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PRACTICE GUIDELINE

Hepatic arterial infusion pump chemotherapy in the management of colorectal liver metastases: expert consensus statement

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ABSTRACT

Despite significant improvements in systemic therapy for patients with colorectal liver metastases (CRLMS), response rates in the first-line setting are not optimal, and response rates in the second-line setting remain disappointing. Hepatic arterial infusion pump (HAIP) chemotherapy has been extensively studied in patients with CRLMS, but it remains infrequently used.

We convened an expert panel to discuss the role of HAIP in the contemporary management of patients with CRLM. Using a consensus process, we developed these statements:

- HAIP chemotherapy should be given in combination with systemic chemotherapy.
- HAIP chemotherapy should be offered in the context of a multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.
- HAIP chemotherapy in combination with systemic therapy should be considered in patients with unresectable crlms who have progressed on first-line systemic treatment. In addition, HAIP chemotherapy is acceptable as first-line treatment in patients with unresectable colorectal liver metastases.
- HAIP chemotherapy is not recommended in the setting of extrahepatic disease outside the context of a clinical trial.
- HAIP chemotherapy in combination with systemic therapy is an option for select patients with resected colorectal liver metastases.

These consensus statements provide a framework that clinicians who treat patients with CRLM can use when considering treatment with HAIP.

KEY WORDS

Colorectal metastases, liver metastases, unresectable metastases, adjuvant chemotherapy, intra-arterial chemotherapy, hepatic arterial infusion pump chemotherapy

1. BACKGROUND

Over the past several years, important progress has been made in the treatment of patients with metastatic colorectal cancer. Median overall survival in these patients now extends beyond 2 years with a combination of modern systemic therapies[1–8]. Approximately 60% of patients present with liver-only or liver-predominant metastases, and if complete surgical resection is achieved in those patients, 5-year overall survival approaches 50%[9–11]. In patients with initially unresectable colorectal liver metastases (CRLMS), systemic therapy can, in up to 30% of patients, produce a tumour response sufficient to allow for resection and the possibility of long-term survival or cure[12,13]. An important goal of aggressive therapy in patients with initially unresectable CRLMS is therefore conversion to resectability.

Although the response rate to systemic therapy is good in untreated patients, response rates to chemotherapy in the second-line setting remain disappointing. The most encouraging results are obtained with the addition of biologic agents to chemotherapy, achieving response rates of up to 20%–35% and a corresponding median survival of up to 1 year in the second-line setting[14–18]. Given the limited efficacy of systemic therapy beyond the first-line setting, patients could benefit from other treatments that would increase response and resectability rates.

Hepatic arterial infusion pump (HAIP) chemotherapy has been extensively studied in patients with CRLMS. The rationale for arterial delivery of

chemotherapy derives from the knowledge that liver metastases are perfused almost exclusively by the hepatic artery, and normal liver tissue receives its blood supply mainly from the portal circulation[19]. The administration of chemotherapy directly to the hepatic artery allows for more selective treatment, increasing the delivery of certain cytotoxic agents to the tumour while minimizing systemic side effects. Although first-pass extraction in the liver improves the delivery of most agents, the pharmacokinetic characteristics of floxuridine (FUDR)—short half-life, 95% first-pass extraction rate, and an increase in tumour exposure by a factor of 400 compared with systemic administration[20]—make it optimal for the HAIP technique. In a study of radiolabeled FUDR, concentrations of the drug in liver metastases were higher by a factor of 15 after infusion into the hepatic artery compared with infusion into the portal vein[21]. To confirm that physiologic finding, researchers conducted a small, elegant trial that randomized 25 patients with CRLMS to receive FUDR administered into the hepatic artery or the portal vein, with the opportunity to cross over to the other arm upon tumour progression[22]. Half the patients receiving arterial chemotherapy responded to treatment; no patient who received portal vein chemotherapy responded.

At least ten randomized controlled trials have examined the efficacy of HAIP alone compared with systemic chemotherapy or best supportive care in patients with unresectable CRLMS; those trials were summarized in a recent meta-analysis[23]. The trials were conducted in an era when the best available systemic therapy was fluorouracil (5FU), which was the comparator in most of the trials. Notably, in two of the trials, 5FU rather than FUDR was infused into the hepatic artery (hepatic uptake of 5FU is much lower than that of FUDR), and in four of the trials, patients who progressed in the control arm crossed over into the HAIP arm, thus limiting the interpretation of survival outcomes. Nevertheless, the pooled data demonstrate a dramatic improvement in the tumour response rate for patients treated with HAIP (43% vs. 18%; relative risk: 2.26; $p < 0.001$). A trend toward improved overall survival was also observed in patients treated with HAIP, although that trend did not reach statistical significance (hazard ratio: 0.90; $p = 0.24$).

