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EDITORIAL

Treatment of liver metastases from colorectal cancer

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ABSTRACT

In recent years several new local as well as systemic treatment options have become available for patients with advanced colorectal cancer. A survey among Dutch hospitals revealed considerable differences in the use of diagnostic and therapeutic strategies. Radiofrequency ablation is a promising technique that is currently being investigated in a randomised trial. The role of adjuvant chemotherapy in patients with resectable liver metastases and of neoadjuvant chemotherapy in patients with nonresectable liver metastases has not been clearly established yet. The current status of local and systemic treatment options for colorectal cancer liver metastases is reviewed.

KEYWORDS

Colorectal carcinoma, liver metastases, (neo)adjuvant chemotherapy, radiofrequency ablation

Colorectal cancer is one of the most common malignant tumours, accounting for at least 1,000,000 new cases worldwide and leading to more than 500,000 deaths each year. About half of the patients with colorectal cancer develop distant metastases during the course of their disease. In recent years, much progress has been made in the systemic treatment of patients with nonresectable advanced disease.[1] This is attributed to new cytotoxic agents, such as oxaliplatin and irinotecan, as well as to the development of oral fluoropyrimidines, capecitabine and uracil-Ftorafur, that are at least as effective but less toxic than intravenous 5-fluorouracil (5-FU).[2,3] More recently, the addition to chemotherapy of the signal transduction inhibitors cetuximab and bevacizumab, was shown to result in increased efficacy. Over a time span of some 20 years this has resulted in an improvement in the median overall survival for patients with advanced colorectal carcinoma from eight months with supportive care alone to approximately 21 months, and of the one-year survival rate from 34 to 74%.[4]

About 10 to 15% of these patients present with metastases confined to the liver that are resectable. In this selected subgroup resection of liver metastases can result in five-year survival rates of 20 to 40%, depending on prognostic factors such as the number and size of the lesions, free resection margins and extrahepatic disease at the time of surgery.[5] Less important factors are time between primary tumour and development of liver metastases, staging of the primary tumour and carcinoembryonic antigen (CEA) level.[6] Approximately 61% of the patients have recurrence of disease after resection of liver metastases, with the liver as the only site of tumour activity in approximately 50%.[7] Although formal randomised studies between chemotherapy and liver metastasectomy have not been performed, surgery is the treatment of choice for liver metastases when a radical resection appears feasible and when no clinical evidence of extrahepatic disease is present. The major reason for this is the very inferior results of systemic treatment in historic controls. However, one should be aware of a pitfall in the interpretation of this comparison, since large databases of patients with resectable disease confined to the liver who have been treated with chemotherapy alone are not available. Therefore, these historic controls consist of many patients who also have extrahepatic disease and with that a worse prognosis, which implies that the true benefit of resection over systemic therapy is unknown.

The article by Bipat *et al.* published in this issue evaluates the diagnostic and therapeutic strategies of 74 Dutch hospitals concerning patients with advanced colorectal carcinoma by means of a survey among oncology committees in the Netherlands.[8] Liver surgery is performed

in 30 out of 73 hospitals. Neoadjuvant or adjuvant treatment combined with liver surgery and local ablative therapies is used in 71 and 64% of the participating hospitals, respectively.

The differences between the participating hospitals nicely reflect the issues of debate in the treatment of patients with metastases confined to the liver. These are: 1) What is the role of (neo)adjuvant chemotherapy in patients with resectable metastases? 2) Can primary nonresectable liver metastases become resectable after downstaging by chemotherapy? and 3) What is the benefit of local ablative therapies, such as radiofrequency ablation (RFA), when some or perhaps all lesions do not appear to be radically resectable?

The survival benefit for adjuvant chemotherapy in stage III and high-risk stage II colon carcinoma patients[9] suggests a possible role of (neo)adjuvant chemotherapy in patients with resectable liver metastases. A phase II study using irinotecan following resection of liver metastases estimates a median relapse free survival of 45.2 months. Two-year overall survival was 85%.[10] Comparing adjuvant systemic or regional chemotherapy with surgery alone shows an improved survival of adjuvant chemotherapy after hepatic resection for colorectal liver metastases in a small series.[11] However, convincing evidence obtained from a randomised controlled trial, supporting the use of neoadjuvant or adjuvant chemotherapy in patients with resectable colorectal liver metastases, is not yet available. The European Organisation for Research and Treatment of Cancer (EORTC) study 40983 compares preoperative and postoperative chemotherapy with 5-FU, leucovorin and oxaliplatin with surgery alone in 364 patients with potentially resectable colorectal liver metastases. The results of this study are expected in 2006.[12] Currently it is not advised to administer adjuvant chemotherapy in this setting outside the scope of clinical trials.

With respect to the second question, neoadjuvant chemotherapy might be used as an approach to increase the resectability rate of liver metastases. Downstaging with systemic chemotherapy ultimately leads to resection in 10 to 40% of primarily nonresectable liver metastases.[13] However, again many data are obtained from small noncomparative studies. A large case series by Adam describes a five-year survival rate of 34% in 95 patients that ultimately underwent resection out of 701 patients treated with chemotherapy for downstaging of liver metastases.[14] However, when the intent-to-treat principle is applied the five-year survival of the total patient cohort was only 4.6%.[1] Comparable survival rates may also be achieved in subgroups of patients with nonresectable liver metastases treated with optimal chemotherapy. Thus, the absolute benefit of resection of liver metastases after downstaging with chemotherapy compared with chemotherapy alone in a subgroup of patients in good clinical condition without extrahepatic disease remains to be established.

The third question concerns the role of a novel experimental local therapy for primary nonresectable liver metastases: radiofrequency ablation (RFA). RFA locally destroys tumour cells by generation of high-frequency current, inducing cell death by heat induction. RFA can be performed percutaneously, via open surgery, or by laparoscopy. The role of RFA in treating liver metastases of colorectal cancer is being studied in EORTC 40004, the CLOCC study. In this study the 30-month survival rate of chemotherapy with or without RFA is established in patients with nonresectable colorectal liver metastases. Results are not yet available. However, several case series studying RFA provide promising results. In a study by Berber *et al*. 135 patients with nonresectable liver metastases underwent RFA,[15] of whom 80% were previously treated with chemotherapy and 30% had extrahepatic disease at the time of RFA. The mean survival was 28.9 months after RFA and 44.6 months after diagnosis of liver metastasis. Extrahepatic tumour progression occurred in 41% of the patients. Local recurrence of disease after RFA occurred in 2 to 40%.[16] Currently, the use of RFA cannot be recommended as a standard procedure in the treatment of colorectal cancer liver metastases.

In conclusion, treatment strategies for colorectal cancer liver metastases are rapidly changing. Ongoing randomised trials are assessing the role of (neo)adjuvant chemotherapy in patients with resectable liver metastases, and RFA in patients with nonresectable disease as an adjunct to chemotherapy. As mentioned by Bipat *et al*.,[8] a national guideline, which is currently in progress, will contribute to an optimal and evidence-based use of the therapeutic options for patients with colorectal liver metastases.

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SHORT REVIEW

Extranodal marginal zone (MALT) lymphoma in common variable immunodeficiency

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ABSTRACT

We describe two patients with common variable immunodeficiency (CVID) who developed extranodal marginal zone lymphoma (formerly described as mucosa-associated lymphoid tissue lymphoma or MALT lymphoma). One patient, with documented pernicious anaemia and chronic atrophic gastritis with metaplasia, developed a *Helicobacter pylori*-positive extranodal marginal zone lymphoma in the stomach. Three triple regimens of antibiotics were necessary to eliminate the *H. pylori*, after which the lymphoma completely regressed. Patient B had an *H. pylori*-negative extranodal marginal zone lymphoma of the parotid gland, which remarkably regressed after treatment with clarithromycin.

Reviewing the literature, we found eight cases of extranodal marginal zone lymphoma complicating CVID, but probably many more cases labelled as non-Hodgkin's lymphoma are hidden in the literature.

Until more data are available on the predictive value of noninvasive screening for pathology of the stomach, we recommend endoscopy to assess the gastric status in CVID patients in order to detect these malignancies at an early stage.

Elimination of *H. pylori* infection is the treatment of choice in *Helicobacter*-positive extranodal marginal zone lymphoma. The possibility of elimination failure, most probably due to frequent and prolonged exposure to antibiotics in this patient group, should be taken into account. Treatment with antibiotics in *Helicobacter*-negative extranodal marginal zone lymphoma must be considered.

KEYWORDS

Common variable immunodeficiency, extranodal marginal zone, *Helicobacter pylori*, hypogammaglobulinaemia, lymphoma, MALT

INTRODUCTION

In 1983, Isaacson and Wright introduced the term mucosa-associated lymphoid tissue (MALT) lymphoma to characterise a primary low-grade B-cell lymphoma originating in the gut-associated lymphoid tissue.[1] Nowadays, the nomenclature has been changed to extranodal marginal zone lymphoma, representing extranodal low-grade B-cell lymphoma with a similar histology, also occurring in the salivary glands and lungs.

The normal gastric mucosa contains no organised lymphoid tissue. Bacterial colonisation of the gastric mucosa leads to lymphoid infiltration, which becomes the basis for the evolution to extranodal marginal zone lymphomas. There are several strands of evidence for a causal relationship between *Helicobacter pylori* and extranodal marginal zone lymphoma. First of all, *H. pylori* infection is present in more than 90% of the patients with this lymphoma.[2-4] Immunological studies show *in-vitro* and *in-vivo* evidence for a causal relationship between *H. pylori* and extranodal marginal zone lymphoma.[5,6] Perhaps most importantly, several studies prove that elimination of *H. pylori* leads to regression of this type of lymphoma in approximately three quarters of the cases.[7-12] Other micro-organisms, such as *Chlamydia psittaci*, *Borrelia burgdorferi* and *Campylobacter jejuni*, have been incriminated to play a causal role.[13-16]

Hypogammaglobulinaemia is a primary immunodeficiency disorder. The two main types are X-linked hypogammaglobulinaemia (XLA) and common variable immunodeficiency (CVID). These diseases do not only predispose to infection but also bear increased risk of cancer. In XLA, there is an increased risk for colorectal cancer,[17] whereas patients with CVID have an almost 50-fold increased risk for gastric cancer and a 30-fold increased risk for lymphoma.[18] The risk for lymphoma in CVID is estimated to lie between 1.4 and 7%.[19-21]

In this paper, we present two CVID patients who incipiently developed extranodal marginal zone lymphoma, underlining the need for awareness of this complication in such patients. We also give a brief review of the cases of extranodal marginal zone lymphoma in CVID described in the literature.

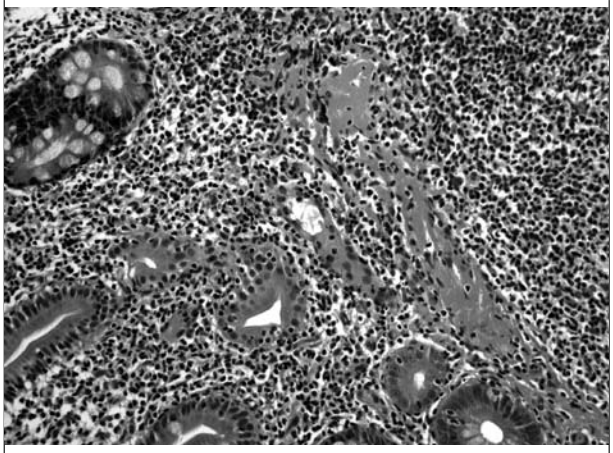
CASE REPORTS AND METHODS

Patient A, a male born in 1937, had suffered from recurrent infections of the (upper) respiratory tract, ear, nose, throat region and gastrointestinal tract since early childhood. In 1965, at the age of 28, the diagnosis of CVID was made. This was a reason to start prophylactic antibiotics. In 1985, pernicious anaemia was diagnosed and vitamin B12 substitution was started. In 1991, the patient was first seen in our hospital and since then has been treated with intravenous immunglobulins. In spite of this treatment, recurrent infections of the respiratory tract necessitated antibiotic prophylaxis.

