Clinics in Surgery

Research Article
Published: 28 Oct, 2022

Unresectable Intrahepatic Cholangiocarcinoma: Retrospective Clinical Trial of Percutaneous Hepatic Perfusion (PHP-M) with Melphalan

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Abstract

Background: Unresectable intrahepatic Cholangiocarcinoma (iCC) has a poor overall prognosis and there is no established second line therapy. The purpose of this pilot study was to evaluate the efficacy of Percutaneous Hepatic Perfusion with high dose Melphalan (PHP-M) as second/last line therapy in patients with advanced or recurrent iCC.

Methods: In this single center approach we retrospectively analyzed 10 patients (mean age 59 Standard Deviation (SD) 10 years) with advanced iCC with PHP-M in a standardized protocol. Overall Survival (OS) from initial diagnosis and from first PHP-M were analyzed. Adverse Effects (AE) were graded by Clavien Dindo and by the CIRSE classification.

Results: Median OS was 26.3 months from initial diagnosis (SD 13.3 month) and 13.7 months (SD 7.0 month) from first PHP-M. The patients had an average tumor load of 263.8 ml (SD 241.7 ml) and were treated with 21 PHP-Ms in total. Tumor load after the first cycle of PHP-M treatment was reduced to 241.7 ml (SD 268.5 ml), and disease control by RECIST 1.1. was achieved in 7/10. No AEs of grade 4 Clavien Dindo or higher occurred during the procedures.

Conclusion: PHP-M can be a safe and feasible therapy for patients with advanced iCC as a last line therapy.

Keywords: Intrahepatic cholangiocarcinoma; PHP-M; Chemosaturation; Tumor load; Overall survival

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Received Date: *07 Oct 2022*
Accepted Date: *20 Oct 2022*
Published Date: *28 Oct 2022*

Citation:
Schneider MA, Warnke MM, Tiede M, Reese T, Wohlmuth P, Hoedtke J, et al. Unresectable Intrahepatic Cholangiocarcinoma: Retrospective Clinical Trial of Percutaneous Hepatic Perfusion (PHP-M) with Melphalan. Clin Surg. 2022; 7: 3587.

Introduction

Intrahepatic Cholangiocarcinoma (iCC) is a severe disease with a poor prognosis and with moderate but increasing incidence [1,2]. Symptoms are presented late and include unspecific signs such as abdominal pain (38%), jaundice due to biliary obstruction (28%), and frequently these tumors are incidentally diagnosed on imaging [3]. The only curative approach is surgery, however only 15% to 30% of iCCs are resectable at the time of diagnosis [3,4]. Without treatment, a patient's median OS is poor, at 3 to 4.7 months [5,6]. In unresectable tumors, first line chemotherapy is Cisplatin and Gemcitabine. The benefit of this regimen was shown initially by Valle et al. to improve median OS to 11.7 months [7], a meta-analysis by the same author group confirmed the beneficial effect [8]. If second line treatment is necessary due to progress or side effects, Capecitabine has been used in selected cases. However, there is no generally established single second line therapy in this situation [9]. Percutaneous isolated Hepatic Perfusion with Melphalan (PHP-M) has been licensed in the European Union (EU) with a CE mark. PHP-M has the advantage of administering high doses of melphalan at the hepatic tumor site while using filters to prevent surplus chemotherapy from recirculating from the liver into the body. This comes at the cost of being a technically advanced

procedure, currently available in selected centers only. Although evidence to date is limited, liver targeted therapies such as PHP-M also hold promise and it's feasibility to non-resectable patients with high tumor load has been demonstrated earlier [10]. Our hypothesis was that PHP-M chemosaturation can be feasible in non-resectable patients as a last line therapy with acceptable complication rates – to be evaluated regarding safety and efficacy in a single center pilot study.