Since that time and despite the emergence of further data, HAIP chemotherapy has been largely confined to a limited number of specialized centres. Given the complexities of interpreting the data and the desire for more effective therapy for patients with unresectable CRLMS, we convened an expert panel to discuss the role of HAIP in the contemporary management of patients with CRLMS.

2. METHODS

We invited 28 medical and surgical oncologists from across Canada and the United States with expertise in CRLM and HAIP to participate in a consensus conference. Respondents were asked to complete a pre-meeting survey to identify initial perceptions about the evidence supporting HAIP in the treatment of CRLMS, the indications for HAIP, and the perceived barriers to implementation of HAIP therapy. Survey results were collated and used to develop an agenda for the meeting and preliminary consensus statements.

On September 7, 2012, 15 physicians representing 9 institutions in Canada and the United States attended a 1-day consensus conference in Toronto, Ontario. Patient representatives were also invited and participated in the meeting. Half the day was allocated for presentation of evidence about HAIP from experts in the field, with the remainder of the meeting dedicated to achieving consensus statements.

We presented the expert panel with a series of topics for discussion and several possible consensus statements for each topic based on the pre-meeting survey responses. The panel discussed each topic and attempted to come to a consensus, if possible. If complete consensus had not been reached at the end of the discussion for each topic, a vote was held, with an 80% majority being considered indicative of consensus.

3. CONSENSUS STATEMENTS

3.1 Role of Systemic Therapy in Combination with HAIP

Initial trials examining the efficacy of HAIP were performed in an era when the best available systemic therapy was 5FU, and patients were treated with HAIP alone. Since that time, the effectiveness of systemic therapy for metastatic colorectal cancer has been significantly improved. Most notably, the addition of irinotecan or oxaliplatin to conventional infusional 5FU has nearly doubled the response rate in metastatic colorectal cancer and significantly prolongs progression-free and overall survival[24–26].

There is a strong biologic rationale for combining HAIP with systemic therapy: In the absence of visible extrahepatic metastatic disease, nearly half the patients undergoing liver resection for CRLM will experience an extrahepatic recurrence, suggesting that occult extrahepatic metastatic disease is present from onset[27]. Given the high hepatic uptake of HAIP FUDR, very little chemotherapy reaches the systemic circulation, and therefore, in the absence of systemic therapy, occult extrahepatic metastases are not exposed to cytotoxic agents. Furthermore, the high hepatic extraction rate for FUDR means that nearly a full dose of systemic therapy can given concurrently, without increasing systemic toxicity.

Although no phase III trials involving HAIP in combination with systemic therapy have been conducted, several groups have examined the safety and efficacy of combination therapy in phase I and II trials. Kemeny and colleagues[28] from the Memorial

Sloan–Kettering Cancer Center studied 46 previously treated patients who received HAIP in combination with systemic irinotecan and found a response rate of 74%, with minimal toxicity. In a similar study with systemic oxaliplatin combinations in 36 patients (89% previously treated), response rates were 88%, with acceptable toxicity[29]. Ducreux and colleagues from Institut Gustave Roussy[30] reported an approach using oxaliplatin HAIP with systemic 5FU and leucovorin, achieving response rates of 64%, with minimal toxicity. These impressive outcomes in combination with the biologic rationale provide a compelling argument in favour of combining systemic therapy with HAIP. In most institutions that use HAIP chemotherapy, the combination of HAIP therapy with systemic chemotherapy remains the standard of practice.

Consensus Statement: Hepatic arterial infusion pump chemotherapy should be given in combination with systemic chemotherapy

3.2 Institutional Requirements for HAIP therapy

Delivering HAIP chemotherapy is a labour-intensive process, requiring multidisciplinary expertise. Enthusiasm for the widespread use of HAIP has been tempered in part by the relatively high rate of complications (both perioperative and long-term) and the high technical failure rate, which limits the infusion of chemotherapy agents into implanted pumps. Even in centres experienced in the technique, pump complications occur in approximately 20% of patients; however, many pumps can be salvaged, allowing chemotherapy to be infused in more than 90% of patients[31]. As with many surgical procedures, implantation of the hepatic arterial pump appears to have an associated learning curve, with fewer complications reported when surgeons have placed at least 25 pumps[31]. There is also almost certainly a relationship between institutional volume and outcomes. Indeed, in some trials, up to 34% of patients randomized to receive HAIP did not receive a single dose of chemotherapy through the pump because of complications; in other trials, all patients received some treatment[23].

Long-term complications, most notably biliary sclerosis, might also limit the duration of HAIP therapy. The overall incidence of biliary sclerosis is 4.6%, with the rate being higher in patients receiving adjuvant HAIP than in those being treated for unresectable disease (5.5% vs. 2.0% respectively)[32]. Although biliary sclerosis is a major complication, it can be effectively managed by inserting a biliary stent, and in the latter series, it did not affect overall survival.

