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Review

Endocrine Treatment of Hepatocellular Carcinoma. Any Evidence of Benefit?

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In the past 20 years, a number of studies have investigated the relationship between sex hormones and liver cancer. Experimental studies indicate that a dynamic process, with sequential modifications in the pattern of sex hormones in the serum and of sex hormone receptors in the liver, occurs progressively during hepatocarcinogenesis. Overall, it seems that both androgens and oestrogens may enhance liver carcinogenesis, while androgens may also support the growth of established liver tumours. Unfortunately, clinical studies of endocrine treatment of hepatocellular carcinoma (HCC) have not adequately tested the suggestions from biological studies. So far, no clinical trial has been performed to test the efficacy of endocrine manipulation for the chemoprevention of HCC in cirrhotic patients nor in preventing relapse after radical resection of primary HCC. Anti-oestrogens have been the most studied agents for the endocrine treatment of established HCC, although the rationale that supports their use is weaker than for anti-androgens. Studies with anti-androgens have produced prevalently negative results, due to either a lack of activity or excessive toxicity. The use of chemical castration, which theoretically could enhance the activity of antihormonal compounds, yielded no benefit at all. In summary, there is, as yet, no definitive evidence that endocrine treatment favourably affects the outcome of patients with HCC. © 1998 Elsevier Science Ltd.

Key words: hepatocellular carcinoma, endocrine treatment, oestrogen, androgens, oestrogen receptor, androgen receptor
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INTRODUCTION

EACH YEAR, more than 250 000 new cases of hepatocellular carcinoma (HCC) are diagnosed in the world. The disease is particularly common in Eastern countries, where death rates per year have increased to 150 per 100 000. In Europe, the death rate per year is approximately 5 per 100 000. A common feature in the different areas of the world is that the disease prevalently affects males, thus suggesting a possible role for sex hormones in the process of hepatocarcinogenesis.

Sex hormone imbalance has been described in men with liver cirrhosis and HCC; namely, reduced serum testosterone levels and increased oestradiol levels [1, 2]. Because oestrogens directly modulate hepatocyte proliferation and oestrogen receptors (ER) are present in liver with cirrhosis and HCC, it has been suggested that sex hormone changes may play a role in liver carcinogenesis. Therefore, in the past 20 years, a number of studies have investigated the relationship between sex hormones and liver cancer. It is now clear that sex hormones can influence liver regeneration and they are considered important factors in the induction and promotion of hepatocarcinogenesis.

Here, we aim to summarise the biological basis of endocrine treatment of HCC, presenting the current status of the knowledge of the relationships between sex hormones and liver cells in different experimental models, such as regenerating liver (following partial hepatectomy in animals), and chemically induced carcinogenesis (both with genotoxic and non-genotoxic inducers); and to examine relationships between sex hormones and benign liver neoplasms, both in animals and in humans. We have also analysed whether the biological hypotheses have been adequately tested in clinical studies of endocrine treatment of HCC, with particular emphasis on the possible confounding variables (both clinical and methodological) of published studies.

This paper is written on the basis of papers retrieved by Medline in December 1996, and on papers found by handsearching pertinent papers in specific journals and in the proceedings of major congresses in the field.

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WHAT ARE THE BIOLOGICAL BASES OF ENDOCRINE TREATMENT OF HCC?

Sex hormones and liver regeneration

Experimental evidence indicating that sex hormones modulate the process of liver regeneration has been found in rats. It has been shown that following a 70% hepatic resection, there is an increase in serum oestradiol levels [3, 4] and an increase in the total number of ERs in the remaining regenerating liver; particularly, the nuclear fraction of ERs increases, while the cytosolic component declines [5–7]. Cell proliferation and DNA synthesis during liver regeneration are inhibited by the anti-oestrogenic drug tamoxifen and this effect is reversed by oestrogens [8]. In female rats, ethinyloestradiol is co-mitogenic with hepatocyte growth factor, transforming growth factor-alpha, epidermal growth factor (EGF) and fibroblast growth factor [9], that are considered very important mitogens for the growth control of the regenerating liver.

The role of androgens seems less important; during liver regeneration both serum testosterone levels [4, 10] and androgen receptor (AR) content in the liver decline, in the cytoplasm as well as in the nucleus of the cells [11]. The process is not significantly affected by the anti-androgen flutamide [12]. Furthermore, the H2-receptor antagonist cimetidine, that binds ARs and reduces their level in the liver, does not modify the regenerative response to resection in the rat [13].

