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Practical Considerations in the Treatment of Hepatocellular Carcinoma

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Summary

Hepatocellular carcinoma (HCC) represents one of the most common neoplasms worldwide. To date, curative treatment options include liver transplantation or resection. Unfortunately, most patients are detected with nonresectable or -transplantable HCC due to disease extension or comorbid factors, and are therefore candidates only for palliative treatments.

Palliative medical treatments, including systemic chemotherapy, immunotherapy or hormonal manipulation, have a borderline activity on HCC and cannot be recommended outside clinical trials. A high response rate has been reported with local therapies such as transcatheter arterial embolisation, intra-arterial chemotherapy or percutaneous alcohol (ethanol) injection, but as there is no clear evidence of a survival advantage for these treatment modalities, further investigations are required. Multidisciplinary treatment, including preoperative cytoreduction or postoperative adjuvant therapy, is currently under investigation, with encouraging survival results. HCC patients should be evaluated within clinical trials, possibly randomised and with homogeneous prognostic factors, in order that we may find the answer to all these important questions.

Although hepatic tumours include numerous histological subtypes, hepatocellular carcinoma (HCC) accounts for more than 90% of primary hepatic malignancies.[1] Different incidence rates for the tumour have been reported worldwide, with a relatively low incidence in North America and Europe and a high incidence in areas of Africa and Asia, where it represents the most common tu-

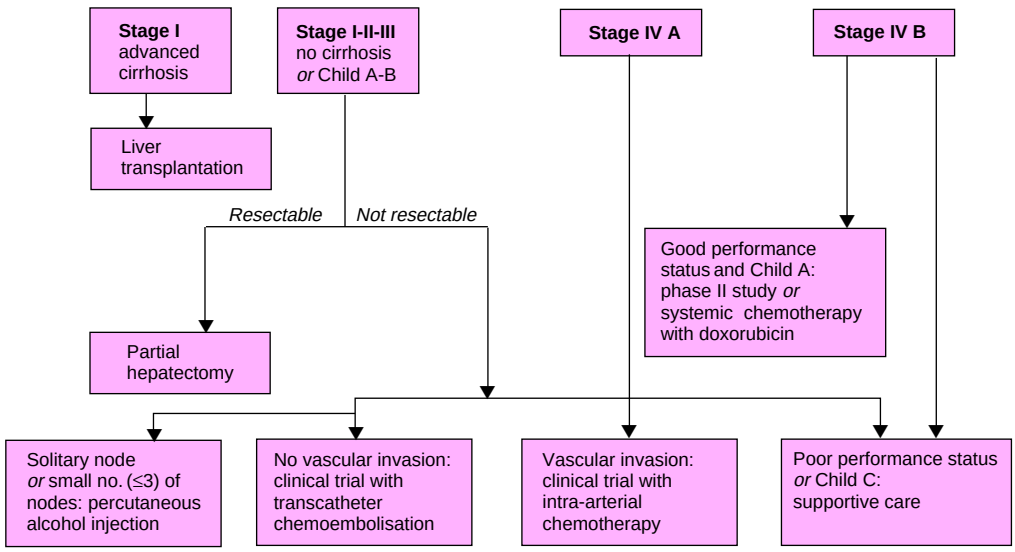

Fig. 1. Treatment options in hepatocellular carcinoma. Stage is defined according to tumour node and metastasis staging system (as per the American Joint Committee on Cancer[5]). Child A = good liver function, no ascites or encephalopathy; Child B = adequate liver function, mild ascites or encephalopathy; Child C = jaundice, ascites, encephalopathy.

mour.[2] In Italy, it is responsible for about 14/100 000 deaths per year and represents the tenth leading cause of tumour-related deaths.[3]

Although early diagnosis of HCC has been improved by screening programmes, most patients are still being detected with nonresectable or -transplantable disease and are candidates only for palliative treatments or at best for supportive care.[1,4] Many nonresectional treatment modalities have been developed and are currently in use. They include intra-arterial chemotherapy (IACT), chemoembolisation, percutaneous alcohol (ethanol) injection (PEI), cryotherapy, radiotherapy and systemic medical treatments. The percentage of patients with cirrhosis at the time of diagnosis of HCC ranges from 55 to 85%.[1] The presence of cirrhosis is not necessarily a contraindication for a major therapeutical approach including surgery, but in the case of advanced cirrhosis or decompensated liver function it may well be (fig. 1). Recent study reports are discussed here to provide a guide for the practical management of HCC with or without concomitant cirrhosis, and for the development of further studies.

1. Orthotopic Liver Transplantation

Recent improvements in surgical technique and the availability of advanced and specifically dedicated instruments has led to a remarkable increase in the resectability rate of liver cancer.[4,6,7] Even so, most patients with HCC present with unresectable tumours due to locally advanced cancer or systemic disease. Moreover, underlying liver cirrhosis often reduces the number of candidates for surgical resection. For these reasons total hepatectomy and liver transplantation have been attempted, with the aim of prolonging survival and improving quality of life. This area is still controversial because of the restricted availability of organ donors, the increased waiting list of patients with benign liver disease,[8] and the high rate of recurrent HCC after liver transplant.