In 1991, gastroscopy yielded chronic atrophic gastritis with a severe intestinal metaplasia of the fundus. Serum gastrin was 250 ng/l (normal range 10 to 70 ng/l). The severe metaplasia was the reason for regular endoscopies, which always showed the same picture. In October 1999, *H. pylori* infection was diagnosed. The patient received a ten-day course of amoxicillin 500 mg three times a day, metronidazole 500 mg three times a day and omeprazole 40 mg once a day. In February 2000 a control gastroscopy was performed. Histology and culture of the biopsies still showed *H. pylori*, which appeared to be resistant to metronidazole and tetracycline and susceptible to amoxicillin and clarithromycin *in vitro*. Treatment was installed with clarithromycin 500 mg twice daily, amoxicillin 500 mg four times a day and ranitidine bismuth citrate 400 mg twice daily. The next endoscopy in August 2000 revealed normal mucosa without evidence of *H. pylori* infection in the biopsies. One year later, active *H. pylori*-associated gastritis with a extranodal marginal zone lymphoma was found localised in the corpus (*figure 1*). No translocation t(11;18) was found with the fluorescence *in situ* hybridisation (FISH) and reverse transcription polymerase chain reaction (tr-PCR) methods. After two weeks of treatment consisting of high-dose amoxicillin (4 g/day), clarithromycin (1.5 g/day) and pantoprazole, *H. pylori* was no longer detectable by histology and C^{14}-urea breath test. Control endoscopy with extensive biopsies in February 2002 did not reveal any signs of extranodal marginal zone lymphoma, neither did any of the six-monthly follow-up endoscopies since then.

Patient B, a male born in 1967, presented in 2001 with a short period of fever and splenomegaly after a tropical journey. A specific tropical disease could not be diagnosed. However, a history of the recent development of frequent upper respiratory tract infections and occasional abdominal pain with diarrhoea directed us to the diagnosis of CVID. Treatment with intravenous immunoglobulins was started in 2001. During the regimen of monthly supplementation, infections remained a problem and immunoglobulins had to be increased by dose and administered every three weeks. In 2004 the patient complained of jaw pains and loss of weight. Physical examination revealed a periauricular tumour. A biopsy showed a low-grade extranodal marginal zone lymphoma from the salivary gland. Positron emission tomography (PET) showed only elevated activity at the cervical site. Gastroscopy with multiple biopsies showed a normal gastric mucosa. There was no evidence for *H. pylori* infection in the biopsies, by culture, PCR and C^{14}-urea breath test. No translocation t(11;18) was found either. Because of the absence of *H. pylori* infection, several other micro-organisms such as cytomegalovirus, Epstein Barr virus, hepatitis B and C virus, human herpes virus 6, *Bartonella henselae, Mycoplasma* and *Chlamydia* species were excluded by PCR in the tissue of the lymphoma. In addition, 16S RNA in the tissue was negative. The patient was treated with high-dose clarithromycin for six weeks. After this treatment the tumour vanished clinically as well as on positron emission tomography.

Figure 1. *Gastric biopsy from the pyloric region with dense, monomorphous small lymphocytic infiltrate and a lymphoepithelial lesion*



Immunohistochemistry showed CD20 positivity, confirming that this represents extranodal marginal zone lymphoma.

REVIEW OF THE LITERATURE

To review the literature on CVID and extranodal marginal zone lymphoma, we performed a PubMed search in English using the following terms: CVID, agammaglobulin(a)emia, hypogammaglobulin(a)emia, lymphoma, extranodal

marginal zone lymphoma, MALT, cancer, neoplasia, and *Helicobacter pylori*.

This search yielded eight cases of extranodal marginal zone lymphoma in CVID, most of which were published quite recently. The pertinent data from these cases are presented in *table 1*. In 2001, Reichenberger *et al*. published a case report of a CVID patient with a pulmonary MALT lymphoma.[23] In 2002, Cunningham-Rundles *et al*. published a cohort study of 248 CVID patients. In a period of 25 years, 22 cases of B-cell lymphoma were found, five of which were classified as MALT lymphomas. Three of these were pulmonary lymphomas, and two where localised in the salivary glands. There are no data of the *H. pylori* status in these patients.[22] Tcheureckdjian *et al*. recently published two CVID patients with nonparotid cranial MALT lymphomas (*table 1*).[24]

DISCUSSION

In this paper, two patients with CVID and extranodal marginal zone (MALT) lymphoma are described. In both patients the diagnosis was not suspected clinically. In one patient the lymphoma was associated with *H. pylori* infection, and both responded to antimicrobial therapy.

Although malignant lymphoma as a complication of CVID is well established,[11-28] there is a limited number of published reports on extranodal marginal zone lymphoma in CVID, and these are recent. Most probably, quite a number of cases of extranodal marginal zone lymphoma are hidden in the older literature on lymphoma and CVID.

In our own series of 49 patients with hypogammaglobulinaemia, published in 2002, patient A was the only case of extranodal marginal zone lymphoma; one other case of non-Hodgkin's B cell lymphoma was encountered in that series.[29]

As described, antibiotics cause regression of *H. pylori*-positive extranodal marginal zone lymphoma and are therefore the treatment of first choice. It turned out to be difficult to eliminate the *H. pylori* in patient A; multiple courses were needed. Why was it so hard to treat the infection? A possible explanation could be the exposure to multiple antibiotics, and subsequent resistance in our patient. The *H. pylori* isolate of patient A was found to be resistant to tetracycline and metronidazole *in vitro*. *H. pylori* resistance to metronidazole is well known; in developing countries resistance is up to almost 100%, whereas in developed countries resistance ranges from 10 to 50%. Detecting resistance to metronidazole predicts the success of treatment. For instance, treatment of a metronidazole-resistant *H. pylori* infection with a triple regimen consisting of metronidazole, clarithromycin and a proton pump inhibitor meets with a success rate of 73% against 97% for a susceptible strain.[30] Finding macrolide resistance (which was not the case here) is a much stronger predictor for treatment failure. *H. pylori* resistance for amoxicillin is rare.[30,31]

Another factor explaining the failure to eradicate *H. pylori* in our patient may be that there is impaired host response against *H. pylori* in CVID. In that respect, Borody *et al*. have attributed treatment failure to low concentrations of interleukin 4 in whole blood.[32,33] We have no information on the interleukin-4 concentration in our patients.

Table 1. *Published cases of extranodal marginal zone lymphoma in common variable immunodeficiency patients*

Case	Ref.	Sex	Localisation	*H. pylori*	Treatment	Result
1	21	F	Parotid	Unknown	1. Radiation and excision 2. Excision, CHOP, rituximab	Recurrence after initial therapy
2	21	F	Lung	Unknown	None	Clinically well
3	21	F	Parotid	Unknown	1. Excision 2. Excision and radiation	Recurrence after initial therapy
4	21	M	Lung	Unknown	1. CVP and rituximab 2. CHOP	Recurrence after initial therapy
5	21	F	Lung	Unknown	Rituximab, CHOP	No recurrence
6	22	F	Lung	Bacterial infection excluded, *H. pylori* not especially mentioned	1. Chlorambucil and prednisone 2. Chlorambucil	Primary partial remission but recurrence
7	23	F	Cranial	Unknown	Dexamethasone, doxorubicin, cyclophosphamide and vinblastine	Complete remission
8	23	F	Cranial	Unknown	Rituximab	Complete remission

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; rituximab = monoclonal antiCD20.

The difficulty to treat *H. pylori* in this patient is reminiscent of the failing treatment of *Campylobacter jejuni* infections in hypogammaglobulinaemic patients, in whom a bactericidal effect of serum is lacking due to the deficiency of IgM.[34] We have found defective bactericidal activity of serum of this patient against *H. pylori* (Desar, manuscript in preparation), but it is currently unclear to what extent this contributed to the difficulty of treatment.

In patient B, *H. pylori* infection could not be demonstrated. It is intriguing that the tumour nevertheless responded to antibiotic treatment. The hypothesis was that in this patient, who had been treated regularly with β-lactam antibiotics such as amoxicillin-clavulanic acid, *Chlamydia* might have been the cause of continuous stimulation of (the lymphatic tissue surrounding) the parotid gland. Lymphoma associated with *C. psittaci* has been reported especially in the ocular region. DNA of *Chlamydia* has been detected in 80% of tumour biopsies and in 50% of peripheral blood mononuclear cells (PBMCs) of these patients.[13] Even regression has been shown with treatment with doxycyclin.[14] Since the tumour has not relapsed so far, it is most likely that this is due to a direct antimicrobial effect of the macrolide. The alternative, an immunomodulatory effect, would probably have led to a more transient success.[35] As described, a variety of microbial agents have been incriminated as potential causes of extranodal marginal zone lymphoma. In our patient, we did not find evidence for other pathogens, especially macrolide-susceptible ones. Further studies on the effect of antibiotic therapy in the treatment of *H. pylori*-negative extranodal marginal zone lymphoma are needed. In the individual patient, one may consider trying antibiotic treatment before embarking on treatment with anti-B-cell monoclonal antibodies, radiotherapy or cancer chemotherapy, as has been done in the literature (*table 1*).

In conclusion, extranodal marginal zone lymphomas are an important complication of CVID. They can arise insidiously. Based on the current knowledge of CVID and the lack of data on the predictive value of noninvasive screening for pathology of the stomach, we believe it is good clinical practice to screen for antrum gastritis, neoplasia (carcinoma as well as extranodal marginal zone lymphoma) and *H. pylori* infection by endoscopy. As mentioned, the risk of gastric carcinoma and extranodal marginal zone lymphoma is high in CVID patients, conform the risk of other tumours in which screening is well accepted.[18-29,36] Symptoms present late in an advanced stage of disease with serious clinical consequences. After an initial evaluation, a follow-up regimen could be scheduled depending on the findings. In case of serious dysplasia, we recommend endoscopic screening on a regular basis at six-monthly intervals; patients with mild dysplasia should be screened each year. If the initial screening shows no dysplasia, screening can be done every three to five years. A cost-benefit analysis of such policy cannot be given at this point in time, but the patient group is limited.

With respect to the noninvasive tests, the value of the urease breath test needs further evaluation in these patients. Because of the failure to mount an antibody response, *H. pylori* serology is not useful. When *H. pylori* is detected in a patient with CVID, it is probably wise to start specific antimicrobial treatment, but eradication may fail. Furthermore, the findings of *Chlamydia* DNA in lymphoma tissue and PBMCs in patients with extranodal marginal zone lymphoma of the ocular adnexa warrant systematic research on other micro-organisms with help of DNA techniques and subsequently considering of antibiotic treatment.

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ORIGINAL ARTICLE

Capecitabine, epirubicin and cisplatin in the treatment of oesophagogastric adenocarcinoma

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ABSTRACT

Background: Inoperable or metastatic oesophagogastric adenocarcinoma has a poor prognosis. From the many different chemotherapeutic regimens used in the past, a combination of epirubicin, cisplatin and continuous 5-fluorouracil infusion (ECF) showed a consistent response rate of ± 50% with acceptable toxicity. Continuous 5-FU infusion may be replaced by oral fluoropyrimidines. Here we evaluate treatment with epirubicin and cisplatin combined with oral capecitabine (ECC), replacing intravenous 5-FU infusion.

Methods: Retrospectively, we analysed 23 consecutive patients who were treated with epirubicin, cisplatin and oral capecitabine for inoperable or metastatic oesophagogastric adenocarcinoma during 2002 and 2003.

Results: The overall response rate was 57%; another 26% achieved stable disease and only 17% had progressive disease. The median duration of response was 6.4 months; the median survival was 9.0 months. Previously treated patients (n=10) had a significantly worse overall response rate (20%) compared with previously untreated patients (85%). A nonsignificant difference in median survival was found between these groups (3.9 *vs* 9.8 months in previously treated *vs* untreated patients). An acceptable incidence of grade 3 and 4 toxicity was found.

Conclusion: Capecitabine in combination with epirubicin and cisplatin is an effective and safe alternative to ECF, without the risks of a continuous venous access.

