

Recent Developments in Isolated Hepatic Perfusion as an Alternative in the Treatment of Unresectable Metastatic Liver Disease Secondary to Colorectal Cancer

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Colorectal cancer (CRC) is the third most common cause of death from cancer worldwide. Nearly 20% of patients present with synchronous metastatic disease at the time of diagnosis and up to 50% of patients will develop liver metastases at some point during the course of their disease. It is said that approximately 85% of patients with stage IV disease present with liver metastases that are considered unresectable at the time of diagnosis. The median survival for these patients without treatment is 6-9 months and it reaches up to 35% at five years when they are converted to resection.

Many techniques for the regional treatment of liver metastases from CRC have been described, based either on ablative therapy (radiofrequency ablation, cryoablation, microwave ablation) or perfusion (chemoembolization, radioembolization, infusion of chemotherapy directly into the hepatic artery); each of these techniques has been shown to be effective within their domain. Still, no comparative studies have been conducted to establish precise indications for opting for one of these techniques over another and the benefits of each. At present the only treatment for unresectable liver metastases from CRC that has been validated continues to be systemic treatment with chemotherapy.

The rationale for isolated hepatic perfusion is based on administering high doses of chemotherapeutic agents by infusing them through the liver under hyperthermic conditions in order to produce maximum antitumor effects while limiting systemic toxicity by temporary interruption of the blood supply to the liver. Numerous studies have reported responses of more than 50-60%, with complete radiologic response in up to 5% of the cases reported and with acceptable transient perioperative morbidity and mortality rates with respect to the other modalities of systemic treatment currently in use.

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The importance of evaluating this new therapeutic tool is that, with the exception of surgical resection with negative margins, overall survival rates for all of the other treatments currently available for patients with unresectable liver metastases from CRC are too low. (J CANCEROL. 2016;3:5-17)

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INTRODUCTION

The liver is the most common site for metastatic spread in patients with CRC and, in turn, CRC is the primary tumor that causes most metastases in the liver; nearly 20% of patients with it present with liver metastases at the time of diagnosis and as many as 50% of patients will develop them at some point during the course of their disease¹. It has been reported that median survival for untreated patients with colon cancer metastatic to the liver is 6-9 months²; in contrast, five-year survival rates of up to 35% have been reported for those patients who are converted to resection³. Nevertheless, up to 80-85% of liver metastases are usually unresectable due to excessive tumor burden, insufficient residual hepatic function of the remnant, or medical comorbidities⁴. In these cases, systemic treatment is usually the only therapeutic alternative and long-term survival is reported to be poor^{5,6}. Moreover, the likelihood of a durable response to second-line treatment is usually very small, with reports of responses under 25% and overall survival of less than 12 months⁷⁻¹¹.

Liver metastases usually receive most of their blood supply from the hepatic artery, while most of the blood flow through the liver tissue comes via the hepatic portal vein. Various methods for the regional treatment of liver neoplasms have been described, of which the infusion of chemotherapeutic agents via the hepatic artery is the most commonly used. Although in comparison to systemic chemotherapy this technique has been shown to increase tumor response rates in the

short term, it has hardly any impact on overall survival due to limitations associated with dose-related toxicity¹². A recent meta-analysis by Gruber, et al. on transarterial chemoembolization as treatment for unresectable liver metastases in patients with CRC showed partial response in 16.7% and stable disease in 48.2%, with survival rates at one and two years of 62 and 28%, respectively¹³. In the same situation, some authors have reported partial response in 29% of patients treated with radioembolization, stable disease in 90%, with survival at one year reported as varying between 37 and 74%¹⁴.

Alternatively, isolation of hepatic circulation from systemic circulation allows higher doses of various drugs to be delivered to the liver parenchyma in comparison with the doses that can be administered directly into the hepatic artery¹⁵⁻¹⁷. Isolating the liver from the systemic circulation allows administration of chemotherapeutic agents at high temperatures and increased doses that would otherwise be lethal if administered systemically.

Several phase I and II studies have shown that there are limitations to the systemic administration of tumor necrosis factor alpha (TNF- α) in humans, secondary to toxicities associated with the dose at which all tumor activity is suppressed¹⁸. In multicenter studies of isolated perfusion of the limbs, Liénard, et al.¹⁹ and Eggermont, et al.²⁰ showed that complete vascular isolation of the limb from the systemic circulation allows high doses of TNF- α in combination with melphalan to be safely administered as it ensures that systemic exposure to the drug is minimal.