Preoperatively, the diagnosis of HCC needs to be confirmed histologically, or supported by a serum α-fetoprotein measurement above 300 μg/L

(since increased amounts of this protein are found in a high proportion of patients with HCC). Patients should also be staged with lung and abdominal computed tomography (CT), to prove the absence of metastatic seedings or nodal disease. The time spent on a waiting list is theoretically detrimental from the oncological point of view, but it has not thus far been proven to be a negative prognostic factor. Although these patients, particularly if affected by large HCC, seem to be managed adequately with the association of transcatheter arterial chemoembolisation (TACE) or chemotherapy in preliminary series,[9-12] there are no definitive data on the value of pretransplant therapy. At the same time, the use of post-transplant chemotherapy remains investigational.

Technical details have been extensively discussed and standardised, thus reducing operative morbidity (cytomegalovirus infection 69%, acute rejection 34.6%, neurological complications 3%, atelectasis 20 to 25%, pleural effusion 20 to 25%, pneumonia 12%, mild to moderate grades of hepatic encephalopathy 12%, invasive fungal infection 11%) and mortality rate (10 to 20%).[4,7-9]

When oncological results are analysed, the worldwide figures for liver transplantation in the treatment of HCC show a 3-year survival rate of 16 to 82% (table I). This wide range of results is not surprising, since 2 different subgroups of HCC patients have been enrolled into orthotopic liver replacement protocols: large and unresectable hepatomas on one side, and small HCCs with concomitant cirrhosis, including the so-called 'incidentalomas' (i.e. the preoperatively undetected, very small HCCs incidentally discovered during histological evaluation of the hepatectomy specimen from those patients who underwent liver transplantation for cirrhotic disease). These 2 populations obviously have a very different prognosis; this is a key point in discussing the oncological results of such an aggressive procedure. In fact, the recurrence rate at 2 years is >80% in the former group of patients and <5% for the latter group.[14-15] Survival is not statistically affected by the patient's age or gender, common markers of chronic liver disease (type of hepatitis virus or Child-Pough stage), extent of donor-recipient loci of major histocompatibility complex (HLA) crossmatching, incidence of graft rejection, type of immunosuppressive regimen, perioperative use of blood products and surgical technique used in graft implantation.[15]

Recent data conflict with the pessimistic view which considers liver replacement a futile procedure for HCC, while confirming the early indications by Starzl et al.[17] who reported an excellent survival rate in patients transplanted for small HCC (<5cm) incidentally discovered by the pa-

Table I. Literature data on liver transplantation for hepatocellular carcinoma

Reference	No. of patients	Survival			
		1y (%)	3y (%)	5y (%)	median (mo)
Dalgic et al.[4]	39	56	32	26	20.7
O'Grady et al.[7]	50	40			
Olthoff et al.[8]	16	40			
Pichlmayr et al.[9]	87			19.6	11.6
Haug et al.[10]	24	71	42		
Moreno-Gonzalez et al.[11]	12	80	16		
Bismuth et al.[12]	60		49		
Chung et al.[13]	29	61	46		
Selby et al.[14]	105	66	39	36	
Mazzaferro et al.[15]	48	85	82	70[a]	
Marcos-Alvarez et al.[16]	22	65	45		

a Mazzaferro et al. (personal communication).

Table II. Literature data on liver resection for hepatocellular carcinoma

Reference	No. of patients	Survival (%)			Operative mortality (%)
		1y	3y	5y	
Bismuth et al.[12]	60		50		
Paquet et al.[18]	122	77		49	13
Makuuchi et al.[19]	362			43.7	1.8
Lin et al.[21]	225	53		18	
Belghiti et al.[22]	47		35	17	
Sasaki et al.[23]	142[a]			44	
	48[b]			68	
Wu et al.[24]	36[a]			45.2	5.5
	34			33.4	0

a Cirrhotic patients (n = 142).
b Noncirrhotic patients (n = 48).

thologist. Thus, orthotopic liver transplantation (OLT) can be considered the best therapy for small but unresectable HCCs in patients with cirrhosis (fig. 1).

2. Surgery

Most authors agree that, whenever feasible, liver resection remains the first-choice treatment in primary liver cancer, representing the only treatment modality associated with significant prolongation of survival.[4,6-10] Although the incidence of HCC is not related to the severity of liver disease,[12-14] the frequent association of this tumour with cirrhosis continues to restrict therapeutic options.[19,15,16] On the other hand, strict follow-up of cirrhotic patients, mainly by ultrasonographic examination, has improved the early diagnosis of small resectable HCC.[18-20] Cirrhotic condition, assessed before surgery in most cases, is still a major determinant of survival.[19] In noncirrhotic patients, partial hepatic resection is associated with a 5-year survival in more than 30%.[18] Therefore, for noncirrhotic patients (or patients with mild clinical liver dysfunction), partial hepatectomy represents the treatment of choice.