KEYWORDS

Capecitabine, chemotherapy, inoperable, metastatic oesophagogastric carcinoma

INTRODUCTION

Adenocarcinoma of the distal oesophagus and stomach often presents at a late stage with locally advanced or metastatic disease, which explains the poor prognosis. The incidence of oesophageal adenocarcinoma and cancer originating at the gastro-oesophageal junction is rising, in contrast to oesophageal squamous cell carcinoma and the even declining incidence of distal gastric cancer.[1-3]

The tumour readily spreads to adjacent, mediastinal and supraclavicular lymph nodes, peritoneum, liver, lungs and pleura. Only a minority of patients with oesophageal or gastric cancer is considered for curative resection and even then, there is high rate of local or metastatic recurrence, resulting in an overall five-year survival of less then 10%.[1,2] The local extension of the disease can be measured with CT scan and endoscopic ultrasound. Chemotherapy with single agents has a limited response rate in advanced oesophagogastric cancer. Many former reference regimens such as FAM (5-FU, adriamycin and mitomycin) and FAMTX (5-FU, adriamycin and methotrexate) have fallen into disregard, as the initial response rates of 40 to 50% were only 10 to 20% in confirmatory phase III trials.[4-6] A general phenomenon in comparative studies is a survival of 9 to 11 months for the 'best' regimen *vs* six to seven months for the 'former best' regimen, but a mere three to five months with best supportive care only.[7] This story has been somehow repeated with the ECF regimen, although this regimen has consistently shown a response rate of ± 50% and limited toxicity.

The ECF regimen was developed because of the single-agent activity of epirubicin, cisplatin and 5-FU and the synergy between 5-FU and cisplatin in experimental models.[8] An anthracycline was added to enhance cytotoxicity; epirubicin was preferred to minimise side effects in terms of mucositis and cardiac toxicity. The

choice for continuous venous infusion of 5-fluorouracil was based on the data of an enhanced response rate and less bone marrow toxicity in colorectal cancer.[9] The first phase II results showed an impressive response rate of 71%.[10] In a multicentre phase III study response rate was 45%, but still significantly superior to the 'reference' FAMTX regimen that showed only a 21% response rate. Toxicity data, time to progression and survival (8.9 months *vs* 5.7 months) were also all significantly in favour of the ECF regimen.[6,11] The high response rates and manageable toxicity, also with the venous access system, have been confirmed by others.[10,12-14]

With the introduction of oral 5-FU analogues an alternative for prolonged or continuous administration of intravenous 5-FU has become available. The oral fluoropyrimidine capecitabine has proven to be at least as effective as 5-FU with leucovorin in the treatment of metastatic colorectal and breast carcinoma.[15-17] The drug is absorbed rapidly from the intestine as an intact molecule and converted to 5-FU in the liver and tumour cells. Patients with colorectal cancer treated with capecitabine as compared with intravenous bolus of 5-FU showed significantly less grade 3-4 mucositis and neutropenia, but significantly more grade 3 hand-foot syndrome and uncomplicated grade 3-4 hyperbilirubinaemia.[15,16] A dose-finding study of epirubicin, cisplatin and capecitabine replacing infusional 5-fluorouracil has already been performed in patients with inoperable oesophagogastric cancer.[18]

We started to treat patients with locally advanced or metastatic adenocarcinoma of the oesophagogastric region with epirubicin and cisplatin in combination with oral capecitabine (ECC) instead of the previously used intravenous 5-FU (ECF-regimen). In this paper we describe the side effects as assessed by Common Toxicity Criteria (CTC), the efficacy or response rate of this treatment regimen, as well as the duration of response and the overall survival.

MATERIALS AND METHODS

We analysed retrospectively all the patients in our hospital who had started treatment with ECC for inoperable or metastatic oesophagogastric adenocarcinoma from January 2002 to December 2003. The ECC regimen was repeated every three weeks. Epirubicin and cisplatin were both given intravenously at day one at a dose of 50 mg/m^2 and 60 mg/m^2, respectively. Capecitabine was given at a dose of 1000 mg/m^2 twice daily for 14 days. Standard supportive care with an HT-3 antagonist plus dexamethasone as well as pre- and posthydration to prevent cisplatin-induced nephrotoxicity were used and required hospital admission for two days.

Data were collected concerning doses and dose adjustments, response to therapy, side effects, duration of response, and survival. Response to therapy was measured after every second or third cycle and at the end of treatment by means of CT, ultrasound, or X-rays. If the lesion could not be measured by X-ray, endoscopy was used. Response was defined according to RECIST criteria.[19] Toxicity was graded according to the USA National Cancer Institute CTC scale version 2.0. Nausea and vomiting, hand-foot syndrome, neuropathy, anaemia, leucopenia, thrombocytopenia, hyperbilirubinaemia, transfusions, infections, and hospital admissions were evaluated.

Duration of response was defined as the period from the first day of treatment until documented progression, while the duration of overall survival was defined as the period from the first day of treatment until death or end of follow-up.

Statistics

Survival data were examined using the Kaplan-Meier method. The log-rank test was used to test for between-group differences in survival. Between-group differences in proportions were compared using the χ^2 test.

RESULTS

Patient characteristics

During 2002 and 2003, 23 patients (19 men and 4 women) with inoperable or metastatic oesophagogastric adenocarcinoma were treated with ECC in our hospital. All patients had a World Health Organisation performance score of 0 to 2. A median of 5.5 courses (range 1 to 8) was delivered. Clinical data are presented in *table 1*. There was a male

Table 1. *Patient characteristics*

	Patients (n)	%
Male	19	83
Female	4	17
Median age (range), years	61 (42-71)	
Primary tumour site		
Distal oesophagus	6	26
Gastro-oesophageal junction	2	9
Gastric	15	65
Metastatic disease	20	87
Histology (differentiation)		
Adenocarcinoma		
Poor	7	30
Intermediate	7	30
Good	1	4
Unclassified	7	30
Nonspecified carcinoma	1	4
Previous treatment		
None	13	57
Resection	6	26
Radiation	1	4
Radiation with chemotherapy	3	13

predominance (83%). Twenty of 23 patients had metastatic disease. The six patients who had undergone previous resection, five with curative intent, presented from one month until 13 years (median 12 months) after operation.

Efficacy and survival

The response results are presented in *table 2*. Three patients had a complete response (CR) and ten patients a partial response (PR), resulting in an overall response rate of 57%. Another six patients (26%) had stable disease. Three patients could not be evaluated for response; two of them died shortly after their first course, and a third patient chose not to continue because his physical condition declined rapidly after the first cycle of chemotherapy. The median duration of response was 6.4 months; the median survival was 9.0 months (*figure 1*).

No relation between response and tumour location, or differentiation grade was found. However, there were differences in outcome in the previously treated group compared with the previously untreated group. In ten patients who had received treatment for their oesophagogastric carcinoma in the past (resection, brachytherapy or radiation plus cisplatin therapy in six, one and three patients, respectively), only two patients (one with a resection and the other with radiation plus chemotherapy in the past) achieved a partial response (20%). Compared with an overall response of 85% (3 CRs and 8 PRs) in the group of 13 patients who had not received previous therapy, this is a significant difference in response rate ($p<0.01$). Also a difference in median survival was found between the previously treated group (3.9 months) and the previously untreated group (9.8 months), however this difference was not significant ($p=0.39$), probably due to the small number of patients.

Adverse events

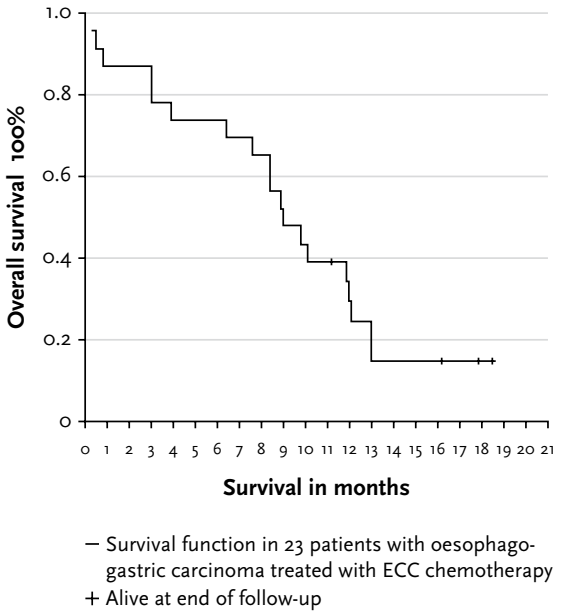
The adverse reactions are presented in *table 3*. Most side effects were mild, grade 1 or 2. Nausea was the most common side effect (n=15), but only one patient had grade 3-4 vomiting. Also, most haematological toxicity was of grade 1-2 severity. Serious haematological side effects were limited to grade 3-4 anaemia in two and leucopenia in four patients. The latter resulted in one period of febrile neutropenia. Erythrocyte transfusions were given to nine patients. Erythropoietin was not used. Miscellaneous infections (herpes simplex infection, rhinitis, bronchitis, wound infection, jaw abscess, and streptococcal bacteraemia) were reported in six patients, requiring hospitalisation in three of them. The wound infection developed during a period of grade 4 leucopenia; the abscess and bacteraemia with grade 1 leucopenia. Three other patients were admitted for treatment-related problems (nausea, dehydration and a brachial vein thrombosis).

Table 2. *Response rates in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*

Response	Patients (n)	%
Overall response (CR and PR)	13	57
Complete response	3	13
Partial response	10	43
Stable disease	6	26
Progressive disease	4	17
Documented progression	1	4
Not evaluable	3	13
Total	*23*	*100*

ECC = a combination of epirubicin, cisplatin and oral capecitabine; CR = complete response; PR = partial response.

Figure 1. *Survival in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*



ECC = a combination of epirubicin, cisplatin and oral capecitabine.

Shortly after the first course one patient died of a massive ischaemic cerebrovascular accident and another patient died probably due to massive pulmonary embolism.

Dose adjustments

Dose reduction was considered necessary in eight patients. In three this was due to hand-foot syndrome, in four because of nausea and/or vomiting, and in one because of neuropathy. Reductions were made after a median of three courses (range 3 to 6) resulting in administration of 96, 95 and 87% of intended epirubicin, cisplatin and capecitabine doses, respectively. Dose interruption took place in two patients for one and two weeks, because of nausea and hand-foot syndrome, respectively.

Table 3. *Adverse events in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*

Toxicity*	Grade 1-2		Grade 3-4	
Nonhaematological	**Patients (n)**	**%**	**Patients (n)**	**%**
Nausea	15	65	1	4
Vomiting	4	17	1	4
Stomatitis	1	4	0	0
Diarrhoea	1	4	0	0
Hand-foot syndrome	5	22	2	9
Neuropathy	5	22	2	9
Hyperbilirubinaemia	1	4	0	0
Haematological				
Anaemia	7	30	2	9
Leucopenia	12	52	4	17
Thrombopenia	6	26	0	0
Red cell transfusion	7	30	2	9

*Toxicity was scored according to the NCI-CTC criteria. ECC = a combination of epirubicin, cisplatin and oral capecitabine.