Sex hormones and liver carcinogenesis

The role of sex steroids in liver carcinogenesis has been studied mainly in animal (rats and mice) models of experimental carcinogenesis (Table 1). Oestrogens promote the development of liver tumours induced by genotoxic agents such as diethylnitrosamine and aflatoxin [14–16]; this effect is largely dependent on the time of exposure to the hormones and occurs in both female and male rats [17]. In mice, androgens also act as promoters after induction by genotoxic agents; male mice castration decreases the incidence of chemically induced HCC [18], while the chronic administration of testosterone to females or castrated male animals promotes the growth of preneoplastic liver foci and chemically induced HCC [19, 20]. Furthermore, in rats, chemical hepatocarcinogenesis is also associated with a significant increase of nuclear ARs that can be prevented by orchidectomy or anti-androgen treatment [21, 22]. The role of ARs in liver carcinogenesis is supported by the observation that AR-deficient mice are much less susceptible to diethylnitrosamine-induced HCC than normal mice [23]. Finally, anti-androgen treatment reduces the size and the number of liver tumours induced by chemical agents and decreases the growth rate of established tumours [21].

Sex steroids could also be important in the mechanisms by which non-genotoxic carcinogens induce liver cancer [24]. The phthalic acid ester di(2-ethylhexyl)phthalate (DEHP) induces hyperplasia and tumour development in the rat liver through a non-genotoxic mechanism, as it is not mutagenic [25] nor binds to DNA [26]. One of the earliest metabolic events induced by DEHP is the loss of activity of oestrogen sulphotransferase and oestrogen 2-hydroxylase, key enzymes in sex hormone metabolism. This can increase hepatocyte oestrogen concentration [27], which could play a crucial role in the induction of hyperplasia [28]. During the early phase of carcinogenesis, an increase in ERs and nuclear ARs is also evident. In the late phase (i.e. in tumour-bearing livers), AR activity remains high, while ER levels strongly decrease. Thus, it has been suggested that both androgens and oestrogens are important for the early phase of carcinogenesis, but oestrogens are less important for the growth of established tumours [27].

Oestrogens, administered alone, induce the development of hyperplastic foci and HCC in female Wistar rats; the percentage of animals developing such alterations is highly variable (8–75%), depending on the dose and length of the hormonal treatment [29–32]. The effect of oestrogens is mediated by ERs [33], as confirmed by the increase in the amount of oestrogen–ER complexes during carcinogenesis [32]. Macroscopically, oestrogen administration to rats induces an increase in liver weight [34]. At a molecular level, oestrogens lead to the formation of DNA adducts [35], maximally during the early stage of carcinogenesis, to the activation of oncogenes [36], and to an overall stimulation of DNA synthesis [34]. The anti-oestrogen tamoxifen completely suppresses oncogene activation and the development of both hyperplastic nodules and HCC; in contrast, it has no effect on the formation of DNA adducts [37]. *In vitro* studies have shown that oestradiol is co-mitogenic with EGF and other hepatic mitogens in eliciting an increase in DNA synthesis in hepatocyte cultures [38, 39]. In addition, the generation of free radicals, which may cause cancer development by damaging DNA bases and inducing mutations, could be a further mechanism for the carcinogenic effect of oestrogens. It has been recently demonstrated that during ethinyloestradiol-induced carcinogenesis there are increased activities of detoxifying enzymes (such as glutathione *S*-transferase) along with increased levels of 8-hydroxydeoxyguanosine that peak 1 month after oestrogen administration [40].

Table 1. *Summary of relationships between hormones, antihormones and receptor expression and different pathological settings*

	Experimental carcinogenesis induced by			Human liver tumours	
	Genotoxic agents	Non-genotoxic agents	Oestrogen	Benign	HCC
Promotion	oestrogen androgen	oestrogen androgen	oestrogen	oestrogen, androgen, progestins	
Inhibition	tamoxifen anti-androgens		tamoxifen		
ER levels	increase	early increase late decrease	increase	increase	stable or decrease or mutant
AR levels	increase	increase			increase

HCC, hepatocellular carcinoma, ER, oestrogen receptor; AR, androgen receptor.

Sex hormones in the development of human liver tumours

Since the first description by Baum [41], the link between the administration of preparations containing a variety of oestrogenic and progestational steroids and the development of hepatic adenoma, focal nodular hyperplasia and HCC has been well established [41–44]. Observational studies have shown that oestrogens may play a role in the development of hepatic adenoma and focal nodular hyperplasia in both males and females [45–47]. In some cases, the regression of these benign lesions has been obtained by withdrawing hormone administration [48].

Several studies indicate a positive association between the use of oral contraceptives and primary liver cancer in developed countries [44, 49, 50]; an increased risk continues to be evident more than 10 years after stopping their use and its magnitude is directly related to the length of consumption [50].