For cirrhotic patients, operative mortality is over 10%, although patients who survive the operation have a 5-year survival of 25 to 30%.[18,20] The Child-Pough classification reflects disease severity, and hepatic reserve of functionality also correlates with survival.[6] Furthermore, the indocyanine green 15-minute retention rate has recently been suggested to be a useful instrument in preoperatively defining the liver reserve (>10% retention rate = normal).[12]

When the oncological results are taken into account, the recurrence rate, although variable over a wide range, is unfortunately still quite high (20 to 70%) with most patients developing cancer recurrence (table II). However, it is often difficult to differentiate local recurrence from new HCC. Almost all relapses occur within 2 years of surgery,[23] with a 1 year mean time to recurrence. Mean survival time from diagnosis of tumour recurrence averages 9 months; there seems to be no significant difference in survival whether the recurrence is treated (9.1 months) or not (8.9 months).[23]

Since almost 80% of recurrences affect the liver (followed by lung 18% and bone 2%), there might be a role for adjuvant chemotherapy. To date, there is no clear evidence of utility for postoperative adjuvant chemotherapy, although recent retrospective data indicate a possible advantage for either systemic or regional chemotherapy.[1,18] The results of preoperative TACE are controversial. Although uncontrolled studies have reported an advantage for preoperative arterial embolisation or preoperative TACE,[25,26] another study indicates that this approach may be useful only in patients with good hepatic function and should not be performed routinely.[27]

In terms of survival rates, resection and transplantation yield the same results (50 *vs* 47%, respectively, at 3 years) according to a series reported by Bismuth et al.[12] However, transplantation achieves a better recurrence-free survival rate at the same time interval (46 *vs* 27%; $p < 0.05$), and when the small (<3cm) uninodular or binodular HCCs are analysed separately, transplantation has much better results (83 *vs* 18%; $p < 0.001$).

In conclusion, the indication for resective surgery *vs* OLT should be carefully tailored according to the hepatic reserve, tumour dimension, local facilities such as the number of grafts available and consequent stay on the operative list, as well as health economic analysis. Moreover, no conclusive data are currently available when the oncological results of surgery are compared with the success of other nonsurgical procedures: this is due to the lack of prospective trials and to a selection bias, since patients with different stages and various degrees of liver failure are being unevenly assigned to these therapeutic modalities.

3. Percutaneous Alcohol (Ethanol) Injection

The injection of alcohol (ethanol) into the tumour became feasible in the mid-1980s, when the routine use of ultrasound improved the detection of small HCC. The mechanism of action is probably based on a protein degenerative effect and a thrombotic effect.[1,28] Alcohol injections have been used to treat patients in whom hepatic resection is very risky, although some authors have employed PEI to attempt cure.[29,30] It is generally accepted that tumours <3cm in size and <3 in number are the best candidates for PEI, although some investigators also perform the therapy for larger liver tumours (up to 10cm).[28] Preliminary data focused on the treatment of single lesions, but now most investigators use PEI in patients with up to 3 lesions.[28,29]

PEI is contraindicated in the presence of gross ascites, clotting failure or obstructive jaundice.

The procedure is inexpensive and relatively simple; local anaesthesia is administered at the skin site, through the abdominal wall and to the liver capsule. A 22-gauge Chiba needle is introduced percutaneously into the liver tumour. The needle tip is generally placed at the core of the lesion, but when repeated procedures are required in treating larger lesions, peripheral areas should be injected as well. Absolute alcohol (99.5%) is slowly injected. The needle is shifted often to achieve uniform and adequate distribution to the neoplastic lesion. The procedure can be repeated several times in a week, according to the size of the tumour and patient compliance.

Okuda and Okuda[31] reported, in 125 patients treated with PEI, a 5-year survival rate of 44% in Child A patients (good liver function and no ascites or encephalopathy) and 34% in Child B patients (adequate liver function, mild ascites or encephalopathy). Similar encouraging results were noted by Livraghi et al.[28] in 207 patients treated with PEI. The 3-year survival rate was 63% for patients with a single lesion and 31% in those with multiple lesions. Child status dramatically influenced the results, with 76% survival at 3 years for Child A disease and 0% for Child C disease (jaundice, encephalopathy and ascites). It is noteworthy that for patients with lesions smaller than 5cm, the prognosis after PEI was similar to that of a matched group of historical controls who underwent resection. Sound selection criteria for intratumour alcohol injection are:

- tumour size smaller than 3cm;
- no severe hepatic dysfunction;
- no more than 3 lesions; and
- the presence of Child A or B disease, which are also likely to influence the outcome (fig. 1).

Response to treatment is based on necrosis of the tumour. Shiina et al.[32] reported at least 70% necrosis of tumours in 18 treated patients with PEI. In 13 patients, 100% necrosis was demonstrated.

However, all these studies were uncontrolled. Castells et al.[33] reported a cohort study comparing PEI (30 patients) with surgical resection (33 patients). Tumour recurrence at 2 years was 45% in the surgical group and 66% in the PEI group. The 1- to 4-year survival was not different between the

2 arms. An evaluation of combined PEI and TACE versus TACE alone was recently reported by Yamamoto et al.[30] The survival rate in the combined treatment group was significantly higher than that in the TACE group and further investigation is suggested for this treatment modality. To answer the question definitively, larger and prospective controlled trials would be required; unfortunately, such trials are not likely to be promoted on the base of ethical issues – good surgical candidates would probably not benefit from nonresective management, postponed surgery or any other nonradical option.