DISCUSSION

Patients with locally advanced or metastatic adenocarcinoma of the distal oesophagus or stomach have a poor prognosis. Overall response rates of chemotherapeutic 'reference' regimens used in the past were 9 to 41%.[4,12,20] The ECF regimen is currently considered by many oncologists as the 'new reference' regimen, as the response rate in several phase II and phase III studies is consistently about 50% with acceptable toxicity.[6,10-14] However, because the continuous infusion of 5-FU by a port-a-cath may result in infection or thrombosis of the venous access, we changed the continuous 5-FU (200 mg/m²/day = 4200 mg/m²/cycle) into 14 days of capecitabine (1000 mg/m² twice daily = 14 x 2000 mg/m² per cycle), based on a phase I and pharmacokinetic study.[18]

Our results with the ECC regimen, showing a response rate of 57%, including a complete response rate of 13%, are well in line with previous results obtained with the ECF regimen. In two studies in 111 and 220 evaluable patients, the overall response rates were 45 and 61% with CR rates of 6 and 11%.[6,21] Apart from the overall response rate of 57%, a stable disease rate of 26% may also be of significance provided symptomatic benefit and a low rate of toxicity is observed. In our six patients with stable disease symptomatic benefit was observed in four and significant toxicity was seen in two. Only 17% of patients had progressive disease during treatment.
The median duration of response in this retrospective analysis was 6.4 months and comparable with the data obtained with the ECF regimen.[6,21] This was measured once patients were again symptomatic and not by routine imaging examination. The median survival time of nine months, on the other hand, could be determined accurately, showing a similar survival, compared with studies using the ECF regimen. The study by Bamias *et al.* reported an overall survival of 8.4 months with 6.2 months failure-free survival.[21] Webb *et al.* found a median survival time of 8.9 months with ECF and median failure-free survival duration of 7.4 months.[6] From trials from the early 1990s, the median survival in untreated patients has shown to be three months.[7]

An acceptable incidence of grade 3 and 4 toxicity was found. The primary toxicity was nausea with mainly grade 1-2 severity. More severe nausea and vomiting was reported in just one patient. Most patients suffering from nausea and/or vomiting had these side effects every first week of a treatment cycle. In the future the incidence of severe nausea can possibly be lowered further by administration of new antiemetics such as the NK-1 antagonist aprepitant.[22]
In studies comparing intravenous 5-FU with capecitabine in the treatment of colorectal cancer, 5-FU bolus treatment showed significantly more stomatitis (grade 3-4: 12 to 13.3% *vs* 1.3 to 2%) and grade 3-4 leucopenia (9.7 to 26% *vs* 2 to 2.4%), with leucopenic fever and sepsis (1 to 3% *vs* 0 to 0.3%). On the other hand capecitabine-treated patients suffered significantly more grade 3 hand-foot syndrome (16.2 to 18% *vs* 0.3 to 0.6%) and hyperbilirubinaemia (18.6 to 28.3% *vs* 5.9 to 6.6%).[15,16]
Our data also show a low incidence of stomatitis reported in only one patient. Seven patients developed hand-foot syndrome of which two (9%) severe (grade 3). In all cases it responded to interruption or dose reduction. Overall the doses given were only slightly limited. Remarkably, we did not find hyperbilirubinaemia in our patient group. A possible explanation is the lower capecitabine dose used in ECC: 1000 mg/m² twice daily *vs* 1250 mg/m² twice daily in monotherapy for colorectal carcinoma.

Haematological toxicity grade 3-4 occurred in 17% of patients. In four patients (17%) grade 3-4 leucopenia was found. Only one episode of febrile neutropenia occurred. Two possible treatment-related deaths occurred. Both were due to a thromboembolic event, which has a higher incidence in patients undergoing chemotherapy, especially cisplatin-based.[23,24] Our toxicity data are comparable to the literature.[18]

If equal response rate is to be expected, 89% of patients prefer oral therapy.[25] Considering the fact that the treatment is mostly palliative, patient comfort is of high value. With the ECF regimen a continuous intravenous access was necessary. Apart from the possible complications this is highly uncomfortable since patients, even though treated at home, are hindered. Potential disadvantages of oral administration are patient noncompliance, unpredictable gastrointestinal absorption, and not being able to take the tablets due to stenosis, for example. Our patient compliance was not investigated. Pharmacokinetic studies have shown good absorption profiles, but no separate data for patients with or without gastric resection were provided.[18,26] Although problems in taking oral medication are of special concern in patients with tumours of the oesophagus or cardia, in clinical practice this hardly ever occurs. One patient at first took only smaller 150 mg tablets during the first two courses, until after response he could continue with the 500 mg tablets.
A difference in response with regard to previously treated patients compared with untreated patients was found. Although the numbers are small, untreated patients had significantly better results and also seem to have a (nonsignificantly) better survival. A possible explanation could be a difference in performance status at the time of detection of the recurrence, because a worse performance status is associated with a poor response to chemotherapy. In our patient group we could not confirm this, nor did we find other prognostic factors, but it is likely that the number of patients was too small for a significant difference to be found.
A median survival over 12 months is still a major obstacle in chemotherapeutic regimens in locally advanced and metastatic oesophagogastric cancer, despite an initial response rate of ±50% in various regimens. Symptomatic benefit of symptoms due to metastatic or recurrent disease occurs in over 90% of patients within one or two cycles of chemotherapy, enabling appropriate selection of patients in which continuation of palliative chemotherapy is worthwhile.

With ECF treatment Bamias *et al.* and Webb *et al.* found a higher response rate in patients with locally advanced disease. A potential curative resection was performed in 66 to 75% of responders undergoing surgery.[6,21] This interesting development is gaining more support. Other studies have described preoperative chemotherapy using the ECF regimen where some of the patients with locally advanced disease underwent resection with curative intent if a good tumour response occurred with chemotherapy.[14] In our patient group three patients had locally advanced disease, all located in the oesophagus. Two achieved a partial response; the other had stable disease. The former underwent surgery. A potential curative resection was performed in both. After follow-up of 16.2 and 18.5 months no sign of recurrence has been found. Thus, for a select group of patients ECC can be considered as down-staging chemotherapy. The role of neoadjuvant chemotherapy is not yet established, but an increased disease-free survival has recently been reported.[27]

In conclusion, capecitabine in combination with epirubicin and cisplatin (ECC) appears to be an effective, safe and more comfortable alternative to ECF considering the high response rate and few complications, without the need of a continuous intravenous access with the risk of infection and thrombosis. A larger, phase 2 study is currently being executed to further analyse these results.

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ORIGINAL ARTICLE

Imaging and treatment of patients with colorectal liver metastases in the Netherlands: a survey

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ABSTRACT

Background: Clinical experience has highlighted the absence of a uniform approach to the management of patients with colorectal liver metastases in the Netherlands.

Methods: A written survey on the diagnosis and treatment of patients with colorectal liver metastases was sent to all 107 chairmen of oncology committees in each hospital. Questions were asked concerning: specialists involved in decision-making, availability and existence of guidelines and meetings, factors that needed to be improved, information regarding the diagnostic work-up of liver metastases, detailed techniques of ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), factors influencing resectability, types of surgery performed, the use of (neo)adjuvant chemotherapy, portal vein embolisation performance, considering isolated hepatic perfusion (IHP) or local ablation as treatment options, actual performance of local ablation and the use of systemic as well as regional chemotherapy.

Results: Response rate was 68% (73/107). Specialists involved in the management were mostly surgeons (70), medical oncologists (66) and radiologists (42). Factors that needed to be improved, as indicated by responders, were the absence of 1) guidelines; 2) registration of patients and 3) guidelines for radiofrequency ablation (RFA).

Diagnostic work-up of synchronous liver metastases occurred in 71 hospitals, (by US in 69 and by CT in 2). For the work-up of metachronous liver metastases, US was used as initial modality in 14, CT in 2 hospitals, and 57 hospitals used one or the other (mainly US). As additional modality, CT was performed (71) and to a lesser extent MRI (38) or PET (22). Diagnostic laparoscopy and biopsy were performed incidentally. The choice for an imaging modality was mostly influenced by the literature, and to a lesser extent by the availability and by costs, personnel and waiting lists. Substantial variation exists in the US, CT, MRI and PET techniques. The absence of extrahepatic disease and the clinical condition were considered as the most important factors influencing resectability. Surgery was performed in 30 hospitals; hemihepatectomy in 25, segment resection in 27, multisegment resection in 23, wedge excision in 27 and combination of resection and RFA in 18 institutions. In 52 hospitals (neo)adjuvant chemotherapy was administrated to improve surgical results, partly (35%) in trials. In nine hospitals portal vein embolisation was performed, with the volume of the remnant liver as the most important factor. Local ablative techniques were considered as a treatment option in 48 hospitals and actually performed in 16 hospitals, without clearly defined indications. Experimental IHP was considered a treatment option by 45 (62%) responders, irrespective whether this treatment was available at their centre. Patients with extensive metastases received systemic chemotherapy in all 73 hospitals and regional chemotherapy in ten hospitals.

Conclusion: This survey shows substantial variation in the diagnostic and therapeutic work-up of patients with colorectal liver metastases. This variation reflects either under- or over-utilisation of diagnosis and treatment options. Evidence-based guidelines taking into account the available evidence, experience and availability can solve this variation.

KEYWORDS

Colorectal neoplasms, diagnosis, liver metastases, survey, treatment

INTRODUCTION

Colorectal carcinoma is one of the commonest solid tumours and is responsible for approximately 10% of cancer-related deaths in the Western world. Liver metastasis is a common consequence of colorectal carcinoma; 50 to 60% patients develop liver metastases. Early and accurate diagnosis of liver metastasis is crucial for clinical decision-making. Surgery is the only therapy that offers any possibility of cure with five-year survival rates after resection of all detectable disease up to 40%.[1-4] Unfortunately, only 20 to 25% of patients are deemed suitable for hepatic resection. To improve the results of surgery, a subgroup of these patients either receive neoadjuvant or adjuvant chemotherapy. Patients not suitable for surgery, due to extensive liver metastases or extrahepatic diseases, in general undergo systemic chemotherapy. Several newer therapies such as cryosurgery, radiofrequency ablation (RFA), portal vein embolisation and isolated hepatic perfusion (IHP) and regional chemotherapy are being evaluated in patients not suitable for surgery due to the number or distribution of liver metastases.[5-11]

Imaging modalities such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and laparoscopy (combined with US) represent important tools in the selection of patients for the appropriate treatment.[12-17]

Most of these diagnostic and therapeutic modalities are available in the Netherlands and there are concerns about variability in diagnosis and treatment policies. Clinical experience has highlighted several problems: variation in diagnostic strategies, factors determining the resectability (presence of extrahepatic diseases), use of neoadjuvant or adjuvant chemotherapy, extent of use of experimental treatment modalities (RFA, portal vein embolisation, IHP and regional chemotherapy) and the use of different systemic chemotherapy regimens. In addition, evidence-based guidelines concerning the diagnosis and treatment are not available in the Netherlands at the moment.

Current policies are usually based on consensus meetings, expert opinions, results from studies, and personal and/or institutional experience and preferences, resulting in variable and inconsistent choices and regimens among specialists and institutions.

By means of a written survey, we evaluated the policies on the management of patients with colorectal liver metastases in the Netherlands. The primary aim of this survey was to summarise the extent of variation in the diagnosis and treatment strategies. The second aim was to obtain relevant information for developing and implementing evidence-based guidelines.

MATERIALS AND METHODS

A written survey on the management of colorectal liver metastases was sent to all Dutch hospitals dealing with this group of patients in November 2002. A total of 107 questionnaires were sent to chairmen of the oncology committees in each hospital. All eight academic hospitals participated in this survey. The replies were returned in prepaid stamped envelopes and collected until June 2004. Due to the diversity of specialists involved in the work-up, the questionnaire was divided into three parts: 1) In the general part, questions were asked about the presence of registration systems, the number of patients diagnosed and/or treated, specialists involved in the treatment policy, availability of guidelines, existence of meetings, factors that needed to be improved and research on both diagnostic and treatment field. 2) In the diagnostic part, information on the availability of modalities and the complete diagnostic work-up of synchronous and metachronous liver metastases was requested. This included information on technical details of US, CT, MRI and PET and the factors influencing the choice between these approaches. 3) In the treatment part, questions were asked about factors influencing the choice for surgical treatment, the types of surgery performed, whether (neo)adjuvant chemotherapy was administrated, whether liver perfusion and local ablation were considered as treatment options irrespective of availability, types of local ablation performed, portal vein embolisation performance and whether systemic or regional chemotherapy was administrated. In addition, information on schedules of the chemotherapy approaches was requested.

RESULTS

Response rate

Seventy-four (69%), 73 (68%) and 73 (68%) replies were returned for the general, diagnostic and treatment parts of the questionnaire, respectively, (including from all eight academic institutions).

General

Specialists involved in the management were surgeons in 70, medical oncologists in 66, radiologists in 42, internists in 21, gastroenterologist in 17 and nuclear medicine specialists in three hospitals. In all hospitals meetings were held frequently (once every two weeks) between

specialists of one hospital (25), specialists of more hospitals (11) or between specialists and consulting specialists of the Comprehensive Cancer Centre in most centres (58).