Also, the long-term use of androgenic anabolic steroids can induce benign tumours in the liver [51, 52]. A retrospective study, using serum samples from a cohort of 9691 male adults, showed that elevated serum testosterone levels represent a risk factor for the development of HCC in humans [53].

Sex hormone receptor levels in benign and malignant liver neoplasms

Binding studies have demonstrated the presence of cytosolic and nuclear ER in normal human liver and hepatic adenoma. Compared to normal tissue, an increase in nuclear ER fraction, which is the more biologically active form of the receptor, has been found in liver adenomas and focal nodular hyperplasia [4]. In contrast, ER expression is either normal or completely suppressed in established HCC [54, 55]. In male patients with HCC, Villa and associates reported the presence of mutated ERs, which are post-transcriptionally truncated and unable to bind the ligand, but constitutively activate transcription. Furthermore, in patients with mutated ERs in the tumour, the peritumoral cirrhotic tissue shows increased expression of the same variant ER transcript compared with normal (non-cirrhotic) liver tissue, suggesting that a gradual transformation, that may take place during progression of the cirrhotic process, can represent an early event of hepatocarcinogenesis [56]. In contrast to ERs, the studies performed in HCC and normal liver showed that the expression of ARs is enhanced by malignant transformation [54, 55]. On the basis of published studies, it can be estimated that approximately 70% and 30% of HCCs are positive for AR and ER, respectively [54, 57–60].

Prognostic role of sex hormone receptors

Only two studies have investigated the prognostic role of sex hormone receptors in patients with HCC. Both studies were retrospective and included a small number of patients who had undergone radical resection of their primary HCC and had been followed up for recurrence. Both studies suffer from methodological shortcomings such as small sample size, multiple subgroup analyses and lack of multivariate analysis.

Nagasue and associates [59] found that 69% (46/67) of tumours expressed ARs and that the expression was significantly correlated with a shorter recurrence-free survival (0 versus 55% at 5-year follow-up, $P = 0.0072$). Only 31% (21/68) of the tumours expressed ERs, which did not significantly correlate with a shorter recurrence-free survival (10% versus 24% at 5-year, $P = 0.17$). Normal adjacent liver cells showed a similar rate of AR expression (23/33 cases—70%) but higher ER expression (22/41 cases—54%) compared with tumour cells. No data were reported on the correlation between tumoral and non-tumoral receptor status. However, the receptor status of the surrounding liver did not affect the risk of recurrence.

Conflicting data have been reported by Boix and associates [60]. They analysed 43 cases for AR expression both in the tumour and in the non-tumoral (prevalently cirrhotic) liver. The rate of AR positivity was 65% and 70% in the two groups of tissues, respectively; surprisingly, there was no significant correlation between tumoral and non-tumoral receptor status ($r = 0.013$, $P = 0.93$). No correlation was found between AR expression in the tumour and the risk of recurrence, while a significant relationship was found when taking into account AR expression in the non-tumoral liver samples: 49% versus 80% 2-year recurrence-free survival ($P < 0.03$) for AR-positive versus AR-negative cases. Overall, the prognostic role of sex hormone receptor expression in HCC is a completely open field, and other studies are warranted.

Summary of biological bases for endocrine treatment of HCC

Taken together, experimental evidence indicates that a dynamic process with sequential modifications in sex hormone serum levels and sex hormone receptors in the liver occurs progressively during carcinogenesis. Overall, it seems that both androgens and oestrogens may enhance liver carcinogenesis while androgens may also support the growth of established liver tumours. On the basis of this knowledge, the following therapeutic hypotheses could be stated:

(1) both anti-androgenic and anti-oestrogenic compounds could be active as preventive treatment in cirrhotic patients at high risk of developing HCC or in patients radically resected;
(2) anti-androgenic drugs and, to a less extent, anti-oestrogenic drugs could be active as treatment of established HCC;
(3) only tumours expressing functioning receptors for either type of sex hormone should be sensitive to antihormonal treatment.

HAVE THE HYPOTHESES RAISED BY THE BIOLOGICAL EVIDENCE BEEN ADEQUATELY TESTED IN CLINICAL TRIALS OF ENDOCRINE TREATMENT?

The drugs currently available allow three distinct strategies of endocrine treatment:

(1) to antagonise or counterbalance the effect of oestrogens by the use of anti-oestrogens or progestins;
(2) to antagonise or counterbalance the effect of androgens by the use of anti-androgens;
(3) to reduce both androgen and oestrogen circulating levels by chemically induced castration with LH-RH (luteinising hormone–releasing hormone) superagonistic analogues. Each of the first two options may be conceptually combined with the third option.