4. Cryotherapy

Neoplastic tissue can be devitalised by freezing; hence, the delivery of liquid nitrogen (at a temperature of –200°C) has been attempted via a vacuum-insulated cryoprobe, which can be inserted under ultrasonic guidance or during laparoscopic/laparotomic procedures. While the procedure is being conducted, a hyperechoic ice-ball signal is seen growing. It was suggested that at least 1cm of healthy tissue surrounding the liver lesion should also be frozen.[34] Once again, the best candidates are small (<6cm) and solitary HCC.

The procedure is performed under general anaesthesia, and the treatment is most commonly delivered during laparotomy, although it is technically feasible during laparoscopy. The major concern with the procedure is related to the possible damage to nearby structures and organs, more specifically portal and hepatic veins. Temperature rise and liver failure are not uncommon after cryotherapy; pleural effusion and basal atelectasis have also been reported.[35]

Preliminary experience is likely to support the feasibility of cryotherapy, but no conclusive evidence is available at present with regard to its real efficacy. The largest reported series, including 87 Chinese HCC patients, recorded no operative deaths; survival data were also quite interesting: 60.5, 32.0 and 20.2% at 1, 3 and 5 years after treatment (92.6, 66.6 and 50.8% respectively, for small HCC).[36] Western experience on cryotherapy is scanty, and the procedure requires further investigation.

5. Intra-Arterial Chemotherapy

The rationale for chemotherapy delivered through the hepatic artery is based on at least 3 major points: (a) the liver has a dual blood supply: the normal liver derives its blood supply from the portal vein, whereas liver tumours draw most of their blood from the hepatic artery; (b) uncontrolled tumour in the liver is the major cause of death in HCC, despite the fact that extrahepatic metastases are apparent in up to 25% of patients at diagnosis and in 90% of patients at autopsy; and (c) the administration of drugs with a high degree of hepatic extraction and consequently with production of fewer toxic metabolites can lead to lower systemic toxicity and a high concentration of the drug in tumour tissues.[37]

From these considerations, fluoropyrimidines probably represent the best agents for intrahepatic use.[37-39] Intra-arterial delivery of fluorouracil can give a 40- to 100-fold increase in hepatic drug exposure compared with intravenous delivery.[1] Moreover, floxuridine is well known to be associated with a 95% extraction at the first hepatic passage, resulting in low systemic drug concentrations[39] (table III). Anthracyclines have also been administered since these drugs are primarily eliminated by hepatic metabolism and biliary excretion, but only a 2-fold pharmacological advantage can be hypothesised.[42,44] Although a response rate of >20% has been obtained with anthracyclines, important hepatic toxicity has been described.[39] Other single drugs have been administered intra-arterially, such as mitomycin, cisplatin and mitoxantrone, with a <20% response rate.[40,41,45]

Unfortunately, most of the reported trials often employed inadequate drug dosages, and the differences in regimen and dosages as well as the small numbers of patients (which are rarely adequate for statistical analysis) preclude any evaluation, as yet, of the role of IACT. Moreover, such studies suffer from the fact that patients receiving IACT are characterised by good performance status (since they

Table III. Intra-arterial chemotherapy in the treatment of hepatocellular carcinoma

Reference	Drug	No. of patients	Response rate (%)	Survival (mo)
Wellwood et al.[1]	FUDR	28	52	7
Patt et al.[38]	FUDR	31	41	15
	LEUC			
	DOXO			
	CDDP			
Patt et al.[39]	FUDR	30	67	8
	DOXO			
	MMC			
Kinami et al.[40]	MMC	14	50	7
Onohara et al.[41]	CDDP	33	55	
Doci et al.[42]	DOXO	19	42	3.5
Ando et al.[43]	EPI	54	15	
Carr et al.[44]	CDDP	25	52	
	DOXO			
Shepherd et al.[45]	DHAD	23	25	3

Abbreviations: CDDP = cisplatin; DHAD = mitoxantrone; DOXO = doxorubicin; EPI = epirubicin; FUDR = floxuridine; LEUC = calcium folinate (leucovorin); MMC = mitomycin.

are capable of tolerating either a laparotomy or angiography in order to place the catheter), by limited extent of disease (patients with locally advanced or metastatic disease frequently not included) and by good liver function. Therefore, the prolongation of survival sometimes claimed in phase II studies of IACT can be explained by selection bias rather than by the effectiveness of the regimen employed.

A randomised study comparing IACT with hepatic artery ligation or symptomatic treatment reported no difference in survival.[1] Moreover, no difference was seen in a small randomised study of intra-arterial versus intravenous epirubicin plus fluorouracil.[46] However, as shown in table III, the remission rate observed for IACT is generally higher than that observed with intravenous chemotherapy. In a recently reported study, Carr et al.[44] observed a response rate of >50% with intra-arterial doxorubicin and cisplatin. Patt et al.,[38] combining the same drug plus a 4-day infusion of floxuridine and calcium folinate (leucovorin), reported a 64% response rate but with significant toxicity (3 treatment-related deaths). Such data, although encouraging, need confirmation in a large number of patients before a phase III study can be proposed. No definite advantage for this treatment modality can be claimed until a well conducted phase III study has been performed comparing best supportive care or intravenous chemotherapy with IACT.