Materials and Methods

Patients

As a single center approach a total of 14 patients were retrieved from the hospital's database with initial treatment from 2013 to 2020. If no further follow up of at least 3 months after PHP-M was available, patients were excluded (n=2) or if data were incomplete (n=2). Ten patients remained for detailed analysis (mean age 59 ± 10 years; range from 38 to 73 years; 3 males, 7 female). The histology of cholangiocarcinoma was determined by explorative surgery in two cases, Endoscopic Retrograde Cholangiopancreatography (ERCP) in one case, and in the remaining cases by transcutaneous biopsy. No primary liver disease was found in any of our patients before the diagnosis of the iCC. The cohort of 10 patients included 3 postsurgical patients. One patient had received previous extended left hemihepatectomy, one had a segment V resection and, after recurrent iCC, one patient had a segment VI resection. There was intrahepatic tumor recurrence in all three cases. 8 of 10 patients were given systemic chemotherapy before their first cycle of PHP-M while the other 2 had been treated by TACE. Of the 8 patients with chemotherapy, 7 patients received 1st-line therapy with Cisplatin/Gemcitabine. For reasons unknown to us in an outside center, one patient received Capecitabine as a 1st-line therapy, only to switch to Cisplatin/Gemcitabine later. Because of tumor progression one of the 1st-line patients later received a 2nd-line therapy with Mytomycin/Capecitabine. Inclusion criteria for PHP-M were an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 with adequate hematological, renal, and hepatic function (hemoglobin >8 g/dl; leukocyte count >3.000/nl; platelets >65,000/nl, serum creatinine <130 µmol/L, bilirubin ≤ 2 × Upper Limit of Normal (ULN)), liver dominant disease (lymph nodes <10 mm, lung nodules <8 mm), and a specialized tumor board vote. Exclusion criteria for the PHP-M procedure were widespread disease (e.g., distant extrahepatic metastases), recent history of transient ischemic attacks, heart failure or significant chronic obstructive or restrictive pulmonary disorder, as well as liver disease exceeding Child Pugh A or ECOG >1. All patients were planned for second or third treatment in case of Stable Disease (SD) or Partial Response (PR) according to the RECIST 1.1 criteria. In case of Complete Response (CR) or Progressive Disease (PD) patients did not receive an additional PHP. Safety was an major issue in our evaluation; thus all procedures were evaluated retrospectively graded by the Clavien-Dindo Classification [12] and the CIRSE classification [13]. All Clavien-Dindo complications that arose during the inpatient stay as part of the procedure were recorded. It seems necessary to mention, that patients were contributed from our center to the retrospective evaluation of Marquard et al. [10]; the data overlap are two patient data sets.

PHP-M chemosaturation procedure - technical description

For the PHP-M procedure, a dedicated filter system (CHEMOSAT® 2nd generation, Delcath Systems Inc., New York, NY, USA) was used as previously described [11]. For arterial infusion, a 6 French catheter was positioned via femoral access into the common hepatic artery, and a 2.7 French microcatheter (ProGreat®, Terumo, Japan) was used for selective chemoperfusion of the liver in 1-3 supraselective positions. For venous access, an 18 French double-balloon catheter (Delcath, see above) was inserted through the contralateral femoral vein and facilitated isolation of the hepatic inferior cava segment. Next, the upper balloon was inflated in the right atrium, and as the subsequent step was pulled back to cover and occlude the diaphragmatic portion of the inferior vena cava. As the third step, the lower balloon was inflated in the hepatic portion of the vena cava below entry of the hepatic veins. This position was controlled for tightness in a separate series. A separate access in the right internal jugular vein was used for blood return. During the infusion phase, 500 ml of melphalan solution was administered at a rate of 0.4 ml/sec; with intermittent fluoroscopy to ensure correct flow. This transarterial chemoperfusion was performed with a dosage of 3.0 mg/kg ideal body weight up to a maximum dose of 220 mg of melphalan (Alkeran®). As suggested by the manufacturer, a subsequent washout was performed with the filtration circuit running for 30 min after cessation of the arterial infusion. To maintain an Activated Clotting Time (ACT) above 400 s, which was mandatory for safe extracorporeal hemofiltration, heparin was administered as needed. The procedures were performed under general anesthesia. For the first night following the procedure, all patients were monitored in intensive or intermediate care units for blood pressure, coagulation, access sites and laboratory findings. On the day after the procedure, in our institution, G-CSF (Neurolasta®) was given routinely to all patients. Staging and restaging was based on the available external and internal imaging by two of the authors using the RECIST 1.1. criteria. In most cases, the patients underwent a chest and abdominal CT scan prior to their first PHP-M. Two patients were examined by abdominal MRI. Further follow-up imaging was carried out every 2 to 4 months using either CT or MRI.