Registration and guidelines
Registration of patients with colorectal liver metastases was only carried out in 26 hospitals. The number of patients for diagnosis ranged from 10 to 150, for surgical treatment from 1 to 40 and for palliative chemotherapy from 6 to 45 patients. Practical guidelines were available in only 16 hospitals; however these guidelines were not evidence-based. In addition, most hospitals (66) indicated they preferred national or regional evidence-based guidelines.

Factors needing improvement
The most important points of concern in the daily practice, according to the responders, were the absence of general guidelines for diagnosis and treatment of patients with colorectal liver metastases, absence of registration systems and to a lesser extent absence of guidelines for indications and performance of radiofrequency ablation (RFA).

Diagnosis
Availability of imaging modalities
US and CT were available in all 73 hospitals, MRI in 71 and PET in 11 hospitals, respectively. Diagnostic work-up of synchronous liver metastases occurred in 71 (97%) hospitals; in 69 mainly by US and in two by means of CT. Diagnostic work-up of metachronous liver metastases was performed step by step, starting with an initial screening modality followed by an additional modality for further detection and characterisation of liver metastases. As initial modality US was used in 14 hospitals, CT in two hospitals, while 57 hospitals used one or the other (mainly US). As additional modality for characterisation and determining resectability, CT was generally performed (71) and to a lesser extent MRI (38) or PET (22). In 33 hospitals a one-stop-shop imaging (for detection, characterisation and determining resectability) was performed by means of CT. Diagnostic laparoscopy and biopsy (US-guided or CT-guided) were performed incidentally in 14 and 67 hospitals, respectively.
Factors affecting the choice for a diagnostic modality were mostly influenced by the literature, to a lesser extent by availability and occasionally by costs, personnel and waiting lists.
The technical details on US, CT, MRI and PET were provided by 62, 62, 60 and 7 hospitals, respectively.

Ultrasonography (n=62)
In all hospitals a convex transducer was used for imaging; the use of an additional linear transducer for detailed visualisation of the liver surface was limited to seven hospitals. US with 'harmonic frequency' in combination with conventional US was performed in 43 hospitals. The use of contrast agents for the assessment of vascularisation of focal lesions was limited to two hospitals.

Computed tomography (n=62)
In 57 hospitals spiral CT scanners were used, including 37 multislice scanners. The number of detectors in the multislice scanners varied from 2 to 16 (modus: 4) and the slice thickness ranged from 1 tot 11 mm (modus: 5 mm). The introduction of multislice scanners made it possible to perform scanning with lower slice thickness and therefore to improve the detection of smaller lesions. In most institutions (36), four-phase scanning was performed (unenhanced, arterial, portal and late phase). In general the unenhanced and the portal phases are used for detection of liver metastases; however, arterial and late phases are helpful in distinguishing other lesions. The amount of iodine ranged from 24 to 72 g (modus 30 g). Detection of liver metastases is expected to improve by using large amount of iodine.

Magnetic emission tomography (n=60)
The magnetic strength of the MRI equipment was mainly 1.0T or 1.5T (n=47). The most frequently used contrast agent was nonspecific gadolinium (n=42); to a lesser extent (n=14) liver specific contrast agents such as Endorem® (dextran-coated ferumoxide), Resovist® (ferucarbotran), Teslascan® (mangafodipir trisodium) and Multihance® (gadobenate dimeglumine) were used to increase detection of small liver metastases, due to selective accumulation of contrast agent in liver parenchyma.

Positron emission tomography (n=7)
Six centres had a dedicated full-ring scanner. The amount of fluoro-2-deoxyglucose varied from 150 to 600 MBq and the analysis was mostly qualitatively and incidentally semi-quantitatively.

Treatment
Factors influencing resectability are summarised in *table 1*, with absence of extrahepatic disease and the clinical condition considered to be the most important factors.
Surgery was performed in 30 hospitals: hemihepatectomy in 25, segment resection in 27, multisegment resection in 23 and wedge excision in 27, and a combination of resection and RFA in 18 institutions.
In 52 (71%) hospitals either neoadjuvant or adjuvant chemotherapy was administrated to improve surgical results with a substantial variation in the treatment regimens, mostly 5-fluorouracil + leucovorin or 5-fluorouracil + leucovorin + oxalipatin, while irinotecan was administrated less often. Approximately 35% (18) of the responders explicitly mentioned that (neo)adjuvant chemotherapy was administrated in trials.

Table 1. *Factors influencing resectability of liver metastases*

Factor	Number of hospitals
Number of lesions	57 (78%)
Size of lesions	40 (55%)
Location of lesions	58 (79%)
Ro resection (clear surgical margins)	26 (36%)
Extrahepatic metastases	63 (86%)
Anatomic structure of the liver	26 (36%)
Stage and grade of the primary tumour	14 (19%)
Age of the patient	27 (37%)
Clinical condition of the patient	69 (95%)
Wish of the patient	52 (71%)
Time between primary tumour and metastases detection	24 (33%)

Response: 73 (68%) hospitals.

Portal vein embolisation was only performed in nine hospitals to achieve a hypertrophy of the remnant liver. The most important factor determining the choice for portal vein embolisation was the volume of the remnant liver.

Ablation techniques were considered treatment options in 48 hospitals (47 RFA, 19 cryoablation, 10 laser-induced interstitial thermotherapy). The actual use of these techniques was limited to 16 hospitals (RFA in 15, cryoablation in two and laser-induced interstitial thermotherapy in one hospital), however without evident indications or guidelines.

Of the responders, 62% (45) indicated that they considered experimental IHP to be a treatment option irrespective of whether this treatment was available at their centre. IHP involves complete vascular isolation of the liver to allow regional delivery of high-dose chemotherapy to the liver with little systemic toxicity. This experimental technique is being evaluated at Leiden University Medical Centre and Erasmus Medical Centre in Rotterdam.

Patients with extensive metastases are only suitable for chemotherapy, either systemic or regional. In all 73 hospitals patients received systemic chemotherapy and in ten regional chemotherapy was given. For systemic chemotherapy, several protocols were used: 5-fluorouracil and leucovorin with either oxalipatin or irinotecan and the use of capecitabine (instead of 5-fluorouracil).

DISCUSSION

In most institutions, the strategy for diagnosis was comparable: US was used as an initial screening imaging modality to detect patients with liver metastases. Easy availability and noninvasiveness are some of the reasons for the widespread use of US. As additional modalities mostly CT and to a lesser extent MRI were used; however, with a substantial variation in CT and MRI techniques, such as the use of different phases and amount of contrast for CT and different contrast agents for MRI. The variation is mostly a consequence of technical developments (e.g. introduction of multislice CT and liver specific MRI agents)[12-17] and uncertainties in the literature (different outcomes), indicating the need for evidence-based guidelines.

In general, diagnostic laparoscopy is performed in selected cases to detect extrahepatic disease, thereby preventing unnecessary laparotomies. However, in patients selected for surgery based on extensive imaging, the prevalence of extrahepatic disease will be low and therefore the additional value of diagnostic laparoscopy will be limited.[18-20]

There were concerns about surgery in patients with extrahepatic disease. However, most of the responders indicated that extrahepatic disease is a major contraindicative factor for surgery. In 52 hospitals (neo)adjuvant chemotherapy was given to improve surgical results. Due to the structure of the written survey, no data on the frequencies of neoadjuvant or adjuvant therapy are available. (Neo)adjuvant chemotherapy was also administrated in trials, explaining part of the variation. We were aware of this variation and tried to summarise the extent of use of (neo)adjuvant, without describing regimens and/or indications. In addition, the effect of (neo)adjuvant chemotherapy has not been significantly proven.[21,22]

Portal vein embolisation was performed in nine hospitals, with the volume of the remnant liver as the most important selection criterion. RFA was considered as a treatment option in most hospitals; however, this technique was performed in a limited number of hospitals, with no uniform indications or selection criteria. A paper by Mutseart *et al.* reporting on the initial experience with RFA of malignant hepatic tumours in the Netherlands showed recurrence in 52% of the patients.[23] In addition, there are no randomised trials; RFA is being evaluated in an ongoing randomised trial comparing chemotherapy plus local ablation with chemotherapy (CLOCC) alone. The advice of the British National Institute for Clinical Excellence (NICE) is as follows: Current evidence of the safety and efficacy of local tumour ablation by RFA for colorectal cancer metastases does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.[24]

Most of the responders (62%) indicated that they considered IHP a treatment option for selected patients with extensive liver metastases. IHP has good efficacy in terms of response rate and duration; however, due to the high toxicity rate, the use of this technique is appropriately limited to research protocols at dedicated centres.[25-29]

The value of regional chemotherapy in patients with nonresectable tumours is unclear. A higher response percentage is obtained compared with intravenous 5-FU; however, no improvement of survival is shown.[30] This technique is therefore performed in limited cases in the Netherlands.

An important limitation of this survey is the suboptimal response (69%), not representing the overall situation in the Netherlands. However, all the academic hospitals and institutions using the experimental treatment options were included in this survey, thus indicating that the hospitals that did not respond represent hospitals with a limited number or no patients with this disease.

Two major points of concern in the management of patients with colorectal cancer which need to be addressed are the absence of guidelines and registration systems. Registration systems are important tools in evaluating management. The collaboration between specialists and consulting specialists of the Comprehensive Cancer Centres will make it possible to establish a national registry. A national evidence-based guideline is being developed to overcome the problem concerning the absence of guidelines.

Substantial variation exists in the diagnostic and therapeutic work-up of patients with colorectal liver metastases. This can be explained by recent developments, the availability of techniques, expertise, uncertainties in the literature (e.g. diagnostic value, effect, survival) and mostly by the absence of guidelines. Research and evidence-based guidelines taking into account the available evidence, experience and availability can solve this problem.

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PHOTO QUIZ

An unusual cause of a cerebral tumour in a young patient

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A 30-year-old man was admitted because of progressive left-sided muscle weakness, headache and nausea. His medical history was unremarkable. He was born to unrelated Turkish parents and grew up in the USA. His father had suffered from hemiparesis and aphasia since the age of 35, without definite diagnosis. Physical examination revealed a left hemiparesis and left central facial nerve palsy. His upper body was covered with pustules. Fever, oral or genital ulcerations, joint pain, and pulmonary, cardiac or gastrointestinal abnormalities were absent. Routine laboratory investigations, including C-reactive protein, were normal except for moderately elevated liver function tests due to excessive alcohol consumption. The leucocyte count was slightly elevated (12.1×10^9/l) with normal differential. Urine microscopy showed erythrocytes and hyaline casts and there was mild proteinuria. Antinuclear and antineutrophil cytoplasmic antibodies were absent; HLA-B51 was negative. A brain MRI scan showed a large lesion in the right frontoparietal region, resembling glioblastoma, metastasis or a possible infectious cause (*figure 1*). Two needle aspirates of the lesion only revealed nonspecific inflammation without malignant cells. To exclude an infectious cause, serological tests for Epstein Barr virus, HIV, *Mycoplasma pneumoniae*, *Chlamydia* spp., *Bartonella* spp., syphilis, toxoplasmosis, echinococcosis and cysticercosis were performed and were negative. Cerebral spinal fluid analysis showed normal cell counts, normal levels of protein, lactate and glucose, no micro-organisms and no malignant cells. Because of progressive nausea, oral dexamethasone was started, which was followed by a rapid improvement of the neurological signs. However, after the patient had stopped his medication independently, he was readmitted with increasing left-sided weakness, nausea, headache and photophobia. Eye examination revealed evidence of retinal vasculitis and vessel occlusion. An open brain biopsy was performed and showed dispersed lymphocytic vasculitis of small vessels (*figure 2*). No micro-organisms and no neoplasm were found.

See page 163 for the answer to this photo quiz.