DEVELOPMENT OF ISOLATED HEPATIC PERFUSION

The first description of a technique for isolated hepatic perfusion was described by Ausman²¹ in 1961 in a canine model and subsequently carried out in five patients, with reports of significant morbidity. Although there are no reports of follow-up, significant therapeutic effects were observed in two patients. In 1969, Skibba²² was able to demonstrate the synergistic effects of the regional application of chemotherapeutic agents in hyperthermic conditions by using perfusion, which became the standard for perfusion that at present has been extrapolated to the liver region. In any case, this technique did not gain acceptance during the following three decades due to its significant morbidity and potential mortality, with only a few isolated reports of small series at individual institutions, whose patient selection criteria and perfusion parameters were very variable^{15,22,23}. It was not until 1992 that Liénard and Lejeune¹⁹ resumed the matter of isolated perfusion with a combination of TNF- α and melphalan with the aim of limb salvage in patients with sarcoma and melanoma.

At present, the development over the last 20 years of better technologies that permit proper monitoring of toxicity related to leakage during perfusion has allowed several protocols to be designed, which allow an assessment of the efficacy and safety of using isolated hepatic perfusion as an alternative in the treatment of unresectable metastatic liver disease. In a prospective phase II study of 34 patients with unresectable metastatic liver disease (in 60% of whom it was secondary to metastatic CRC), Alexander, et al.²⁴ reported an overall response rate of 75% of cases of patients with reversible grade III hepatic toxicity after using TNF- α at a dose of 1.0 mg and melphalan at 1.5 mg/kg in association with hyperthermia, thereby establishing the use of TNF- α and melphalan in isolated hepatic perfusion as a viable option for the treatment of unresectable metastatic liver disease.

ROLE OF ISOLATED HEPATIC PERFUSION IN COLORECTAL CANCER WITH UNRESECTABLE LIVER METASTASES

Given their relative frequency, several studies have been conducted to evaluate the role of isolated hepatic perfusion in the treatment of unresectable metastatic liver disease secondary to CRC, in which, although the criteria for deeming metastases unresectable are very heterogeneous, most studies agree that definition includes an average of 10 lesions in the liver or a replacement of the liver parenchyma by the tumor of at least 25%.

In a sequential prospective clinical study at the National Cancer Institute (NCI), Alexander, et al.²⁵ reported that median overall survival was 17.4 months in 120 patients with unresectable metastatic liver disease secondary to CRC who were treated with isolated hepatic perfusion. Melphalan alone was used in 69 patients, TNF- α and melphalan in 41 patients, and TNF- α alone in 10 patients; furthermore, 46 patients received additional treatment with hepatic arterial infusion using floxuridine. As much as 80% of the patients had received prior systemic chemotherapy treatment. Treatment-related mortality was observed in five patients (4%); however, three of the mortalities occurred in a previous phase I study in which the main objective was to determine the standard dose of medication for isolated hepatic perfusion. Response was observed in 114 patients, two of whom achieved complete response, with partial response in 67 according to imaging studies (59%). Thirty-two patients (65%), including those in whom complete response was recorded, were in the group treated with isolated hepatic perfusion and additional treatment with hepatic arterial infusion using floxuridine; 33 patients (57%) were in the group treated with isolated hepatic perfusion alone, and four patients were in the group treated with TNF- α alone in perfusion and no additional treatment. A median time to hepatic progression of seven months was reported. The patients who received additional treatment with hepatic arterial

infusion using floxuridine had a longer time to hepatic progression (13 months) than those who did not receive additional treatment (5.8 months) and those in whom TNF- α alone was used in perfusion (three months). The most common toxicities reported were transient elevations in serum transaminases and total bilirubin. Independent factors that were associated with better response were high doses of melphalan (≥ 200 mg) and the use of TNF- α . On the multivariate analysis, only the use of additional treatment with hepatic arterial infusion using floxuridine and a preoperative serum carcinoembryonic antigen (CEA) level of ≤ 30 ng/ml were statistically significant with regard to better overall survival.