6. Transcatheter Arterial Chemoembolisation

TACE was developed in an attempt to prolong the duration of contact between drug and tumour tissues, and it combines IACT with intermittent blocking of the hepatic artery through embolic materials. Theoretical advantages of this treatment are prolongation of the contact time between the cytotoxic agent and the tumour, the presence of induced ischaemia in the tumour, and the redistribution of arterial blood towards hypoperfused portions of the tumour.[47-51] Chemoembolisation is an important element in causing massive necrosis of the tumour; it is a rare event after intra-arterial catheter chemotherapy, but has also been reported after diagnostic hepatic angiography with ordinary contrast media and no ethiodised oil (lipiodol).[51]

Selective blood flow interruption has been obtained with various techniques and veno-occlusive materials. The most frequently employed materials are gelatin foam powder or particles, and ethiodised oil. The former consists of powder (40 to 50 μmol/L) or particles (250 to 590 μmol/L) that, when injected in the hepatic artery, transiently blocks circulation and within 48 to 72 hours is absorbed in the circulation. The use of gelatin powder would produce a more distal arteriolar occlusion and is theoretically hampered by the risk of inducing ischaemic bile duct necrosis; however, this event was not clinically relevant in any reported series. The latter compound consists of a lipid derived from poppy-seed oil containing iodine, which has been used in the past as a contrast medium and which is selectively retained by the tumour.[47]

Table IV. Chemoembolisation in hepatocellular carcinoma

Reference	Regimen	No. of patients	Response rate (%)	Survival (mo)
Okuda et al.[2]	MMC, LIP/GEL	112		10
Kanematsu et al.[48]	DOXO/LIP	70	47	28
Stuart et al.[50]	DOXO, LIP/GEL	47	43	16
Colleoni et al.[52]	DHAD/LIP/GEL[a]	26	54	11
Audisio et al.[53]	MMC microspheres	36	43	7
Beppu et al.[54]	ACL microspheres, CDDP	66	50	24
Pelletier et al.[55]	DOXO, LIP/GEL	42	33	24%
	vs no treatment			31% (1y)
Trinchet et al.[56]	CDDP, LIP/GEL	96		62%
	vs no treatment			43% (1y)
Vennok et al.[57]	DOXO, MMC, CDDP, LIP/GEL	50	24	7
Sasaki et al.[58]	CDDP, LIP/GEL	20	75	8
Kasugai et al.[59]	CDDP, LIP/GEL	52	38	20
Ohnishi et al.[60]	MMC microspheres	20	38	9
Shibata et al.[61]	CDDP/LIP	71	47	
Madden et al.[62]	EPI, LIP/GEL	50		6.8
	vs no treatment			7.2

a Plus intra-arterial chemotherapy.

Abbreviations: ACL= aclarubicin; CDDP = cisplatin; DHAD = mitoxantrone; DOXO = doxorubicin; EPI = epirubicin; FU = fluorouracil; LIP/GEL = ethiodised oil (lipiodol)/gelfoam; MMC = mitomycin.

The development of transcatheter arterial embolisation alone has been limited by the fact that, although often effective on the primary tumour, it has little effect on secondary nodules, tumour embolic and extracapsulary invasions.[46,51] On the basis of these considerations, we recently combined IACT and chemoembolisation and were able to report more than a 50% objective response without an increase in adverse effects.[52]

Various anticancer drugs have been combined with both embolic materials. In fact, most trials combined chemotherapeutic agents with ethiodised oil and gelfoam, as shown in table IV. Unfortunately, due to the large variation in chemoembolisation protocols, it is difficult to compare the real efficacy of these treatments and the impact on survival. In particular, although doxorubicin and cisplatin have been the most commonly used agents in combination with ethiodised oil and gelfoam powder, at present no combination can be considered as the benchmark treatment. Recently reported data on ethiodised oil and doxorubicin with or without gelfoam have suggested that the addition of the latter increases the response rate.[48] Similar data have been reported for cisplatin, where the addition of gelfoam increased the response rate from 25 to 58% and 1-year survival from 38 to 62%.[51]

The role of chemotherapeutic agents in addition to TACE has been evaluated in 2 randomised studies. Results were conflicting, with a trend towards a better response rate in a large study involving 289 patients with the addition of doxorubicin to TACE and a worse prognosis in 46 patients treated with cisplatin in addition to TACE.[63,64]

Another treatment modality included the use of microspheres combined with chemotherapeutic agents such as mitomycin and doxorubicin. Audisio et al.,[53] using mitomycin microspheres, reported an objective response of 43% with a median survival of 7 months, and similar results in terms of remission rate have been reported by other authors.[51] A recent report employing aclarubicin microspheres in combination with cisplatin suspended in ethiodised oil reported 50% objective responses but significant related complications

such as cholecystitis, pancreatitis and liver failure.[54] A study from Carr et al.,[49] employing degradable starch microspheres in conjunction with doxorubicin and cisplatin, reported 63% objective responses, with about half of the patients surviving 1 year.