Figure 1. *MRI scan ring-enhancing lesion, with central necrosis, surrounding oedema and midline-shift*

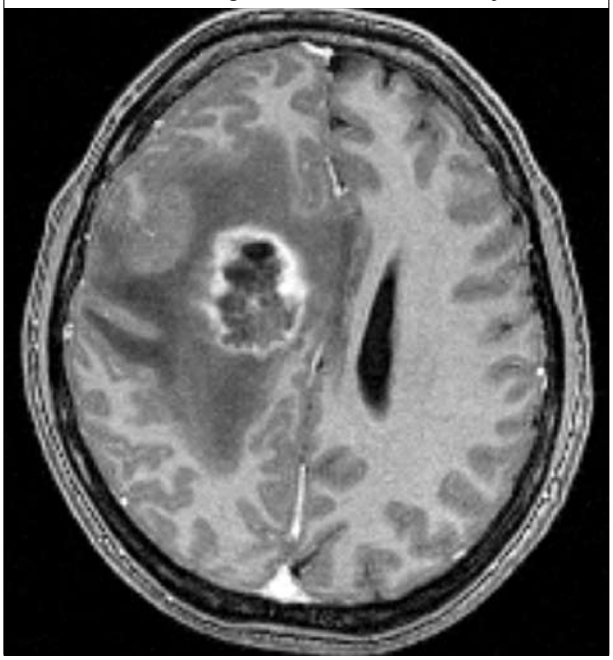
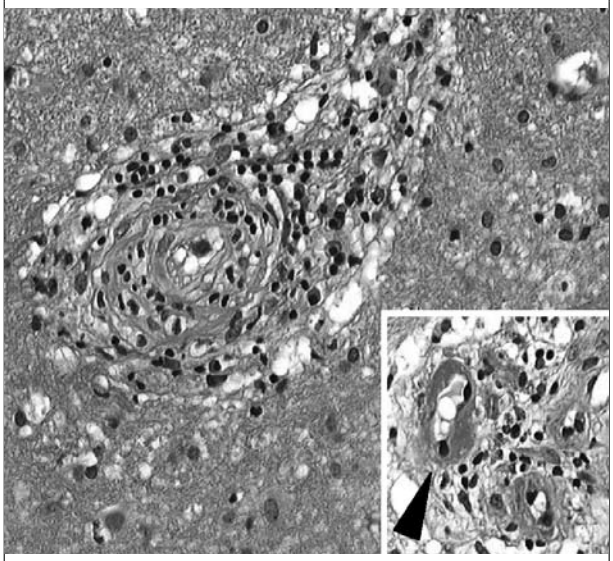


Figure 2. *Lymphocytic inflammation of the wall of small cerebral blood vessel*



The inset in the lower right corner shows fibrinoid necrosis of another cerebral microvessel (arrowhead). Haematoxylin and eosin staining, original magnifications x 200.

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CASE REPORT

Serious envenomation after a snakebite by a Western bush viper *(Atheris chlorechis)* in the Netherlands: a case report

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ABSTRACT

Venomous snakebites are a rarity in the Netherlands. In this report we describe the case of a 26-year-old male amateur snakekeeper who was bitten in his left index finger by a Western bush viper (*Atheris chlorechis*). His clinical condition deteriorated rapidly with acute renal failure and considerable blood loss due to coagulopathy. Antidote was not readily available and was finally supplied by a zoo in Antwerp, Belgium. One day after admission the blood loss diminished.

KEYWORDS

Antidote, *Atheris chlorechis,* bites, coagulopathy, F(ab), renal failure, venomous snake

INTRODUCTION

In the Netherlands, snakebites are rarely seen. The only natural occurring venomous snake is the *Vipera berus*, which seldom bites humans. We present the case of a patient who developed severe coagulopathy, anaemia and acute renal failure after a bite by a Western bush viper.

CASE REPORT

A 26-year-old man was admitted to hospital after being bitten in his left index finger while feeding his pet snake, a Western bush viper (*Atheris chlorechis*). One year earlier he had been admitted to the same hospital for observation after a bite by a *Gila monster*, a venomous lizard. There was no other relevant medical history and he was not taking any medication.

The patient arrived at hospital immediately after being bitten. He remained calm and had not applied any bandages to the bite wound. His distal left index finger was swollen and very painful. There were no other symptoms and physical examination did not reveal any abnormalities. Laboratory examination showed a slight thrombocytopenia (128 x 10^9/l). Because of a developing compartment syndrome, fasciotomy of the distal phalanx was performed after which the patient was admitted to the general ward for observation.

Seven hours after the bite, the pain increased while the swelling had progressed to his wrist. Also, the patient became dizzy. Laboratory research revealed severe coagulopathy and worsening of renal function (*table 1*). It was decided to give an antidote. Since it was not available in the Netherlands, it had to be sent for from Belgium (zoo in Antwerp, 300 km). In the mean time he was taken to the operating theatre for a second fasciotomy. The finger was now opened from the distal to proximal phalanx under general anaesthesia, while fresh frozen plasma (FFP) was given in order to optimise coagulation. After this procedure, he was admitted to our intensive care unit.

The patient was sedated and remained intubated. His left hand was packed with a pressure bandage, out of which blood was continuously leaking. A nasogastric tube yielded blood and coffee-ground material. He had been anuric since ICU admission. Further physical examination did not reveal any abnormalities. Laboratory results are shown in *table 1*. Due to treatment with FFP during surgery the activated partial thromboplastin time (APTT) and prothrombin time (PT) had normalised. Nonetheless, massive bleeding continued and worsened. In the first six hours on the ICU the patient lost approximately five litres of blood. More FFP and thrombocyte-concentrate were given. The antidote (FAV AFRIQUE, Aventis Pasteur, France)

arrived 12 hours after the bite. First, a small amount of antidote was given subcutaneously. No adverse reactions were seen within half an hour. Then two 10 cc vials of antidote were diluted in 500 cc saline 0.9% and given intravenously in two hours. This was repeated twice. Red blood cells, crystalloids and vasopressors were additionally started to keep a systolic blood pressure above 80 mmHg. The blood loss slowly diminished in the following hours. The wound and insertion sites of lines kept leaking for up to four days. On the second day in the ICU sedatives were stopped and he was successfully extubated. His neurological function was normal. Anaemia persisted in combination with an elevated lactate dehydrogenase (LDH) (*table 2*), suggesting haemolysis. Unfortunately no other laboratory parameters proving haemolysis are available. Because of anuria he required haemodialysis. Six days after admission to the ICU the patient could be transferred to the general ward. After two weeks the number of platelets normalised (*table 2*) and in the third week renal function returned to normal. The finger healed well except for a small necrotic area at the distal phalanx.

DISCUSSION

In this case report we describe the consequences of a bite by an *Atheris chlorechis* and will discuss the treatment of this patient step by step. The *Atheris chlorechis* is similar to the pit viper, a member of the family *Viperidae*, one of the venomous snake families. Not every bite by a venomous snake results in envenomation. For example, of all pit viper bites, 25% do not result in envenomation and another 15% are so trivial that they only require local cleansing and tetanus prophylaxis.[1]

Table 1. *Laboratory results on the first day after a snake bite*

	Admission	+5.5 hours	+11.5 hours (admission ICU)	+14 hours	+17.5 hours
Leucocytes (4.0-10.0 10^9/l)	3.3	9.5	5.9	4.5	6.3
Haemoglobin (8.7-10.6 mmol/l)	9.4	8.7	6.1	4.0	5.8
Haematocrit (0.420-0.520v/v)	0.434	0.398	0.272	0.180	0.270
Platelets (150-350 10^9/l)	128	83	56	59	43
Sodium (132-144 mmol/l)	142	141	141	142	140
Potassium (3.6-4.8 mmol/l)	4.1	4.0	5.0	3.9	4.8
Urea (3.3-6.7 mmol/l)	8.5	12.6	15.1	16.2	17.2
Creatinine (62-106 umol/l)	108	206	268	292	314
LDH (114-235 U/l)	267	1458	1266	1050	982
ASAT (0-40 U/l)	23	71	73	64	73
ALAT (0-30 U/l)	28	30	32	44	51
Total bilirubins (3-26 µmol/l)	10	76	58	51	42
Direct bilirubins (0-5 µmol/l)	6	30	19	16	14
PT (11-16 sec)	13.3	>120	17.0	16.9	15.7
APTT (26-36 sec)	28.1	>200	40.6	39.2	34.8
Fibrinogen (1.7-3.5 g/l)	2.0	0.7	0.6	0.9	1.1
Antithrombin (75-125%)	102	105	106	NA	NA

During the first 14 hours FFP and thrombocyte-concentrate were given. NA = not available. LDH = lactate dehydrogenase; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; PT = prothrombin time; APTT = activated partial thromboplastin time.

Table 2. *Laboratory results follow-up during ICU stay*

	Day 1			Day 2	Day 3	Day 4	Day 5	Day 6
Haemoglobin (8.7-10.6 mmol/l)	9.4	8.7	4.0	3.9	3.7	4.1	4.3	3.7
Platelets (150-350 10^9/l)	128	83	59	35	24	22	19	34
LDH (114-235 U/l)	267	1458	1050	2217	3761	5144	5750	3561
PT (11-16 sec)	13.3	>120	16.9	13.5	13.3	13.6	13.0	NA
APTT (26-36 sec)	28.1	>200	39.2	29.4	30.6	33.2	29.8	NA
Fibrinogen (1.7-3.5 g/l)	2.0	0.7	0.9	1.0	1.4	NA	2.1	NA
Antithrombin (75-125%)	102	105	NA	114	NA	NA	112	NA

NA = not available. LDH = lactate dehydrogenase; PT = prothrombin time; APTT = activated partial thromboplastin time.

Snake venom is a chemically complex mixture of water, enzymes and a large number of peptides. The venom has two purposes. The first is killing the prey and the second is digesting the prey as early as possible. Injecting the digestive enzymes is more effective than digesting from the outside, especially if the prey is swallowed whole without chewing. The composition of venom varies with the species and age of the snake. The various proteins and peptides induce endothelial damage by causing blebs, dilating the perinuclear space, and breakdown of the plasma membrane with accumulation of extravascular fluids and cells. The digestive enzymes in snake venom cause both local and systemic damage to human tissue. At least 26 different digestive enzymes have been identified although no single snake venom contains all of them. Among the enzymes are:

- Phospholipases, which damage the fatty acid phospholipid fraction of cell membranes. In red blood cells this and other factors contribute to the development of intravascular haemolysis;
- Hyaluronidase, which decreases the viscosity of connective tissue to allow venom spread beyond the bite site;
- Proteolytic enzymes such as R-Nase, D-Nase, and 5' nucleotidase are present that can damage muscle fibre proteins;[2]
- Amino acid esterase and other thrombin-like enzymes that promote fibrin formation resulting in a consumptive coagulopathy with prolonged clotting times and hypofibrinogenaemia.

Other manifestations of coagulopathy and causes of bleeding after a snake bite are: a) reduced coagulability of blood, anticoagulant effect of the venom, b) direct damage to blood vessels, c) diminished platelet function and d) secondary effects due to shock.

As a general rule, field management after a snakebite involves keeping the patient calm and seeking help immediately.[3] The patient knew the type of snake he was bitten by and did not apply a tourniquet. Viper venom primarily produces local necrosis and localisation of toxin may in fact worsen the syndrome. In the emergency room and on the general ward, it was decided to perform a fasciotomy because the patient developed signs of compartment syndrome. The repeated fasciotomy in combination with the developing coagulopathy resulted in life-threatening blood loss. The evidence of a surgical approach is sparse as Hall discussed in surgical intervention in *Crotaline* snake envenomation.[4] The *Crotaline* species also belongs to the viper family, as does the *Atheris* species. Their venom mimics signs and symptoms of compartment syndrome closely. True compartment syndrome is thought to occur rarely and the presenting signs are caused by myonecrosis related to the action of the venom components rather than to elevated compartment pressure that causes vascular insufficiency. We feel that in our case manipulation to the bite site may have contributed to the clinical deterioration.