Similarly, van Iersel, et al.²⁶ reported median overall survival of 24.8 months and a partial response rate of 50% in 105 patients with unresectable metastatic liver disease secondary to CRC who were treated with isolated hepatic perfusion using high doses of melphalan (200 mg); treatment-related morbidity was found to be similar to that observed in the NCI study²⁵. A median hepatic progression-free survival period of 7.4 months was recorded, while the median duration of hepatic response was 11.4 months. They also observed that the use of adjuvant chemotherapy was an independent factor related to the degree of response and progression-free survival in the multivariate analysis. It should be mentioned that they randomly used the portal vein with and without the use of the gastroduodenal artery as the site of access into the perfusion circuit; the multivariate analysis showed that use of the portal vein was an independent factor associated with a higher rate of postoperative complications and reduced overall survival (possibly in direct relation to the postoperative complications secondary to its use).

Using this same group of patients in a case-control study, van Iersel, et al.²⁷ compared systemic treatment with chemotherapy and isolated hepatic perfusion with melphalan in patients with unresectable metastatic liver disease secondary to CRC,

without finding significant differences between the two groups. The systemic chemotherapy group consisted of 111 patients who were previously enrolled in the capecitabine, irinotecan, oxaliplatin (CAIRO) study of the Dutch Colorectal Cancer Group. A total of 111 patients received either sequential chemotherapy with first-line capecitabine, followed by second-line irinotecan and third-line capecitabine and irinotecan or a combination of capecitabine and irinotecan as first-line treatment, followed by second-line capecitabine and oxaliplatin. Of the 99 patients treated with isolated hepatic perfusion, 35% presented with postoperative complications and the reported treatment-related mortality was 6%. In the systemic chemotherapy group, a 52% rate of morbidity was recorded, which was associated with grade III/IV toxicities and treatment-related mortality was 2%. The response rate for the isolated hepatic perfusion group was 47%, with median time to hepatic progression of 7.3 months. In the chemotherapy group, the rate of response to first-line therapy was 37%, with a median time to hepatic progression of 7.9 months. The reported overall survival was 25 months for those treated with isolated hepatic perfusion as opposed to 21.7 months for the group treated with chemotherapy.

The role of isolated hepatic perfusion in patients with unresectable metastatic liver disease secondary to CRC who progress to systemic treatment with chemotherapy was analyzed by Alexander, et al.²⁸ in 25 patients who received chemotherapy with 5-fluorouracil (5-FU) as first-line treatment. In 22 cases, irinotecan was added to the first-line treatment and all 22 patients received second-line treatment based on irinotecan. The observed rate of response was 60% (one patient achieved complete response and another 14 reached partial response), with a median duration of response in the liver of 12 months. Systemic progression was seen in 13 patients (54%) after a median of five months following the end of treatment; median overall survival was 12 months, with a two-year survival rate of 28%. These results are favorable compared with the second-line of treatment, in which the rate of

response that was observed was < 25% and median overall survival was less than 15 months.

All these data together appear to suggest that the use of isolated hepatic perfusion does not provide greater survival benefit compared with systemic chemotherapy as first-line treatment in patients with unresectable metastatic liver disease secondary to CRC; so its main role may be as second-line treatment in select cases, for patients refractory to systemic treatment²⁹.

SURGICAL ASPECTS

Total vascular exclusion of the arterial and venous circulatory systems of the liver with respect to systemic circulation needs to be performed under direct vision in order to instill a perfusate containing chemotherapeutic agents at high doses under hyperthermic conditions, while limiting systemic leakage to none or virtually none.

Patients who show evidence of peritoneal dissemination or distant metastatic lymph node disease are classified as non-candidates, although involvement of lymph nodes in the porta hepatis is not a contraindication as long as they are resected as they have not been shown to be associated with a worse prognosis with respect to overall survival^{29,30}.

As it is necessary to interrupt the venous flow through the retrohepatic inferior vena cava and in order to maintain systemic venous return, it is necessary to create a venovenous bypass system using, for the sake of convenience, the right great saphenous vein and the left axillary vein to create the circuit. For anatomical reasons, the gastroduodenal artery is the ideal access site for delivery of the perfusate to the liver parenchyma. To prevent dilution of the perfusate and maintain a uniform hyperthermic temperature in the liver parenchyma, the blood flows through the portal vein and the common hepatic artery must be occluded.

The perfusion circuit consists of a roller pump, a membrane oxygenator, and a heat exchanger to ensure the maintenance of controlled uniform temperature within the circuit. The uniform perfusion of the liver parenchyma can be observed through temperature probes to maintain even distribution of the temperature in both lobes.