Despite the fact that TACE is widely performed, and the consequent number of reports, no prospective, randomised study supporting its effectiveness has been conducted in Eastern countries. Conversely, there have been 2 randomised studies in Europe, but neither could significantly support the survival advantage for TACE-treated patients. Pelletier et al.[55] randomised 42 inoperable HCC patients to receive TACE *vs* no treatment, and recorded a 1-year survival of 24 and 31%, respectively.

Similarly, the French Group trial[56] reported a nonsignificant survival increase (62 *vs* 43.5% 1-year survival for TACE and controls, respectively); interestingly, the treatment group did show a trend to survival advantage, reduced tumour growth and portal obstruction, but a high incidence of liver failure was also recorded (60%). A third randomised study by Madden et al.[62] in 50 patients failed to demonstrate an advantage for TACE versus symptomatic treatment. A comparison between TACE and IACT with epirubicin in 38 patients reported a trend towards a benefit for TACE, although this was not significant.[65]

Three randomised trials evaluated the role of TACE as adjuvant treatment used either pre- or postoperatively. Unfortunately, patient numbers evaluated in these studies were only 50, 52, and 40, respectively. The first 2 studies reported a worse outcome for patients treated with postoperative TACE including doxorubicin and/or mitomycin;[66,67] the third reported an increased relapse-free survival with pre- and postoperative chemoimmunotherapy.[68]

The number and size of neoplastic liver lesions have been found to be relevant prognostic factors after TACE,[42,51] since complete necrosis is seldom achieved in lesions of >5cm and patients with larger lesions have a worse prognosis. Contraindications to TACE include insufficient liver reserve, severe clotting defect, thrombosis of the main port l vein and important arteriovenous shunting to the portal/hepatic vein. Adverse drug effects are frequent, involving more than 60% of patients,[47-56] but most often transitory: they represent the so-called 'postembolisation syndrome' and are secondary to liver capsule stretching, gallbladder infarction, pancreatitis, gastric and duodenal ulcer and necrosis, in cases where the chemotherapy drug is inadvertently injected into these sites. The occurrence of dull pain at the upper right quadrant, temperature (up to 39°C), and vomiting is more important and frequent when TACE is delivered into the hepatic artery, rather than superselectively into the tumour-bearing liver segment. The administration of dipyrone (noramidopyrine) or hydrocortisone can control these adverse effects in most cases.

7. Systemic Chemotherapy

Systemic chemotherapy has been widely explored in HCC, but the reported response rates rarely exceed 20% of objective remissions, with a median survival in the range of 2 to 6 months.[1,46,69] Many results have been reported on small groups of patients with unfavourable prognostic factors such as impaired liver function, jaundice, ascites or poor performance status. In such patients, the doses and regimens employed are suboptimal. It is actually well established that patients with these characteristics should not be included in clinical trials, and that the predictable impact of anticancer drugs is limited. Moreover, standard response criteria have rarely been adopted.

From an historical point of view, the first drug employed in HCC was fluorouracil.[1,70,71] The drug has been administered in most cases intravenously but with a large variation in dosages and regimens. However, fluorouracil never demonstrated significant activity in HCC, with a response rate ranging between 0 and 10% and a median survival of a few months. The addition of biochemical modulators such as calcium folinate or interferon did not seem to significantly enhance its activity,

whereas toxicity sometimes became unacceptable, as reported by Patt et al.[72] using a combination of fluorouracil given as continuous infusion and interferon. The administration of fluorouracil through continuous infusion together with epirubicin and cisplatin demonstrated interesting activity in a small group of patients with HCC and requires further investigation.[73]

The use of anthracyclines, and particularly doxorubicin, was initially reported in a small trial from Uganda and was characterised by a dramatic response rate (80%).[1] However, numerous confirmatory trials failed to demonstrate this remarkable response rate, and reported rates ranging from 3 to 32%.[74-75] Many problems are evident when analysing the data. In fact, the metabolism of anthracyclines includes detoxification through the liver, so that impaired liver function and in particular, bilirubin, may limit the administration of adequate dosages of the drug. However, in a large group of 52 patients who received an adequate dosage of doxorubicin, the response rate was only 12%,[1] thus suggesting that doxorubicin has only limited activity in HCC irrespective of the dosage employed.

There have been few randomised, controlled trials concerning systemic chemotherapy. In only one trial has doxorubicin been compared with no treatment, and an advantage was observed although it was not statistically significant.[75] The drug was also more effective than zinostatin (neocarzinostatin) and amsacrine in a randomised trial.[76]

The chemoresistance of HCC to the most commonly used agents may be related to baseline expression of biological features. HCC is associated with high expression of the multidrug resistance (MDR) gene product P-glycoprotein (Pgp), a multidrug efflux transporter. The most effective single agents in the treatment of primary liver carcinoma belong to the anthracycline family, yet several anthracyclines are known to be substrates for Pgp.[77] Moreover, chemotherapeutic drugs are cytotoxic by induction of apoptosis in drug-sensitive cells. Normal p53 tumour suppressor gene function is known to be correlated with apoptosis. Its normal function is required for an efficient activation of apoptosis following irradiation or treatment with chemotherapy and lack of p53, as demonstrated in HCC cells, may correlate with their resistance to treatments.[78]