Statistical methods

Continuous data were summarized as means ± standard deviations or as medians [25th and 75th percentiles] as appropriate. Differences between pre- and post-PHP measurements were presented with medians and inter-quartile ranges and analyzed with the Wilcoxon-Pratt signed-rank test. Overall survival from diagnosis and PHP treatment were estimated with the Kaplan-Meier method. Kaplan-Meier plots and median overall survival was shown (Figure 1). Pre- and post-PHP tumor load was shown with a scatterplot (Figure 2). All p-values were two-sided and a p-value <0.05 was considered significant. All calculations were performed with the statistical analysis software R (R Core Team, 2020).

Results

Median OS was 26.3 months from initial diagnosis (SD 13.3 months) and 13.7 months (SD 7.0 months) from the first PHP-M. The Kaplan Meier curves are given in Figures 1a, 1b.

All patients completed a first cycle of PHP-M (n=10), 7/10 patients received a second and 3/10 patients received a third cycle of the procedure. Details of the baseline data and of the laboratory findings before and in the days 1 to 5 following first PHP-M are given in Table 1. Platelets exhibited a marked decrease, and hemoglobin declined by more than two points, but bilirubin and serum creatinine were stable before and after the therapy. The average tumor load was high in the cohort with an average of 263.8 ml (SD 241.7 ml) before intervention. This load was reduced to an average of 241.7 ml (SD 268.5 ml) following the first cycle. However, the reduction