The perfusate is the mechanism through which the chemotherapy agents and hyperthermia are delivered, and it must also ensure adequate oxygenation of the liver parenchyma during the perfusion, when it will be exposed to controlled ischemia. In order to generate a significant therapeutic effect, the minimum time of exposure to the chemotherapeutic agents required for perfusion is 20 minutes and the maximum time of exposure is 60 minutes; after 60 minutes of ischemia, irreversible liver cell damage occurs. The optimal rate of infusion is generally between 600-800 ml/min, with a maximum flow rate of up to about 1,200 ml/min, as the aim is to keep the pressure in the arterial line of the circuit between 100 and 200 mmHg. It must be noted that pressure in the hepatic artery is significantly lower. The flow rate for the axillary to saphenous venovenous bypass should be between about 1,800 and 2,000 ml/min.

Intraoperative monitoring to assess perfusate leak into the systemic circulation can be performed using I¹³¹ serum albumin, although evidence of leakage is next to zero when this technique is employed, so the value of monitoring leakage into the systemic circulation has fallen out of favor among many authors. Likewise, a change in the volume of outflow from the venous reservoir during perfusion suggests incomplete isolation of the hepatic blood flow with respect to systemic circulation²⁹⁻³¹.

HEMODYNAMIC EFFECTS

Heaney originally described vascular isolation of the liver in 1966 as an attempt to limit the risk of bleeding and gas embolism during hepatectomy.

Occlusion of venous flow through the retrohepatic inferior vena cava together with selective occlusion of the suprahepatic veins serves the purpose of obstructing flow in the suprahepatic veins while preserving portal venous flow. This isolation must be continuous, occluding blood flow through the inferior vena cava just above the renal veins in order to prevent the release of chemotherapeutic agents into the renal circulation. Hemodynamic changes vary from one patient to another depending on the patient's age, circulating blood volume, myocardial function, and presence of spontaneous portacaval shunts.

Occlusion of blood flow in the vena cava is associated with an approximately 10% fall in arterial blood pressure, which can translate into a 50% reduction of cardiac output, a decrease of approximately 25% in pulmonary artery pressure, a 40% reduction in cardiac index, and a decrease in systemic vascular resistance of up to 80%. Complete sensitivity to total vascular isolation of the liver, which consists in a > 30% decrease in arterial blood pressure and a reduction in cardiac output > 50%, is generally less than 15%.

For this reason it is necessary to use a bypass to promote the return of the venous flow in the portacaval vein back to the central circulatory system, the same one that is used for the axillary to saphenous venovenous bypass; because of the length and complexity of the procedure, an extracorporeal pumping system is needed to maintain constant flow in order to sustain the central venous pressure^{32,33}.

Isolating the venous blood flow in the liver causes cytolysis, secondary to hepatic parenchymal ischemia, which is accompanied by transient elevation of serum transaminases in proportion to the duration of ischemia (serum transaminases generally return to baseline levels within 15-20 days). The consequences of isolating hepatic venous flow from the kidneys and gastrointestinal mucosa are usually well tolerated in humans, to the extent of being irrelevant³⁴.

When major hepatectomy is performed in a noncirrhotic liver, the hepatic vein may be isolated for up to 90 minutes before irreversible liver damage occurs; an isolated hepatic perfusion procedure usually lasts between 30 and 60 minutes, and oxygenation is usually required for longer periods, which is obtained by adding 300 ml of packed red blood cells to the perfusate.

DRUGS AND SOLUTIONS USED

The doses and the drugs used during isolated hepatic perfusion are not fixed and doses are variable. Molecules with high molecular weight are generally better retained in tumor cells, but molecules that are larger than 5,000 Daltons cannot pass through the cell membrane and thus cannot penetrate the tumor site. Lipophilic molecules can cross the lipophilic barrier of the cell membrane more readily than hydrophilic molecules. Agents that require active transport across cell membranes are generally more likely to encounter chemotherapy drug resistance than those that rely on passive diffusion, due to the genetic mutations in transporters that constitute a classic mechanism of resistance³⁵. The weak binding to proteins in the plasma or perfusate promotes the release of a significant fraction of the drug and also promotes its antitumor activity³⁶. This effect should occur as rapidly as possible (in less than 60 minutes).