The renal failure in snakebites may be the result of a combination of intravascular haemolysis, a syndrome resembling disseminated intravascular coagulation, hypotension or nephrotoxic effects of components of venom. In our patient, because of adequate resuscitation and intensive care facilities, no hypotension was observed. During surgery FFP and thrombocyte concentrate were given to temporarily restore blood coagulability as assessed by prolonged PT and APTT. On admission to the ICU bleeding at the site of the bite, from venipuncture sites, gums and stomach indicated recurrence of incoagulable blood. Since the swelling was progressive with clinical deterioration we decided to give antivenom. Although prospective randomised controlled trials are lacking in the literature some suggest that antivenom immunotherapy is the only effective treatment against severe envenomations.[5,6]

Traditionally, horse serum preparations were used that often produced immediate and late-onset hypersensitivity reactions. Recently, new antivenoms based on the antigen-binding fragments of immunoglobulines (F(ab fragments)) have been produced. FAV AFRIQUE is a polyvalent antivenom made from fragments of IgG, $F(ab')_2$, whose manufacturing process involves several additional purification steps compared with those classically used. Theoretically, Fab_2 fragments do not induce the formation of immune complexes and thus carry less risk in severe antivenom reactions.[7] Chippaux *et al.* demonstrated in an uncontrolled study the favourable safety and efficacy profile of FAV AFRIQUE.[8] FAV AFRIQUE is indicated for the treatment of envenomation caused by most venomous snakes found in Africa. No specific antivenom exists for the *Atheris chlorechis* venom. Twelve hours after the bite the antidote became available for our patient. To prevent early anaphylactoid reactions prednisolone and antihistamine were given intravenously.[9] After administration of six vials of antidote in six hours, cessation of bleeding was achieved. Possible haemolytic anaemia, as indicated by elevated LDH, remained for several days.

In any patient with a coagulopathy the most important aspect of management is the recognition of the underlying disease and removal of the initiating factors. If specific therapy and support is successful and for instance disseminated intravascular coagulation is reversed no replacement therapy is required. Snakebite-induced coagulopathy is not entirely like other forms of coagulopathy. It may present with severe disturbance of laboratory values but in contrast to other diseases this does not equate to actual morbidity in an individual patient.

Experience from personal communications, anecdotal reports, books and reviews[10] has led to the consensus that:

- Antivenom is the treatment of choice for haemostatic failure as an attempt to eliminate the cause of the disease;
- Applying standard wound care protocols or replacement therapy for coagulopathy (e.g. FFP) can be dangerous and may add fuel to the fire with acceleration of fibrinolysis and increased risk of bleeding.[10]

In conclusion, we present a patient in the Netherlands with massive bleeding and acute renal failure due to snake envenomation. We feel that early surgical manipulation to the bite site worsened the local bleeding and failed to prevent remote organ dysfunction and may actually be considered to be harmful and highly controversial. Severe blood loss stopped after treatment with blood products and antivenom. It is tempting but it cannot be concluded from our data that venom neutralisation by FAV AFRIQUE is the major component in treating systemic bleeding and restoring blood coagulability.

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CASE REPORT

A case of abdominal mesothelioma diagnosed by indium-111 leucocyte scintigraphy

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ABSTRACT

We present a case of peritoneal mesothelioma that presented with fever of unknown origin and an elevation in the inflammatory parameters. Radiological imaging did not reveal a diagnosis. Because of tumour-associated inflammatory activity, indium-111 leucocyte scintigraphy enabled us to establish a diagnosis. To our knowledge, the use of indium-111 leucocyte scintigraphy in peritoneal mesothelioma has not been reported previously.

KEYWORDS

Peritoneal mesothelioma, indium-111 leucocyte scintigraphy

CASE REPORT

A 40-year-old man was referred to our outpatient clinic due to fever and weight loss. Because of a productive cough, he was first analysed by a pulmonologist. Chest radiograph, ECG, Mantoux and spirometry were normal. History revealed a fever of up to 39.5°C during the last three months and severe night sweats. He complained of fatigue, thirst, loss of appetite and a weight loss of 12 kg in two months. Other symptoms were nausea and vomiting in the morning. His stools were normal. Medical history was unremarkable. He stopped smoking 20 years ago. His alcohol intake was 0 to 1 unit a day. There was no history of drug abuse or exposure to toxic agents, including asbestos. He was taking 500 mg of paracetamol three to four times a day to suppress his fever. His father and grandfather died of lung cancer. His occupation was forklift truck driver. Physical examination showed a blood pressure of 120/80 mmHg, a regular pulse of 95 beats/min and a temperature of 38.7°C. Enlarged lymph nodes were not detectable. Physical examination of the heart, lungs and abdomen was normal.

Routine laboratory tests revealed a microcytic anaemia (haemoglobin 6.1 mmol/l) and a remarkable elevation of inflammatory markers (C-reactive protein 219 mg/l, erythrocyte sedimentation rate (ESR) 77 mm/h, leucocytes 15.9 x 10^9/l, granulocytes 95% and thrombocytes 663 x 10^9/l). Urinalysis, including cultures on tuberculosis, was negative. Further diagnostics were aimed at infections, autoimmune diseases and malignancy, particularly malignant lymphoma. High-resolution computed tomography (HRCT) scanning of the thorax, ultrasound and a CT scan of the abdomen were reported normal.

The patient was admitted to hospital for further analysis. Repeated cultures of blood, urine and sputum were sterile. Colonoscopy was performed and showed no intraluminal pathology. Echocardiography revealed no endocarditis. Bone marrow investigation was normal. Finally, the case fitted the classical criteria of fever of unknown origin.[1]

In a further search for a possible inflammatory origin of his symptoms, indium-111 leucocyte scintigraphy was performed. Autologous leucocytes were labelled *in-vitro* with the radioactive isotope indium-111 and subsequently reinjected into the patient. Accumulation of leucocytes may occur in infectious or noninfectious inflammatory lesions. Images were obtained with single photon emission computed tomography (SPECT) scintigraphy and showed several hotspots in the upper abdomen. A repeated CT scan 3.5 weeks after the first CT scan clearly showed intra-abdominal fluid and extensive masses in the mesenterium and omentum (*figure 1A*). Comparison of the SPECT scan and the CT scan (*figure 1B*) revealed that the hotspots on the SPECT scan corresponded to the intra-abdominal masses on CT. CT-guided biopsy of one of the tumours established the diagnosis of malignant mesothelioma of the epithelial type.

Figure 1A. *CT scan of the abdomen showing widespread tumoural changes and thickening of the small intestine and mesenterium and ascites*

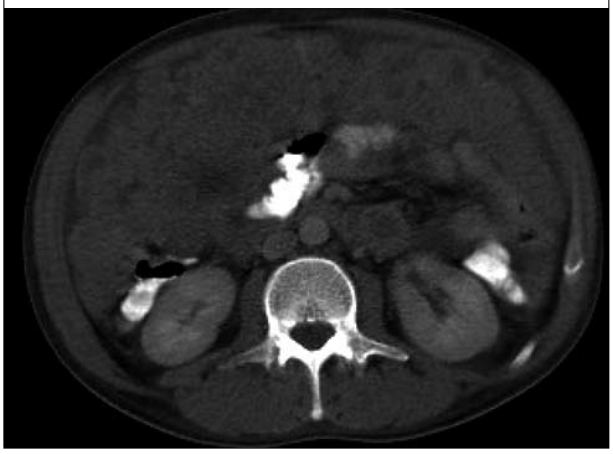
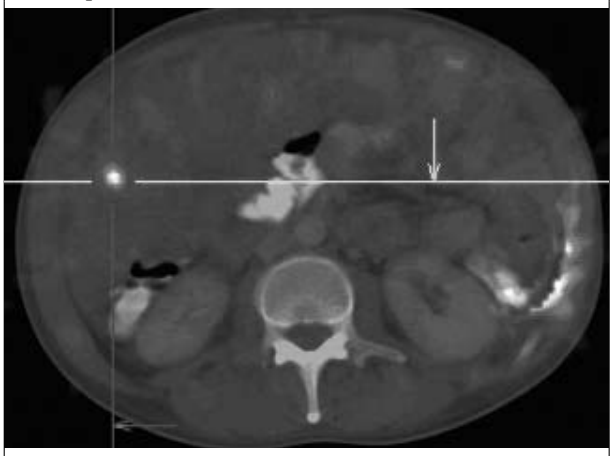


Figure 1B. *Indium-111 leucocyte scintigraphy superimposed on CT scan showing focal areas of leucocyte accumulation in the abdomen*



The right lateral activity is physiological spleen uptake.

Since there is no evidence-based therapeutic regimen for intra-abdominal mesothelioma, the patient was treated with palliative chemotherapy according to the guidelines for pulmonary mesothelioma, using pemetrexed. After two courses, the disease appeared rapidly progressive, leading to death within ten weeks after the first presentation. Autopsy revealed massive tumour involvement of the peritoneum, without pleural localisation of mesothelioma.

DISCUSSION

Mesothelial cells form a monolayer along the abdominal and pleural cavities and on internal organs. Neoplastic transformation gives rise to mesothelioma, a highly malignant tumour, most commonly localised in the pleura. Abdominal mesothelioma, the only primary peritoneal malignancy, is extremely rare (incidence one/million in the USA).[2] Although 90% of mesotheliomas are associated with exposure to asbestos, cases have been reported in which no exposure has been identified.[3] The commonly accepted mechanism leading to an intra-abdominal localisation is inhalation of asbestos fibres, followed by clearance of those fibres by the mucociliary system of the bronchi. Mucus containing asbestos fibres is coughed up and swallowed. Subsequently, passage of the sharp pieces through the intestinal wall may lead to a peritoneal localisation. A latency period of 20 to 40 years is characteristic.[4]

A presentation with nonspecific and mild symptoms despite an advanced disease state is common. Abdominal pain, fever, a slightly raised ESR or a marked thrombocytosis may be the only presenting signs. In a more advanced stage, fever and raised inflammatory parameters are more common. Less frequently bowel obstruction occurs. Because of the nonspecificity of symptoms, diagnosis often relies on imaging. The most common radiological findings of peritoneal mesothelioma are ascites, irregular or nodular peritoneal or intestinal mucosal thickening and omental or mesentery involvement. The nonspecificity and variety of tumour morphology, site and mode of spread within the abdomen explain the diagnostic challenge of peritoneal carcinomatosis.[5,6]

The presence of high fever of unknown origin (FUO) with night sweats and raised inflammatory parameters suggested an infectious or inflammatory disease. De Kleijn *et al.* described a series of 167 patients with FUO. In this study 26% suffered an infection, 13% a neoplasm (0% mesothelioma) and 24% a noninfectious inflammatory disease.[7] In 30% no diagnosis could be established. In this case, the absence of localising signs and symptoms and abnormalities on radiological imaging delayed the diagnosis. Scintigraphic diagnostics aimed at an inflammatory disease finally revealed the diagnosis. Although the patient suffered from inflammatory symptoms during the course of the disease, hardly any literature on primary peritoneal mesothelioma and FUO is found. However, peritoneal mesothelioma may present as a focal or generalised inflammatory disease and may mimic the signs of acute appendicitis, cholecystitis, incarcerated umbilical hernia or inflammatory bowel disease.[8] Although fluorodeoxyglucose-positron emission tomography (FDG-PET) scans are routinely applied for the diagnosis, staging and follow-up of mesothelioma,[9] this is the first report showing the use of indium-111 leucocyte scintigraphy for this diagnosis.

CONCLUSION

Scintigraphic imaging, in particular FDG-PET, may be useful for the diagnosis of peritoneal mesothelioma, especially when radiological imaging does not reveal a diagnosis. Positivity of indium-111 leucocyte scintigraphy in mesothelioma has not been reported before. The overt clinical signs of inflammation and the accumulation of radioactive-labelled leucocytes in the tumour mass show a tumour-associated inflammatory activity.

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CASE REPORT

Acute dystonic reaction to metoclopramide in patients carrying homozygous cytochrome P450 2D6 genetic polymorphisms

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ABSTRACT

Background: Extrapyramidal syndromes (EPS) are clinically relevant side effects of metoclopramide which are often not anticipated.

Patients and methods: Two patients who received metoclopramide developed an acute dystonic reaction. Symptoms disappeared after biperiden or trihexyphenidyl were given. Molecular analysis of the CYP2D6 gene was performed using a PCR-based method.

Results: Both patients were homozygous for inactive CYP2D6 alleles (CYP2D6*4/*4 and CYP2D6*4/*5), which are associated with slow drug metabolism.