The possibility of improving patient tolerance and antitumour activity with anthracycline analogues has been explored. Other studies employing epirubicin at medium to low dosages reported no activity on HCC.[1,46] The use of this doxorubicin analogue, despite the apparent lower myelotoxicity and cardiotoxicity, failed to demonstrate any advantage over doxorubicin. Most of the available data concern mitoxantrone, an anthrocenedione derivative with a mechanism of action and pharmacokinetics similar to that of anthracyclines.[79,80] In our experience in a large group of patients, a limited but definite activity (15%) was observed.[80] Another drug that can be included in the group of cytotoxic antibiotics and that has been widely used is mitomycin.[81] Although this drug has been used extensively, no definite data are available on its actual role in the treatment of HCC due to the different dosages and regimens employed and the fact that the drug was often combined with other chemotherapeutic agents.

A substantial lack of activity has been described for platinum compounds and epipodophyllotoxin derivatives such as etoposide.[79,82] Recently reported data on the favourable pharmacokinetics of etoposide when administered orally over the long term led to the publication of another phase II study with etoposide combined with tamoxifen, but limited activity was described.[83] Other agents that have been investigated in HCC include amsacrine, doxifluridine, zinostatin, vinblastine, ifosfamide, acivicin, fludarabine and zidovudine.[1,46] None of these compounds showed significant clinical activity. Considering that none of the agents employed revealed significant efficacy in the treatment of HCC, it is not surprising that combinations of these agents have not improved the outcome of these patients. The percentage of objective remissions observed as well as the duration of response and survival was superimposable to those observed with

single-agent therapy, and no significant advantage was detected. However, several studies reported significant toxicity.[1,74]

8. Immunotherapy

Research on the field of immunology in HCC is supported not only by the dismal results achieved with conventional neoplastic therapy but also by strong rationale resulting from epidemiological and laboratory data. There is considerable evidence implicating the hepatitis B virus (HBV) in the aetiology of HCC, and interferons are known to play a role in viral reproduction. Moreover, normal lymphokine-activated killer (LAK) cell activity is often depressed in patients with HCC.[84]

Interferons represent the family of biological response modifiers (BRM) which has been studied most extensively. With low doses of human leucocyte interferon (3MU/day), no objective remission was observed in one study,[85] and similar results in terms of lack of activity, but with considerable toxicity, were achieved in other studies at intermediate to high dosages.[86-88]

Better results were reported in a randomised study that compared the activity of doxorubicin and interferon-α,[89] with 10% objective remissions. The treatment was poorly tolerated; all patients developed a flu-like syndrome and drug-related deaths occurred in 4%. Lai et al.[90] randomised 71 patients to high-dose interferon-α or no treatment. Although a median survival of 14.5 months was observed for patients treated with interferon-α versus 7.5 months for untreated patients, the difference was not statistically significant. Arterial administration of interleukin-2 (IL-2) plus LAK cells produced no objective responses on a small group of patients,[91] whereas intratumoural injection of IL-2 in 5 Japanese patients achieved 2 responses.[92] Such negative results are in line with most results achieved in the treatment of solid tumours with BRM.

The limited knowledge on the mechanisms that regulate immunological mechanisms is reflected by the variety of regimens and dosages reported in the literature. Overall, no BRM seems to be of any value in HCC outside a research setting, and the complexity of the treatments with BRM and their cost will probably limit their development. Furthermore, the presence of extensive disease as well as impaired liver function and poor performance status often hinders an immunological approach in HCC patients.

The combination of fluorouracil and interferon reported only 18% objective remissions, mostly in patients with low baseline α-fetoprotein values.[72] Other authors have combined doxorubicin and mitoxantrone with α- and interferon-β, respectively.[46] However, no significant advantage was observed with respect to chemotherapy alone in terms of objective response or response duration.

9. Hormone Therapy

The influence of sex hormones in the pathogenesis of HCC suggested a possible interference in neoplastic growth with hormonal manipulation, as demonstrated for other solid tumours. The precise mechanism of action is not known, but it probably involves activation of carcinogens and/or stimulation of growth factors such as transforming growth factor-α and epidermal growth factor.[93,94] The presence of estrogen receptors has been detected in HCC. However, the percentage of receptor-positive patients does not differ significantly from that observed for healthy liver tissues or cirrhotic liver, and their prognostic significance remains to be determined. One study employed progestins and obtained 2 partial responses lasting 6 and 10 months, in 5 patients.[95] A second study employing megestrol in 14 patients with HCC recorded no major responses.[96] One phase II study with tamoxifen reported no major response,[97] whereas one randomised study from Italy that compared tamoxifen with a control arm reported a statistical advantage in survival for patients receiving that drug.[98]

Four other studies compared tamoxifen with a control (in one study tamoxifen was administered in association with triptorelin).[99-102] Although there was a trend towards increased survival in all studies, only one study demonstrated a borderline

statistically significant advantage in terms of survival. Although interesting, such data are debatable in view of the limited number of patients enrolled (only one trial included more than 100 patients), the absence of antitumour activity in phase II studies for tamoxifen, and the possibility that a difference in the distribution of prognostic factors may have influenced the results. However, the drug is currently under investigation in multicentre, prospective, randomised studies.