It therefore seems unlikely that any chemotherapeutic agent should be able to kill tumor cells with only a 60-minute exposure, even under the best of circumstances. Chemotherapy agents that are not cell cycle dependent and have a long intracellular half-life, such as melphalan, can be effectively delivered as a high-intensity single dose. This is how melphalan has been able to deliver good results in the numerous reports that have been published. In a phase I study using melphalan at doses of 1.5 mg/kg and 1.0 mg of TNF- α in combination with hyperthermia, Alexander, et al. recommended use of normal saline solution for the

perfusate as they are rapidly absorbed and are unable to retain increased volume within the intravascular space. The effects of bolus administration of cytotoxic agents (every 5 minutes) in order to limit toxicity as much as possible have already been assessed, but in the case of melphalan, it has been found that continuous administration (infusion for at least 20 minutes) results in greater antitumor activity while also being associated with a lower rate of complications than when it is administered for a shorter time³⁷.

The advantages of administering TNF- α in combination with melphalan for isolated limb perfusion seem to be clear, but they continue to be debated in isolated hepatic perfusion^{20,25,38}. An experimental test in rats showed it had remarkable effects as a synergist in the treatment of sarcomas of the limbs, but little to no effect on colorectal metastases³⁹.

In a study of 32 patients with CRC, Bartlett, et al. confirmed this effect by administering TNF- α in addition to melphalan at high doses (> 200 mg)⁴⁰, increasing liver or systemic toxicity even in presence of minimal systemic leakage⁴¹. This difference may be explained by the direct effects of TNF- α on endothelial cells and the large amount of vascularity in sarcomas of the limbs compared with liver metastases from CRC, which are often nourished almost exclusively by the blood flow from the hepatic artery²⁰. Likewise, a study of 10 patients with CRC that used TNF- α alone in the perfusate had poor response rates compared to those obtained with the use of high-dose melphalan alone reported in the literature⁴². Moreover, the maximum tolerated dose of melphalan when combined with TNF- α generally decreases from 3.0 to 1.5 mg/kg³⁸.

Nevertheless, in a study of 120 patients with CRC, Alexander, et al. showed that when TNF- α and melphalan were administered at doses of 1.5 mg/kg, higher rates of partial response and complete response were obtained as compared to the use of melphalan alone at a dose of 3.0 mg/kg, with a

median survival rate of 17.4 months²⁵. While the significance of TNF- α in isolated hepatic perfusion is not quite clear, it appears that its usefulness lies in acting as a synergist, boosting the effect of melphalan, more than in its own antitumor activity, with the best response rates, both partial and complete, and the longest progression-free survival periods being reported after it was administered in combination with melphalan at a dose of 1.5 mg/kg, in comparison with administration of melphalan alone at high doses²⁵.

The effects of TNF- α in tumor neovasculature have now been demonstrated as it acts by increasing permeability to various chemotherapeutic agents in the tumor interstitium, which is followed by intravascular coagulation resulting in tumor ischemia^{43,44}.

It is well known that hyperthermic conditions increase the antitumor effects of TNF- α and melphalan; it is even known that including without the administration of any cytotoxic agents, hyperthermia alone is able to induce an antitumor effect in *in vivo* models^{45,46}.

Given its superior effects as a chemotherapeutic agent in gastrointestinal cancer, a phase I trial was conducted to study the use isolated hepatic perfusion with oxaliplatin in combination with hyperthermia in 13 patients with unresectable metastatic liver disease secondary to CRC; the results, however, were not superior to those obtained with TNF- α and melphalan, with a partial radiological response rate observed in 66% of cases (one patient had complete radiological response) but rather high toxicity rates⁴⁷.

ROUTE OF ADMINISTRATION OF THE PERFUSATE

It is well known that metastatic lesions in the liver predominantly derive their blood supply from the hepatic artery; likewise, most of the blood to the liver parenchyma is supplied mainly through the portal vein⁴⁸.

Delivery of the perfusate via the hepatic artery (with access through the gastroduodenal artery) during isolated hepatic perfusion produces a direct cytotoxic effect on tumor cells, avoiding, in part, direct toxicity to liver cells. This effect can be checked by a comparison of the best outcomes in terms of greater antitumor response, long-lasting progression-free survival, and lower rates of perioperative complications when the perfusate is administered via the hepatic artery route to when it is administered through the portal vein route. Also, there seems to be no additional benefit to administering the perfusate through both routes⁴².

There are studies that have compared the administration of the perfusate in isolated hepatic perfusion using a conventional technique as opposed to using a method of retrograde reperfusion so that the perfusion effluent is flushed through the portal vein instead of the inferior vena cava. Delivery of the perfusate and the chemotherapeutic agents to the tumor site remains unchanged, regardless of the route of administration; nevertheless, the flow to the liver parenchyma is reduced by 80% so that using the inferior vena cava for outflow reduces liver toxicity while preserving the antitumor effects⁴⁹.