The heterogeneity in pump failure rates between centers and the requirement for timely interventions in patients with complications underscore the importance of a well-coordinated multidisciplinary approach to HAIP therapy. Implantation of pump catheters requires expertise in hepatobiliary surgery. Medical oncologists with a specific interest in HAIP chemotherapy are critical, because the patients require close monitoring and chemotherapy dose adjustment as needed. Nuclear medicine physicians are required to conduct and interpret nuclear scintigraphy studies to ensure that extrahepatic perfusion is avoided. When extrahepatic perfusion is detected or when catheter-related complications occur, treatment can be salvaged with advanced interventional radiology techniques[33,34]. Finally, given the complexity of the care coordination and the frequency of tests and treatment in patients receiving HAIP therapy, dedicated nursing support is paramount to support a HAIP program.

Consensus Statement: Hepatic arterial infusion pump chemotherapy should be offered in the context of a multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.

3.3 Role of HAIP for Unresectable CRLMs

Novel treatment modalities are constantly expanding for patients with unresectable CRLMS: systemic therapy, HAIP chemotherapy, radioembolization, chemoembolization, and local ablative strategies (radiofrequency ablation, microwave ablation, external-beam radiotherapy)[35]. Few phase III trials have set out to compare modalities, given the challenge of incorporating the rapid evolution of the technologies and the highly selected nature of the patients for whom they are appropriate. Thus, clinicians managing patients with unresectable CRLMS must interpret incomplete evidence and discuss possible benefits and limitations of each approach with their patients when making treatment recommendations.

Apart from systemic therapy, the largest weight of evidence in favour of the various treatment modalities mentioned here lies with HAIP. Indeed, taking into account published reports of independent studies of HAIP, more than 3000 patients worldwide have been treated with HAIP and carefully followed[36]. The accumulated experience confirms that, in experienced centres, HAIP is safe and is associated with excellent tumour response rates.

In the first-line setting, data from randomized phase III trials of HAIP alone suggest an overall response rate of approximately 40%–50%[37–42], which is at least comparable to the best reported results from contemporary systemic therapy[1–3,43–45]. Data from phase I/II trials of HAIP in combination with modern systemic chemotherapy in previously untreated patients report response rates far higher, ranging from 64% to 100%[30,46].

In patients who have received prior chemotherapy, modern systemic chemotherapy combined with biologic agents produces response rates between 20% and 35% at best[14,17]. In contrast, HAIP in combination with systemic therapy after progression on systemic therapy alone achieves tumour response rates ranging from 62% to 85%[28,46,47].

The ability of HAIP to achieve downstaging to resectability deserves special consideration. In studies of systemic therapy, rates of downstaging are highly variable, ranging from 10% to 30%, largely attributed to varying definitions of surgical unresectability[3,5,7,12]. Rendering a patient with initially unresectable CRLMs resectable often requires achieving a durable complete response in at least some of the CRLMs. Unfortunately, at least 80% of patients with radiologic complete responses are found to harbour viable tumour cells when resected or to recur if followed radiologically[48]. In patients with initially unresectable CRLMs treated with HAIP, downstaging to resectability occurs in 25%–50% of patients; the percentage reaches up to 57% in chemotherapy-naïve patients[46,49]. Importantly, responses appear to be durable in patients with viable tumour cells, with local recurrences rarely observed, and 5-year overall survival in patients who undergo subsequent resection approaches 56%[49–51].

Consensus Statement: Hepatic arterial infusion pump chemotherapy in combination with systemic therapy should be considered in patients with unresectable CRLMs who have progressed on first-line systemic treatment. In addition, HAIP chemotherapy is acceptable as first-line treatment in patients with unresectable CRLMs.

3.4 Role of HAIP for CRLMs with Extrahepatic Disease

A large proportion of patients will present with limited extrahepatic metastatic disease and high-volume CRLMs. If the extrahepatic disease is technically resectable, carefully selected patients may also benefit from resection of all hepatic metastases[52,53]. This rationale has prompted some oncologists to consider the role of HAIP in patients with unresectable CRLMs and limited extrahepatic disease. Ammori and colleagues reported outcomes from 145 patients treated with HAIP in the setting of low-volume extrahepatic metastases, although in many of the patients, the presence of extrahepatic disease was uncertain at the time of HAIP implantation[54]. Median overall survival after HAIP implantation was 16 months; it was just 9 months for patients with multiple sites of extrahepatic disease. Given the limited data and overall poor outcomes in this patient population, routine use of HAIP in patients with extrahepatic disease is discouraged.

Consensus Statement: Hepatic arterial infusion pump chemotherapy is not recommended in the setting of extrahepatic disease outside the context of a clinical trial.