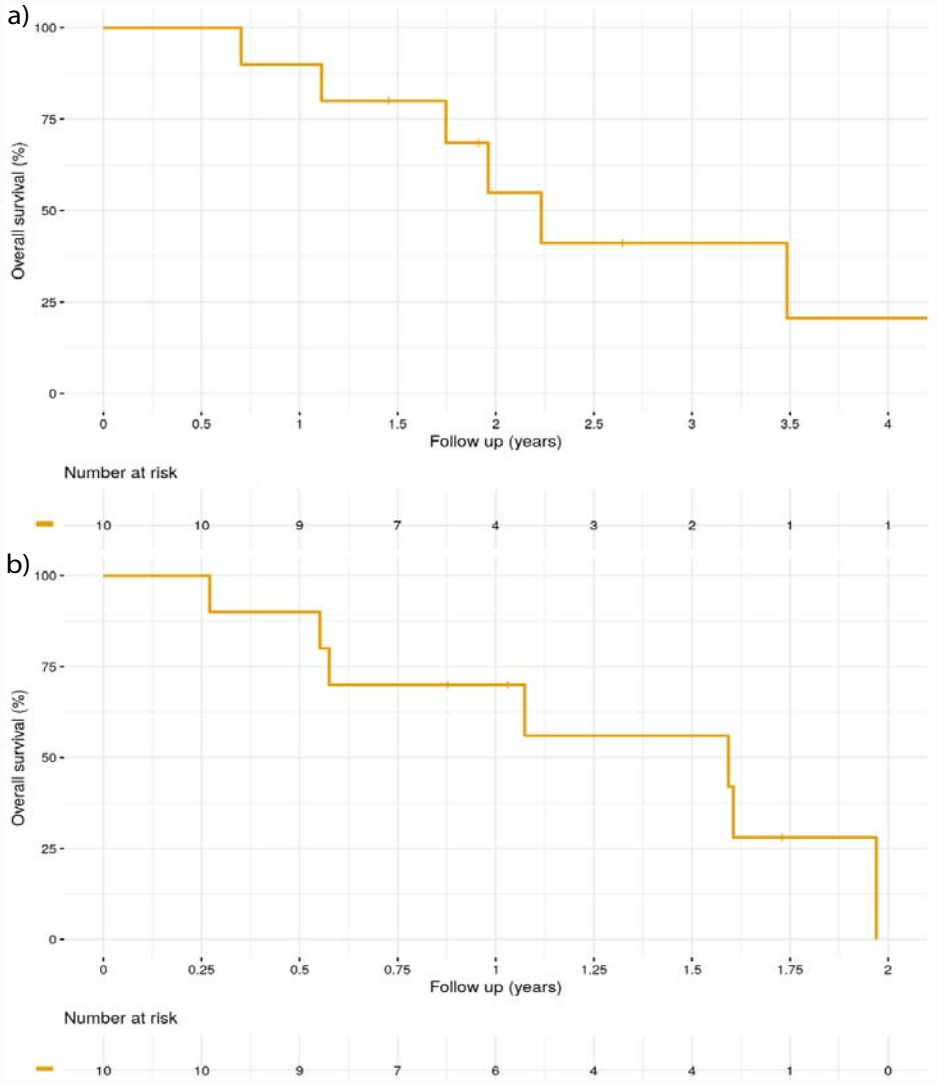

Figure 1: Kaplan Meier curves of overall survival following initial diagnosis and following the first PHP-M treatment.
a) Overall survival Kaplan-Meier curve from initial imaging; also given are the numbers of patients at risk.
b) Overall survival Kaplan-Meier curve from initial PHP-M treatment, also given are the numbers of patients at risk.

in the absolute tumor load did not frequently translate into a partial remission on the RECIST 1.1 scale: Following the initial PHP-M, there were 7 patients with Stable Disease (SD) and 3 patients with Progressive Disease (PD) (2 cases with intrahepatic progression and in 1 case a combined intrahepatic and systemic progression). The seven patients with SD received a second cycle of therapy. In the following restaging imaging of those 7 patients, 3 patients still had SD and underwent a third cycle of therapy. Retrospectively evaluating the complications in our patients in one patient (HHJ), during the setup of the initial PHP-M cycle, one of the central lines from the jugular vein was inappropriate and was presumed to be extravascular, and there was a broadening of the mediastinum in fluoroscopy. For safety reasons, this procedure was terminated; and completed two weeks later without any problems (CIRSE Grade 1). The patient did not develop any symptoms. In another case (BA), peripheral femoral artery occlusive disease was aggravated following the procedure and necessitated a stent graft and a patch (Clavien Dindo 3). In the other 8 patients no major-complications referring to the Clavien Dindo Classification (Clavien Dindo ≥ 3) occurred during the postprocedural inpatient stay of 4 days. Between the hospital stays no major-complication has been reported to us.

Discussion

The revised guidelines for unresectable iCC suggest interventional therapeutic approaches in patients with tumor progression under first-line systemic chemotherapy [14], such as TARE, TACE and Percutaneous Hepatic Perfusion (PHP). Our preliminary data on PHP-M show an average OS of 26.3 months after initial diagnosis and of 13.7 months following the first treatment in a cohort of intrahepatic cholangiocarcinoma's with advanced tumor load and with failed first-line therapy. This OS following PHP-M compares equally or favorably to previous reports: PHP in iCC has been evaluated only in small cohorts but results are promising with long-lasting tumor stabilization in selected patients with cholangiocarcinoma [10,15]. Thus PHP seems feasible to serve as a potential last-line palliative treatment option, even after prior liver surgery [16]. The work of Marquard et al. [10] with a reported median OS was 26.9 months from initial diagnosis and 7.6 months from first PHP is initial work in this field evaluating chemosaturation, recruiting 15 patients from 9 centers throughout Europe. In the submitted work however, we