Some authors have proposed a minimally invasive procedure for percutaneous occlusion of hepatic venous flow using a double balloon catheter system, which allows delivery of the perfusate without need for an extracorporeal pump or a venovenous bypass and with the added advantage of being able administer treatment up to four times (with a one month interval between each treatment), according to the series published^{50,51}; still, experience with this method has shown it results in poor isolation of hepatic venous flow, with significantly high perfusate leak into the systemic circulation secondary to hemofiltration, also resulting in the use of doses that are significantly lower than those used in open techniques, in addition to causing greater reduction in cardiac output than that observed in the open techniques. The lowering of the blood pressure that occurs from dilatation of the

vascular lumen as a result of inflation of the catheter balloon, in conjunction with the physiological depletion of catecholamines through hemofiltration, make it necessary to use more vasoactive agents than when an open technique is used. These reasons, together with the multiple difficulties in obtaining a return flow with a neutral balance within the perfusion circuit because of poor isolation of the hepatic venous flow, make this technique unsuitable^{30,52}.

MONITORING OF PERFUSATE LEAKAGE DURING PERFUSION

During isolated hepatic perfusion, patients undergo physiological changes associated with major surgical procedures such as heat stress caused by hyperthermia as well as the potential for toxicity associated with chemotherapy and hypoperfusion if not managed adequately during surgery. Proper management of fluid balance during hyperthermia is critical for maintenance of optimal organ perfusion and to prevent kidney damage.

The patient should be monitored via an arterial line in the radial artery and via a central access line in the superior vena cava. It is recommended to maintain urine output of 100 ml every 15 minutes during hyperthermic perfusion; diuresis between 50-75 ml every 15 min may be acceptable in some labile patients. In addition, core body temperature should be kept below 39°C³¹.

Several authors note that since hepatic vascular exclusion during the open isolated hepatic perfusion technique is performed under direct vision, full control over potential leakage of perfusate in the systemic circulation during the isolation can be had, unlike during isolated limb perfusion in which a tourniquet is applied to perform the vascular exclusion of the collateral branches. For this reason, the most recently published reports indicate that the need for monitoring systemic leakage in patients has fallen¹⁵⁻¹⁷. For all that, the authors that

describe the technique report that systemic leakage of perfusate during isolated hepatic perfusion using an open technique can be monitored in the same way that it is for isolated limb perfusion, by serial counts using a gamma probe or gamma camera.

After the perfusion and venous return circuits are in place and prior to infusion of the cytotoxic agents into the perfusate, the gamma camera must be positioned above the patient directly over the left ventricle in order to monitor systemic leakage of perfusate by determining counts per minute. The ^{99m}Tc macroaggregates are then injected into the central venous circulation in order to establish baseline values and generate a graph for measuring the continuous changes that may occur during the perfusion procedure. Once the baseline values have been established for the gamma camera graph, a dose of ^{99m}Tc macroaggregates that is 10-fold higher than the one that was previously administered is added directly into the arterial line of the perfusion circuit. In this way, consecutive counts per minute are used to record any variations that are plotted on the graph, which should reflect no changes with regard to the previously recorded baseline values. Any variations on this graph are indicative of an inadequate hepatic vascular exclusion technique and will warrant checking the surgical site for any collateral branches within the circuit that have not been tied.

Any variations in the gamma camera count per minute graph are indicative of leakage; a doubling over the baseline value signifies a 10% leak of perfusate into the systemic circulation; this technique allows even leak rates as low as 1% to be measured^{31,42,53}.

RELATED COMPLICATIONS

It is necessary to separate the complications associated with this procedure from those resulting directly from the use of chemotherapeutic agents and those secondary to the surgical procedure *per se*.

- Systemic toxicity related to the release of chemotherapeutic agents at the end of isolated hepatic perfusion is associated with inadequate washing out of the perfusate after perfusion and before restoration of the liver blood flow to the systemic circulation.
- Systemic toxicity related to the release of chemotherapeutic agents during isolated hepatic perfusion is directly related to insufficient hepatic vascular exclusion and is directly proportional to the surgeon's technique.
- Surgical complications inherent in the surgical procedure such as bleeding, accidental vascular injury, or poor technique in performing vascular at the end of the procedure.