Conclusion: Metoclopramide-induced acute dystonic reactions may occur in patients carrying a CYP2D6 genetic polymorphism.

KEYWORDS

Acute dystonic reaction, chemotherapy, CYP2D6, metoclopramide

INTRODUCTION

Metoclopramide is a selective dopamine antagonist (D2-R) with central and peripheral antidopaminergic effects. Metoclopramide increases peristaltic movements of the gut, it induces pyloric relaxation and has a direct antiemetic effect.[1-3] Extrapyramidal syndromes (EPS) are clinically relevant side effects of metoclopramide, which are often not anticipated. We report two cases of an acute dystonic reaction to metoclopramide in two patients treated with chemotherapy who were homozygous carriers of CYP2D6 variant alleles, making them CYP2D6 poor metabolisers.

CASE REPORTS

Patient A, a 25-year-old female, was diagnosed with acute myeloid leukaemia (AML), French-American-British (FAB) classification AML-M1. She was treated with cytosine arabinoside and idarubicin (chemotherapy). Granisetron (1 mg intravenously) was given as prophylactic antiemetic drug. Because of persisting granisetron-refractory nausea after four days, metoclopramide 10 mg was prescribed intravenously four times daily. After two days, the patient felt cramps in her mouth and right hand, twisting of her neck to the right in combination with turning of her eyes to the right and above and she was unable to speak. After a short period of relaxation, her head and hand turned in the compulsion position again. She remained fully consciousness during this episode.

An acute dystonic reaction was considered. The symptoms disappeared immediately upon administration of 5 mg biperiden (akineton) intravenously. No further dystonic reactions were noticed after stopping metoclopramide.

Patient B, a 34-year-old male, was diagnosed with diffuse large B-cell non-Hodgkin lymphoma and was treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Metoclopramide tablets (10 mg) were prescribed for nausea. The next day the patient developed episodes of torticollis every five minutes. He had cramps in his neck and head to the left and backwards lasting for seconds to five minutes. During these episodes

he could not rotate his neck; he remained fully conscious. There were no signs of urinary incontinence, tongue bite injuries or tonic-clonic seizures.
An acute dystonic reaction (torticollis) was diagnosed, due to metoclopramide. Trihexyphenidyl (artane) 1 mg was administered, upon which the symptoms disappeared. The symptoms did not recur after metoclopramide was stopped.

METHODS

Genomic DNA was isolated from EDTA (Ethylene Diamine Tetra Acetic) blood. Detection of the *4 allele was performed using 5 ng of DNA in a polymerase chain reaction (PCR) with primers 5'-TCATGGCCACGCGCACGTGC-3' and 5'-ACTCCTCGGTCTCTCGCTCC-3', for 35 cycles with conditions [1 min 94°C, 1 min 60°C, 1 min 72°C]. The 460 bp PCR product was digested with BstN1 for two hours at 37°C. The *4 allele will give a specific 347 bp band. For the *5 allele, 20 ng of genomic DNA was amplified with primers 5'-ACCGGGCACCTGTACTCCTCA-3' and 5'-GCATGAGCTAAGGCACCCAGA-3' in a 35 cycle PCR with conditions [1 min 94°C, 30 sec 65°C, 5 min 68°C]. The appearance of a 3.5 kb PCR product indicates the presence of a *5 allele.

RESULTS

Patient A was genotyped as CYP2D6*4/*5 and patient B was genotyped as CYP2D6*4/*4. Both the *4 and *5 alleles encode nonfunctional CYP2D6 enzyme, making both patients poor metabolisers of CYP2D6.

DISCUSSION

Nausea can be induced in several ways. The vomiting centre receives signals from the gut, the vestibular labyrinths and the 'chemoreceptor trigger zone (CRT)', which is located in the area postrema of the medulla oblongata.[4] The dopamine (type 2), serotonin (type 3), histamine (type 1) and muscarine receptors are located here. Emesis is induced when these receptors are activated by their respective neurotransmitters. Specific antagonists of these receptors are used to treat symptoms of nausea.[5]
Metoclopramide is used for treatment of oesophageal reflux, dyspepsia, gastroparesis and for chemotherapy-related nausea.[1,2,6] Metoclopramide blocks the dopamine receptor (D2-R) both centrally as well as peripherally. It stimulates the acetylcholine receptors, which are located on the musculature of the stomach.[7] When metoclopramide is prescribed at a high dose it has an antagonistic effect on the serotonin (5-HT3) receptors.[8] This observation triggered the development of selective 5-HT3-antagonists.[7,9] The antagonistic effects of ondansetron are 100 times more potent than metoclopramide at the chemoreceptor trigger zone.[10]

EPS due to metoclopramide are observed in 1:500 patients.[6,11] Persons at risk are young women, patients with a family history of neurological disorders and those who are treated with neuroleptics.[12]
EPS which have been associated with metoclopramide include tardive dyskinesia, drug-induced parkinsonism, akathisia, malignant neuroleptic syndrome and an acute dystonic reaction.[6,11]
An acute dystonic reaction is defined as sustained muscular spasms producing twisting, squeezing and pulling movements.[6] Specific clinical symptoms are torticollis, opisthotonus, blepharospasms and ocular crises. Respiratory and swallowing problems can lead to life-threatening situations.[6,13] Symptoms often start within 24 hours after administration of a dopamine antagonist and 94% of these symptoms occur within 72 hours.[14]
Several studies indicate that these reactions especially occur in women aged between 12 and 19 years. They have three to four times more chance of developing these side effects.[6,13,15] Acute dystonia is rarely observed in the elderly, due to loss of dopamine receptors.[6]

Metoclopramide is an inhibitor as well as a substrate of the hepatic cytochrome P450 enzyme, subclass CYP2D6. Drug-induced EPS are more frequently observed in patients with a genetic polymorphism in the gene coding for CYP2D6, resulting in an absent enzyme activity.[16,17] Molecular analysis of this gene was therefore performed using a PCR-based method. Both patients were homozygous for inactive CYP2D6, alleles (CYP2D6*4/*4 and CYP2D6*4/*5), making them poor metabolisers. Of the Caucasian population, 5 to 10% are poor metabolisers of CYP2D6. However, the incidence of EPS due to metoclopramide is only 1:500 patients.[17] It is hypothesised that simultaneous use of metoclopramide with drugs that are metabolised by CYP2D6 such as antidepressants and neuroleptics, may provoke EPS. The metabolism of metoclopramide may then be affected more seriously in patients who carry homozygous CYP2D6 nonfunctional alleles, leading to drug accumulation and related toxicities such as EPS.[18]
Both patients were treated with chemotherapy, idarubicin and doxorubicin respectively, which are metabolised by CYP2D6. Therefore, they are more at risk for developing an acute dystonic reaction.
Searching for nonfunctional CYP2D6 would be interesting if a patient is at risk for EPS and if there is no good alternative treatment for metoclopramide. However, there is not much written in the literature about the incidence of patients developing an acute dystonic reaction who are

known as poor metabolisers of CYP2D6. There is a rational relation considering our two patients. More research is necessary before it can be tested routinely.

There are several therapeutic options for acute dystonic reactions after administration of metoclopramide. First of all, metoclopramide should be stopped. Secondly, various therapeutic interventions can be considered. Dysbalance between agonists and antagonists of musculature is seen when a dopamine antagonist, such as metoclopramide, is administered. Through other neurotransmitters (gamma-aminobutyric acid (GABA) and acetylcholine) an extra activation will take place and induce muscular spasms.[19] Blocking these neurotransmitters will inhibit the dystonic reaction. However, GABA derivates (for example baclofen) and dopamine agonists (for example bromocriptine) are only available for oral use, which will produce a delayed effect after 30 minutes.
Direct intravenous administration of anticholinergics (for example biperiden 5 mg or promethazine 25-50 mg) is the treatment of choice for acute dystonic reaction since they provide an immediate effect. Benzodiazepines (diazepam 2 to 20 mg iv or im) induce immediate muscle relaxation and can be used in combination with anticholinergics.[20]
Although both patients are poor metabolisers, they remained free of symptoms after one dose of biperiden and trihexyphenidyl, respectively. Normally the half-life of metoclopramide is four to six hours and for the other drugs 16 to 33 hours and 6 to 12 hours, respectively. The blood level of metoclopramide is probably reduced when biperiden or trihexyphenidyl are eliminated, so that the dystonia does not return.

CONCLUSION

Metoclopramide is an antiemetic drug which can cause a severe adverse event, such as an acute dystonic reaction, especially in patients carrying homozygous CYP2D6 genetic polymorphisms. If a patient is at risk for an acute dystonic reaction and there is a good alternative, metoclopramide use should be avoided. The most rapid treatment of an acute dystonic reaction by metoclopramide is administration of anticholinergics or benzodiazepines intravenously or intramuscularly.

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ANSWER TO PHOTO QUIZ (ON PAGE 152)

AN UNUSUAL CAUSE OF A CEREBRAL TUMOUR IN A YOUNG PATIENT

DIAGNOSIS

Based on cerebral and retinal vasculitis, cutaneous pustules, Turkish ancestry, and by exclusion of other possible causes, the diagnosis Behçet's disease was made, despite the lack of oral and genital ulcers and pathergy. Behçet's disease is a systemic inflammatory disorder of unknown origin first characterised in 1973 as a triad of recurrent oral aphthous ulcers, genital ulcers and relapsing inflammation of the eye. The prevalence of the disease is highest in countries along the Silk Road from the Mediterranean Sea to Japan and varies from 0.1 (USA) to 370 (Turkey) cases per 100,000 population.[1]

There is no diagnostic laboratory test and diagnosis is based on clinical judgement. In some high-prevalence countries the human leucocyte antigen HLA-B51 is associated with the disease.[1] According to the International Study Group for Behçet`s disease, a definite diagnosis requires recurrent oral ulcerations plus two of the following: skin lesions, eye lesions, recurrent genital ulcerations or a positive pathergy test.[2] Other symptoms include arthritis, vascular lesions, and gastrointestinal and central nervous symptoms.[3] Involvement of the central nervous system (CNS) occurs in 2 to 50% of all patients with a higher incidence in the Middle East and Mediterranean countries than in Turkey and the Far East.[4,5] Neurological involvement in Behçet's disease comprises two pathophysiologically different entities: there may either be an inflammatory process of small and medium-sized blood vessels with (multi)focal parenchymal involvement, which is seen in the majority of patients, or large vein involvement in the form of cerebral venous sinus thrombosis.[6] Clinical presentation in patients with parenchymal involvement typically consists of meningoencephalitis with brainstem symptoms, less common are spinal cord involvement, hemiparesis and cognitive-behavioural changes. Neuro-imaging studies usually show multiple lesions in the brainstem or midbrain sometimes extending to the diencephalon. In a case series of 50 patients with neuro-Behçet syndrome (NBS) all five patients who presented with hemisphere syndrome showed multiple white matter lesions in both hemispheres.[7] Patients with cerebral venous sinus thrombosis usually present with symptoms of increased intracranial pressure, with headache and mental changes. NBS presenting with hemiparesis and a mass lesion of the cerebral hemisphere on MRI has only rarely been described.[6,8]

In a minority of patients the neurological symptoms form the first manifestation of the disease as in our case. A study of 200 patients with NBS showed that in only 3% neurological symptoms preceded the onset of Behçet`s disease.[9] However, due to the absence of typical mucocutaneous manifestations, the diagnosis in these patients poses a diagnostic dilemma and is often delayed, sometimes until autopsy.[10-12] In our patient other causes of a solitary mass lesion, including benign and malignant neoplastic lesions, infectious diseases and other noninfectious inflammatory processes had to be ruled out before a likely diagnosis of Behçet's disease could be made. Often repeated investigations including invasive procedures such as open brain biopsy are carried out in search for the correct diagnosis. Behçet's disease should be considered in patients presenting with a cerebral tumour-like lesion, especially when they are of Mediterranean or Asian origin.

In our patient, high-dose prednisone combined with azathioprine was restarted, which led to partial improvement of neurological defects, retinal vasculitis and proteinuria and complete remission of the skin manifestation.

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3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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