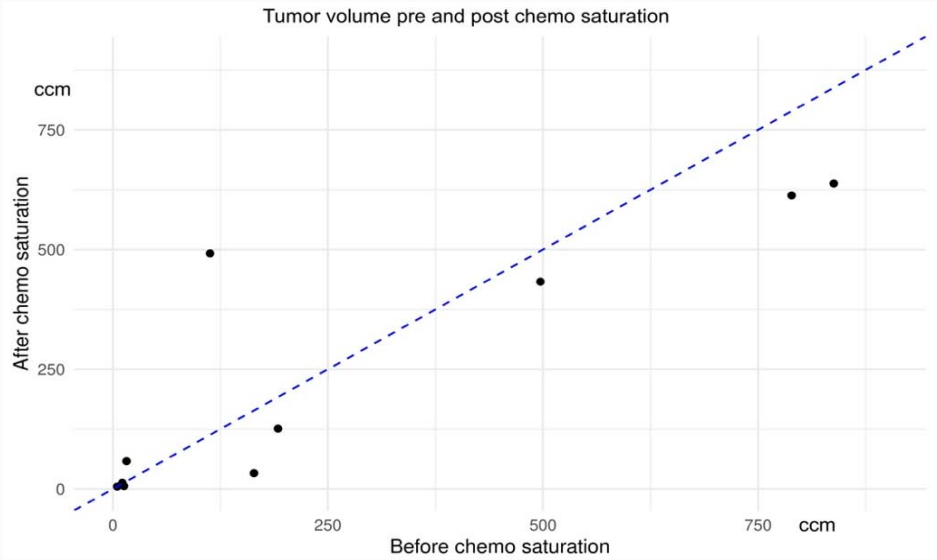

Figure 2: Scatterplot demonstrating tumor volume before and after the 1st cycle PHP-M.