3.5 Role of HAIP After Resection of CRLMs (Adjuvant)

This consensus statement focuses primarily on the use of HAIP for unresectable CRLMs, but substantive data examining the role of HAIP chemotherapy in patients after complete resection of CRLMs (that is, in the adjuvant setting) have been developed. The biologic rationale for this approach is also strong: Although resection of CRLMs extends survival and offers patients the only chance of cure, approximately 80% of patients on long-term follow-up will eventually develop disease recurrence[55]. Furthermore, approximately one third of those patients will develop recurrence in the liver alone[27]. Adjuvant HAIP offers the potential to reduce the hepatic recurrence rate after resection of CRLMs.

Several well-conducted randomized controlled trials and a Cochrane review summarizing the data from 592 patients have examined the efficacy of adjuvant HAIP[56–58]. Inferences from the review are limited, because only three of the trials infused FUDR by HAIP; the remaining trials used 5FU, and only two trials administered concurrent systemic chemotherapy to patients. Allowing for those limitations, no significant difference was observed in overall survival between the pooled groups, although the confidence interval was wide (hazard ratio: 0.89 to 1.33). However, compared with patients receiving HAIP, control group patients experienced double the rate of intrahepatic recurrence.

No phase III trials have compared contemporary adjuvant systemic chemotherapy with contemporary chemotherapy combined with HAIP. In one phase I/II trial in 35 patients treated with FOLFOX (oxaliplatin, 5FU, leucovorin) and HAIP FUDR, the 4-year overall and progression-free survivals were 88% and 50% respectively[59]. The apparent benefit in intrahepatic disease recurrence must be weighed against the toxicity of long-term HAIP, particularly in patients who can potentially be cured[32]. Therefore, although HAIP chemotherapy combined with systemic therapy is an option in patients at high risk of intrahepatic recurrence after resection of CRLMs, further study is needed before the approach is routinely adopted.

Consensus Statement: Hepatic arterial infusion pump chemotherapy in combination with systemic therapy is an option for selected patients with resected CRLMs.

4. AREAS OF FUTURE STUDY

Despite a large body of research examining the efficacy of HAIP in patients with CRLMs, most questions remain unanswered. One avenue of potential study involves the implantation of the infusion pump and whether implantation could be accomplished using a less invasive technique. Several alternatives to laparotomy have been explored, including laparoscopy, robot-assisted techniques, and percutaneous approaches[60–68]. All the techniques have clear advantages over the conventional approach, but none has demonstrated consistently acceptable results with respect to pump function and complication rates.

Laparotomy therefore remains the "gold standard." However, with further innovation, a less-invasive technique of HAIP implantation may be possible.

The two main drugs delivered through HAIP are still FUDR and oxaliplatin. Further research might also explore the selective hepatic uptake of newer agents, and the potential to increase efficacy and reduce systemic toxicity by delivering them directly to the liver. Novel combinations of HAIP with contemporary systemic agents would also be valuable. In one recent trial, the addition of systemic bevacizumab to HAIP FUDR appeared to increase toxicity without improving outcomes; however, other biologic agents have not been studied[69]. Finally, novel functional hepatic imaging techniques might provide further insight into which patients are most likely to benefit from HAIP or might allow clinicians to detect tumour response earlier than is possible with conventional imaging studies.

Given the specialized institutional requirements for offering HAIP, it is likely that this treatment modality will continue to be available at only a few regional centres. A multi-institutional registry including all patients who undergo HAIP placement—regardless of whether they receive treatment—would be invaluable in assessing heterogeneity across centres and in answering some of the critical research questions posed here.

5. SUMMARY

In the increasing array of treatment modalities available for patients with unresectable CRLMS, HAIP chemotherapy has proved its efficacy. Its role in the context of multiple treatment options should continue to be studied and clarified. The consensus statements presented here provide a framework that clinicians who treat these patients can use in considering the role of HAIP (Table I). Further research is sorely needed, both to determine which patients can be optimally treated with HAIP and to improve the outcomes of patients who are treated using this approach.

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7. CONFLICT OF INTEREST DISCLOSURES

No financial conflict of interest exists for the authors.

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TABLE I Summary of consensus statements

HAIP chemotherapy should be given in combination with systemic chemotherapy.
HAIP chemotherapy should be offered in the context of a multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.
HAIP chemotherapy in combination with systemic therapy should be considered in patients with unresectable colorectal liver metastases who have progressed on first-line systemic treatment. In addition, HAIP chemotherapy is acceptable as first-line treatment in patients with unresectable colorectal liver metastases.
HAIP chemotherapy is not recommended in the setting of extrahepatic disease outside the context of a clinical trial.
HAIP chemotherapy in combination with systemic therapy is an option for select patients with resected colorectal liver metastases.

HAIP = hepatic arterial infusion pump.

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