No significant activity has been reported for ketoconazole or buserelin.[51,103] One study with cyproterone reported 20% objective remissions in 25 evaluable patients.[103] However, one randomised study from the European Organisation for Research and Treatment for Cancer (EORTC) compared luteinising hormone-releasing hormone (LH-RH) agonists plus or minus antiandrogens versus placebo and demonstrated no activity in 244 patients with HCC.[104]

10. Radiotherapy

The use of external radiotherapy has a very limited role in the treatment of HCC because of the radiosensitivity of healthy hepatocytes. In fact, the maximum tolerated dose in healthy liver is between 25 and 30Gy.[1] Intra-arterial iodine-131-ethiodised oil targeted radiotherapy was developed to increase the dose received on the tumour bed and to reduce the dose delivered to the whole liver. Objective response rates were observed in 40 to 52% of treated patients, but median survival was discouraging and did not exceed 8 months.[105]

Yttrium-90 is a pure β-emitter that is more powerful than iodine-131. The results achieved in published series indicate a high response rate, but survival remained poor.[106] Further trials are needed to prove the safety and activity of this treatment modality.

11. Discussion

As reported above, most trials have been characterised by methodological problems such as the absence of standard response and toxicity criteria and by inclusion of patients with unfavourable prognostic factors such as impaired liver function and poor performance status.[29] Better identification of prognostic factors and stratification of the patients through prognostic variables such as performance status, age, gender, cirrhosis, jaundice, α-fetoprotein values and liver functionality parameters should clarify therapeutic results such as response to therapy and survival.

New drugs such as camptothecin derivatives and new classes of antimetabolites have been identified. Further phase II trials investigating these agents should consider methodology issues in order to improve therapeutic results. Furthermore, until new modalities have been compared with standard therapies, or (preferably) with supportive care, no superiority of one treatment over another can be claimed. A review of reported data indicates that, in general, the limited number of published randomised studies on HCC have included less than 100 patients.[107] Since most of the therapeutic treatment strategies compared in randomised trials (IACT, chemoembolisation) can provide only moderate additional benefit to the best supportive care, a larger number of patients must be studied. To generate reliable answers, further phase III trials comparing new interesting treatment modalities should include substantial numbers of patients.

In the decision making process applied to HCC patients, it is necessary not only to ascertain the stage of the tumour, but also to estimate other factors such as performance status, comorbid factors and the degree of underlying hepatic disease (fig. 1). Until now, the role of medical treatment in HCC has generally been limited to advanced disease stages, since conventional resectional surgery still remains the best treatment option for patients with limited disease and no cirrhosis or limited Child status. Another treatment choice in patients with advanced cirrhosis and limited stage of disease is liver transplantation. In particular, in patients with stage I disease and a tumour of <5cm in diameter, superior results to other treatment options are obtained. Preliminary results on small numbers of patients indicate a possible benefit of added regional chemotherapy in stage I to II disease, but whether

neoadjuvant or adjuvant chemotherapy will be most useful in decreasing post-resection or post-transplant recurrence has yet to be determined.

In patients in whom hepatic resection is risky (i.e. those with concomitant cirrhosis), PEI should be considered in view of the encouraging results in terms of minimal morbidity and efficacy achieved, although, at present, data establishing a definite benefit in survival are still lacking. Unresectable large solitary tumours or multiple tumours limited to one lobe with vascular invasion (stage III) have a very poor prognosis, especially if associated with cirrhosis (less than 10% survival at 3 years). In this group, a locoregional approach should be considered although at present it is not known which is the most effective. Therefore, chemotherapy with intra-arterial anthracyclines (or chemoembolisation, if vascular invasion is not present) can be considered, but in the future, comparison with other treatment modalities must be performed in order to assess their real benefit. Patients with bilobar HCC or with a major vascular tumour thrombus (stage IV A) have a very poor prognosis.

Several studies have indicated that IACT (or chemoembolisation in patients without vascular invasion) can lead to prolonged survival, especially in patients with Child's A or B cirrhosis. Such patients are, however, ideally suited to well conducted phase II to III trials. Although moderate activity has been reported with anthracyclines, no data at this stage support the use of available systemic chemotherapy in stage IV B patients (metastatic disease). In the case of a patient's request for treatment, 2 courses of systemic doxorubicin can be offered with treatment withdrawal if there is no response. However, such patients must be candidates for phase II clinical trials using novel agents, when performance and Child status are acceptable. In the case of liver failure, with jaundice or ascites, consideration should be given to the provision of no treatment but only best supportive care. Finally, combined modality treatment may offer an improvement of patient outcome in resectable disease.

As discussed above in section 2, results have been reported in series of patients with initially unresectable tumours who underwent a combination of preoperative radiotherapy, cryotherapy, embolisation and systemic chemotherapy, with encouraging survival data.[108,109] Although preoperative multimodality treatment appears to be worthwhile, prospective randomised trials are needed to confirm these data.

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