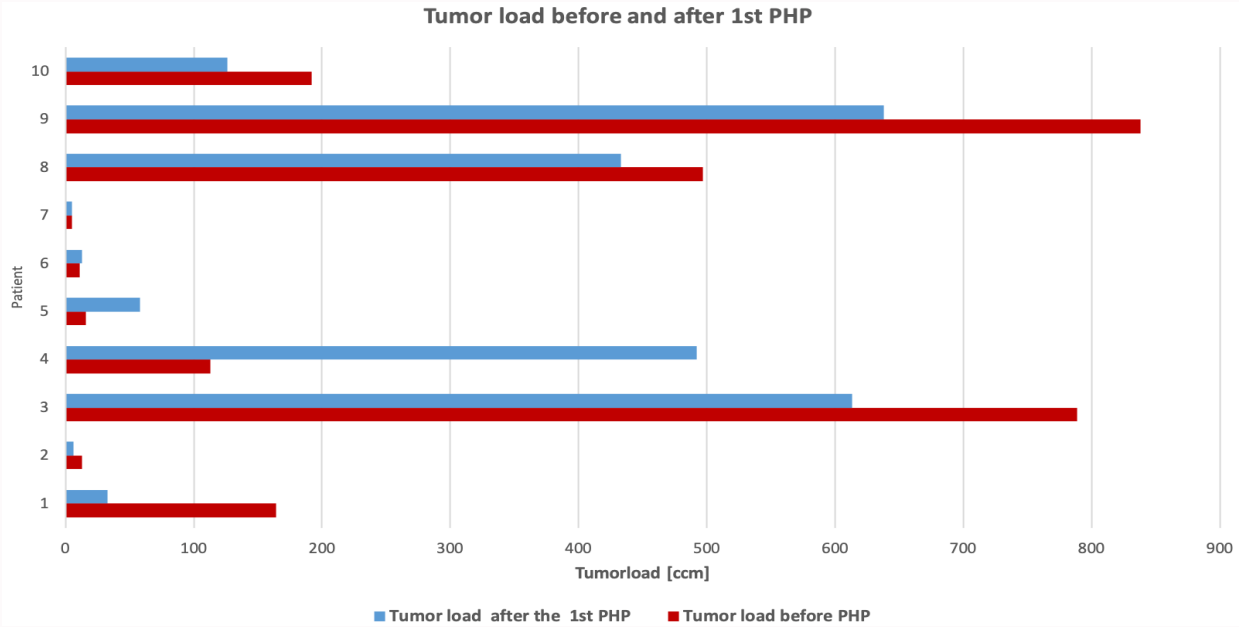

Figure 3: Diagram of Tumor load (ccm) before and after 1st PHP-M.

retrospectively followed 10 patients single center, at the same time establishing more rigid exclusion criteria. We assume, that the longer OS from first treatment (13.7 month) in our retrospective analysis compared to Marquard is assisted by this rigid patient selection. Further differences in recruiting are based on the inclusion criteria where for example bilirubin was allowed to be 3 times the normal values in the work of Marquard and 2 times the normal values in this work. A large single center cohort recruiting 88 patients treated by TACE exhibited an OS of 9 months [17], whereas the retrospective multicenter analysis of Luo et al. gave a median OS of about 13 months [18]. Another recent study confirms that TACE provides a survival benefit compared to best medical treatment and resulted in an OS of 105 weeks if combined with chemotherapy and of 43 weeks if used alone [19]. To date, embolization materials and medication vary widely, making it difficult to compare the different studies. Regarding TARE, recent data from a multicenter evaluation showed that TARE in the subgroup intrahepatic cholangiocarcinoma had an OS of 14.6 months (95% CI 10.9-17.9) [20], where, in the same study group, quality of life remained stable [21]. These data disagree with the work of Rafi et al. [22], who reported a median survival of 11.5 months from initial treatment. A systematic review of Al-Adra revealed a weighted median survival of 15.5 months [23]. Thermal ablation can be an alternative to the transarterial approach in iCC patients if the intrahepatic lesions are smaller than 4 cm and if tumor load generally is limited. In a recent paper, Giorgio compared microwave ablation to radiofrequency ablation and reported an OS in this selected cohort of 45% at 60 months with microwave ablation having an advantage [24]. For patients with irresectable iCC there are many other palliative therapy options including PHP. A recent meta-analysis comparing chemotherapy, TACE, radiotherapy and chemoradiotherapy

Table 1: Baseline and laboratory findings before and after the 1st cycle of PHP chemosaturation (Data are summarized in the following way: a **b** c represents the lower quartile a, the median b, and the upper quartile c for continuous variables. x ± s represents X ± 1 SD. N is the number of non-missing values. Numbers after proportions are frequencies).

		Wilcoxon-Pratt Signed-Rank Test p-value
Age (years)	59 ± 10	
Hemoglobin (g/dl) before PHP	11.5/**12.7**/13.7	
Hemoglobin (g/dl) after PHP day 1-5	8.9/ **9.7**/10.8	
Hemoglobin (g/dl) before - after	1.6/**2.6**/3.4	0.002
Leukocyte count (/nl) before PHP	5.7/**6.9**/7.5	
Leukocyte count (/nl) after PHP day 1-5	3.5/ **7.0**/15.4	
Leukocyte count (/nl) before - after	-8.90/-**0.25**/ 2.10	0.320
Platelets (/nl) before PHP	150/**200**/267	
Platelets (/nl) after PHP day 1-5	54/ **82**/109	
Platelets (/nl) before - after	62/ **98**/168	<0.001
Serum creatinine (mg/dl) before PHP	0.80/**0.80**/0.90	
Serum creatinine (mg/dl) after PHP day 1-5	0.62/**0.70**/0.80	
Serum creatinine (mg/dl) before - after	0.10/**0.10**/0.10	<0.001
Bilirubin (mg/dl) before PHP	0.43/**0.55**/0.83	
Bilirubin (mg/dl) after PHP day 1-5	0.73/**0.85**/1.10	
Bilirubin (mg/dl) before - after	-0.50/-**0.35**/-0.17	0.008
Tumor volume (ml) before PHP	14/**138**/421	
Tumor volume (ml) after PHP day 1-5	18/ **92**/477	
Tumor volume (ml) before – after	-1.5/ **35.5**/114.8	0.297