Independently of the presence of perfusate leak into the systemic circulation, approximately 3.5-7.0% of the patients in the series in which TNF- α was used as part of the perfusate solution experienced severe hypotension within the first 12-24 hours of the immediate postoperative period following isolated hepatic perfusion. This morbidity has been associated with induction of interleukins 6 and 8 (IL-6 and IL-8) secondary to TNF- α infusion, demonstrated by an elevation of serum cytokines within 4-6 hours after perfusion. Furthermore, melphalan usually produces postoperative grade 3-4 toxicity in the liver parenchyma secondary to perfusion. This toxicity is reflected in the sudden rise of serum transaminases and bilirubin in more than 50% of patients, with a peak at 3-4 days, which usually returns to normal within 15-20 days^{43,44}.

Chemotherapy prior to the isolated hepatic perfusion procedure does not seem to modify this situation. At the same time, no cases of death caused by severe hepatic failure have been reported in the literature. With regard to the potential for toxicity secondary to systemic leakage of the perfusate, it is directly proportional to adequate vascular exclusion of the liver. In the literature, rates of mortality secondary to hematologic toxicity caused

by systemic leakage of the perfusate vary between 0 and 10%^{26,42,47,54,55}.

The use of doses higher than 1.0 mg of TNF- α during perfusion has been associated with severe coagulopathy²⁵. In the majority of these series, veno-occlusive disease was reported as the leading cause of mortality, ranging in incidence from 5-22%. This complication appears to be directly related to the administration of melphalan at a dose > 1.5 mg/kg in the perfusate^{25,30}. Some other complications have been sporadically reported, including thrombosis or dissection of the hepatic artery, splenic rupture, sepsis, residual portal hypertension, and post-operative ileus, complications that seem to result from the surgical procedure (Table 1).

CURRENT STATUS OF TREATMENT FOR UNRESECTABLE METASTATIC LIVER DISEASE SECONDARY TO COLORECTAL CANCER AND ISOLATED HEPATIC PERFUSION

At present, the therapeutic approach for diffuse, unresectable liver metastases from CRC is in constant development. Due to the significant increase in efficacy of new combinations of chemotherapeutic agents in systemic treatment regimens based on irinotecan or oxaliplatin with or without bevacizumab as first and second lines of systemic treatment^{56,57}, response rates allowing for surgical resection of liver metastases have been achieved in as many as 20% of patients^{58,59}. Nevertheless, despite overall response rates greater than 50%, most of these responses are partial and the duration of the responses is usually less than one year^{56,60-63}. Furthermore, patients whose lesions often become undetectable to CT scans, and who subsequently benefit from surgical treatment, have been shown to have persistent viable disease in as much as 80% of the previous sites of disease⁶⁴. Unfortunately, treatment with second-line systemic chemotherapy usually has very

limited clinical benefit, with response rates as poor as 25%⁶⁵⁻⁶⁷.

Today we know that the blood supply to liver metastases comes almost exclusively from the hepatic artery so that regional treatment via infusion of chemotherapeutic agents through the hepatic artery selectively enhances the antitumor effect on tumor cells, while limiting the associated systemic toxicity⁶⁸. Regional treatment with chemotherapy administered through isolated hepatic perfusion, as second-line treatment for those patients whose disease remains confined to the liver despite progression after first-line treatment, has proved its efficacy by inducing tumor regression in patients with disseminated disease who were not considered candidates for resection^{68,69}. It is associated with response rates above 50-60%, which even reach 80% if stable disease is included as a criterion for response, and without being adversely influenced by the amount of disease in the liver, the number of lesions, or the percentage of tumorous replacement of the hepatic parenchyma. The rates of local response in the liver following isolated hepatic perfusion do not seem to be subject to a history of systemic chemotherapy treatment, which reinforces the hypothesis that it may have potential therapeutic utility as an option for regional treatment in second-line systemic treatment, in a context of patients with diffuse, unresectable, metastatic liver disease secondary to CRC, especially in those cases in which progression has remained confined to the liver following first-line therapy.

