PVE) were allowed for inclusion since an effect of PVE on outcome in patients with SD was observed in a single study only [33].

2.2. Search methods for identification of studies

Search strategies in international databases Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences Literature (LILACS) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were performed between 01.01.2004 and 09.06.2015 using the following keywords (adjusted to the relevant database and including synonyms): "sinusoidal obstruction syndrome", "hepatic veno-occlusive disease", and "Stuart-Bras syndrome". Publication date of the search strategy was set from January 2004 onwards because the widely used criterion for scoring SD from Rubbia-Brandt et al. was developed in this year [1]. The Embase strategy was independently peer reviewed by a second information specialist using the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist [34]. No language restrictions or other limitations were applied. Details of the search strategy can be found in Appendix 2.

2.3. Data collection and analysis

Records were downloaded in EndNote® X7 and duplicates were automatically and manually removed. All abstracts were screened by two independent reviewers (KvM, JZ), and in the rare case of no consensus the abstract was considered for full-text scanning. One of the reviewers (KvM) screened citations of all full-text articles for additional records on the base of title or abstract. Previous research from the authors on this topic resulted in an extensive own library which was also checked for references. Records considered for full-text assessment were screened independently by two reviewers (KvM, JZ). Full-text articles were screened for inclusion in *qualitative* analysis and/or *quantitative* analysis. Articles without postoperative mortality in the study population were described qualitatively due to lack of contribution to quantitative analysis.

2.4. Data extraction and definitions

Data extraction was performed independently by two reviewers (KvM, JZ) using a data extraction form in Excel specifically created for this study. Any dissimilarity in data was discussed and solved by consensus. Inter-observer agreement was calculated with Cohen's kappa coefficient. All information on study design and characteristics, main outcomes and possible overlap in cohort data was recorded. SD was defined according to the grading system of Rubbia-Brandt et al. [2]. In short; SD 0: absence of signs of SD; 1: mild SD (centrilobular involvement limited to one-third of the lobular area); 2: moderate SD (centrilobular involvement extending in two-thirds of the lobular area) and 3: severe SD (complete lobular involvement or centrilobular involvement extending to adjacent lobules with bridging congestion). In all analyses, 'SD' was defined as the presence of grade 2 or 3 SD whilst 'no SD' was defined as grade 0 or 1. We considered SD grade 2–3 clinically more relevant than grade 0–1, since rupture of sinusoidal wall integrity is present in grade 2 and higher. Major liver resections were defined as resection of ≥3 Couinaud segments. All outcomes were measured between 30 and 90 days after partial hepatectomy or during initial hospital admission ('in-hospital'). Primary outcomes were overall morbidity, liver failure, and overall mortality after liver resection. Secondary outcome was liver-related morbidity after partial hepatectomy. Overall morbidity was defined as any complication (i.e. surgical and medical, excluding death) after liver resection, irrespective of severity [35]. Mortality was defined as death due to any cause after liver resection. Since consensus on the definition of liver failure is lacking [36–38], definitions were specified in the Results Section. Liver-related morbidity was