confirmed a heterogeneous but measurable benefit of each therapy, but differences between therapies did not reach significance. Consequently the authors suggest that these data need further evaluation [25]. Unfortunately, PHP was not included. Resection still remains the only curative option in iCC. Unfortunately, only few patients are eligible for resection upon first imaging [26]. Endo the reported overall survival range following resection in a larger cohort was 36 months; recurrence was observed in 62.2% of patients at a median follow-up of 26 months [27]. Whereas Ohtsuka reported an overall survival of 25.5 months [28]. Recently, new developments in surgery and the ability to aid resection by hypertrophic concepts such as Associating Liver Partition and Portal Vein Ligation (ALPPS) [29,30] and Portal Vein Embolization (PVE) [31] have enlarged the subgroup of patients potentially benefitting from extended hemihepatectomy. Yet it is unclear how these new developments in surgery will influence locoregional and systemic therapies, may even improve overall survival by combining therapies. Even in resected patients, recurrence remains a challenge. Recent data from a multicenter evaluation from Germany showed that the R status of first liver resection and the median time to recurrence were significant determinants of repeated resectability. The group calculated a median OS in the repeated resection group of 65.2 months [32].

Local tumor control/RECIST

Our own results are negatively biased by a high average tumor load; however, in this early work on chemosaturation in iCC patients we were not able to select further. High tumor load is known to have negative effects on OS, as recent data on iCC and the postsurgical work-up confirm [33]. Our results do not exhibit a significant downstaging according to RECIST 1.1, but volumetry shows a reduction in tumor load and there were comparable rates of tumor control (in 7/10 patients). This contrasts with restaging data from other methods such as TARE, where Hoffmann et al. found a Partial Response (PR) in 12/33 treated patients [34]. In a study by Park et al. using TACE (n=72), PR was achieved as the best tumor response to treatment in 15 patients (23%), SD was attained in 44 patients (66%) and PD in seven patients (11%) according to RECIST at the 1-month follow-up (mean 1.1 ± 0.34 months) [35]. The technical effort necessary for PHP-M using high dose melphalan and external filters led to two complications in our study group (a mediastinal bleeding and a peripheral artery occlusive disease). Other reported post-procedural complications such as pneumonia, stroke, pseudoaneurysm or acute renal failure [10], as mentioned in many other prospective and retrospective studies [36], did not occur in this cohort. The known and common hematological changes e.g., drops in platelets and leucocytes as well as anemia were frequently monitored and were manageable in all cases.

Limitations

The presented data were analyzed in a retrospective fashion and were single center based. There are limitations as the number of patients included and the numbers of procedures were small, and there was no control group regarding this novel treatment of chemosaturation. Furthermore, some of our patients received their follow-up imaging externally from our clinic, therefore some follow-up data such as laboratory controls were not available retrospectively. However, there are no prospective studies and no larger retrospective analysis available to date comparing PHP-M to the other transarterial approaches such as TARE and TACE, as discussed above.

In conclusion, in selected patients with advanced iCC for second or last line treatment, PHP-PHP-M seems a reasonably safe procedure with promising survival rates as a last line therapy. As our data can only be preliminary, further studies are warranted to allow evaluation of benefits over other locoregional therapeutic approaches or systemic therapy in order to provide optimal treatment options.

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