CONCLUSIONS

Isolated hepatic perfusion is a regional therapy for the treatment of unresectable liver metastases of diverse etiologies, which can be used in patients with unresectable metastatic liver disease secondary to CRC. Numerous studies have reported local response rates of more than 50-60% (80% if stable disease is included as a criterion for response),

Table 1. Results and morbidity associated with isolated hepatic perfusion reported in the literature

Study	Year	Patients	Perfusion	Severe morbidity	Operative mortality (45 days)	Partial response	Complete response	Progression-free survival in liver	Overall survival
Skibba, et al. ²²	1986	5 CRC 2 MM 1 Other	Hyperthermia w/o chemo	-	25%	83%	-	-	-
Hafstrom ⁷⁰	1994	4 CRC 10 MM 15 others	29 melphalan 20 cisplatin	-	13.8%	20%	-	-	17.2% at 3 years
Marinelli ⁷¹	1996	9 CRC	Mitomycin C	66%	11%	-	-	-	12 months
Alexander, et al. ²⁴	1998	34	Melphalan + TNF- α	75%	3%	72%	3%	9 months	-
Lindner, et al. ³⁴	1999	5 CRC 2 MM 4 others	Melphalan + TNF- α	54.5%	18.2%	50%	0%	6 months	20 months
Vahrmeijer, et al. ³⁷	2000	24 CRC	Melphalan	-	14%	23.5%	5.8%	-	-
Libutti, et al. ³¹	2000	37 CRC 8 MM 5 others	Melphalan + TNF- α + hyperthermia	-	4%	73%	2%	6 months	-
Bartlett, et al. ⁴⁰	2001	51 CRC	32 melphalan + TNF- α + hyperthermia 51 melphalan + hyperthermia	14%	2%	76%	0%	10.5 months	-
Rothbarth, et al. ⁴²	2003	73 CRC	Melphalan	41%	5.6%	59%	4.2%	7.7 months	37% at 3 years
Alexander, et al. ⁷²	2003	29 MM	Melphalan + TNF- α	65%	0%	52%	10%	8 months	12 months
Savner, et al. ⁵²	2003	3 CRC 1 other	Melphalan 10 sessions (4 open + 6 PHP)	50%	0%	25%	0%	-	-
Alexander, et al. ²⁸	2005	25 CRC	Melphalan + hyperthermia	-	-	60%	4%	5 months	28% at 2 years
Pingpank, et al. ⁵¹	2005	13 MM 2 CRC 13 others	Melphalan, PHP, 2-4 sessions per patient	19%	0%	21.4%	7.1%	-	-
van Iersel, et al. ⁷³	2008	12 MM 7 others	Melphalan	26%	0%	MM: 30% 37%	MM: 20% 5%	-	MM: 10 months Others: 29 months CRC 18 months
Verhoef, et al. ⁷⁴	2008	18 CRC 4 MM 2 others	Melphalan	25%	0%	58%	4%	9 months	CRC 18 months
van Iersel, et al.	2008	105 CRC	Melphalan	37%	7%	47%	3%	7.4 months	24.8 months
Zeh, et al. ⁴⁷	2009	10 CRC	Oxaliplatin	30%	10%	55%	11%	-	-
Alexander, et al. ²⁵	2009	120 CRC	Melphalan \pm TNF- α	-	4%	61%	1.7%	7 months	34% at 2 years
van Iersel, et al. ²⁷	2010	99 CRC	Melphalan + hyperthermia	35%	6%	44%	3%	-	25 months
Voron, et al. ⁷⁵	2012	1 HCC 1 NET	Melphalan + bevacizumab + hyperthermia	50%	0%	=	-	HCC 7 months NET 27 months	HCC 41 months NET 48 months

PHP: percutaneous hepatic perfusion (when the route of administration is not specified, it is open isolated hepatic perfusion); CRC: colorectal cancer; MM: melanoma; HCC: hepatocellular carcinoma; NET: neuroendocrine tumor.

with complete radiologic response in as many as 5% of the cases reported, and with acceptable transient perioperative morbidity and mortality rates with respect to the other modalities of systemic treatment. While the use of systemic chemotherapy continues to be the standard of care, isolated hepatic perfusion may have a role as second-line treatment for patients who are refractory to systemic treatment, who progress on first-line systemic chemotherapy, and in whom, in carefully selected cases, it may improve survival in the short and medium term when added to conventional treatment with second-line systemic chemotherapy. However, the medical community remains skeptical to the use of isolated hepatic perfusion due to lack of prospective studies showing improved survival in comparison with current treatments.

As there are not enough prospective studies evaluating the role of isolated hepatic perfusion in patients with unresectable metastatic liver disease secondary to CRC, it is necessary to consider the possibility of potentially improving survival and the progression-free period without providing a significant commitment with regard to morbidity and mortality, in comparison with the treatments already being used.

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