Anti-oestrogens and progestins

Eight reports are available on the use of tamoxifen in HCC, five of which address its role as a single agent (Table 2). Paradoxically, there are four randomised trials and one phase 2 study only, the latter with negative results. In 1990,

Table 2. Summary of studies on anti-oestrogens and progestins

Author [Ref]	Study arms	Number of patients	Stage of disease	Responses (%)	Median survival (months)	*P*
Single-arm studies						
Engstrom [61]	Tamoxifen	33	advanced	—	6	
Cheng [69]	Tamoxifen + Etoposide	33	unresectable unembolisable	8 (24%)	resp: 8 non-resp: 3	
Friedman [70]	Progestins	5	unresectable	2 (40%)	NR	
Chao [72]	Megestrol	32	unresectable unembolisable	—	3	
Colleoni [71]	Megestrol	11	unresectable unembolisable	—	4	
Comparative studies						
Melia [68]	TAM (20 mg/day) + Dox versus Dox	59	advanced	4 (16%) versus 3 (11%)	2.5 versus 2	NS
Farinati [62]	TAM (30 mg/day) versus Nil	38	advanced unresectable	NR	9 versus 2	< 0.02
Elba [64]	TAM (60 mg/day) versus placebo	22	advanced unresectable	NR	17 versus 12	0.04
Martinez Cerezo [63]	TAM (20 mg/day) versus Nil	36	advanced	NR	9 versus 6	< 0.01
Castells [65]	TAM (20 mg/day) versus placebo	120	advanced	NR	14 versus 6*	NS

TAM, tamoxifen; resp, responders; NR, not reported; Dox, Doxorubicin; Nil, no treatment; NS, not significant.
*Graphically extrapolated from the published curves.

Engstrom and associates [61] showed no responses in a series of 33 patients with advanced HCC, receiving 40 mg/day of tamoxifen. The same year, Farinati and associates [62] published the first randomised study. 38 patients with advanced disease randomly received either tamoxifen 30 mg/day or no treatment: a large and statistically significant difference in median survival (9 versus 2 months) was found, despite the very low number of enrolled patients. Two other small randomised trials were published in 1994. Martinez Cerezo and associates [63] published the results of a trial planned to verify a 40% absolute gain in 1-year survival of treated (tamoxifen 20 mg/day) versus untreated patients; an interim analysis showed a significant ($P < 0.01$) benefit for the treated arm (9 versus 6 months median survival, 48% versus 9% 1-year survival) and prompted stopping the trial after the randomisation of only 36 patients. Elba and associates [64] randomised 22 patients with advanced disease to receive either tamoxifen (60 mg/day) or placebo. The dose of tamoxifen was chosen because previous unpublished experience of the same authors indicated that the dose of 30 mg/day had not improved patients survival. With the higher dose, median survival was longer for treated patients (17 versus 12 months, $P = 0.04$). By the end of 1995, the largest randomised trial was reported by Castells and associates [65]; 120 patients with advanced disease were randomly assigned to tamoxifen (20 mg/day) or placebo. The size of the trial was planned on an expected 25% net benefit in survival for treated patients. Unfortunately, only a non-statistically significant advantage in survival was found for tamoxifen-treated patients (51% versus 43% 1-year survival; $P = 0.75$).

A large-scale multicentre randomised clinical trial comparing tamoxifen (40 mg/day) versus no treatment, the CLIP-01 trial, is now ongoing [66]. 496 patients have been randomised after 2 years of recruitment, and results will be available by the end of 1997. A further randomised clinical trial comparing tamoxifen (40 mg/day) versus placebo has been planned by the EORTC [67].

Tamoxifen has also been used in combination with cytotoxic drugs. In 1987, Melia and associates [68] randomised 59 patients to doxorubicin alone or combined with tamoxifen (20 mg/day); there was no difference in response rate (11 versus 16%) nor median survival (2 versus 2.5 months). Nevertheless, they concluded that tamoxifen could have a role in maintaining doxorubicin-induced remissions, based on one long-term surviving patient who had received both drugs. More recently, tamoxifen (40 mg/day) has been associated with etoposide (50 mg/m^2 orally from days 1 to 21 recycling every 5 weeks). The rationale for this treatment schedule was that chronic oral administration of etoposide should enhance its activity as a type II topoisomerase interacting drug, while tamoxifen could partially counteract the effect of the p170 glycoprotein, produced by the multidrug-resistance (*MDR*) gene, one of the major causes of resistance of cancer cells to etoposide. Unfortunately, the phase II study reported by Cheng and associates [69] does not allow any conclusions to be drawn: 33 patients were treated, 8 (24%) experiencing a partial response. No significant toxicity has been reported with the exception of skin toxicity that is rarely described with etoposide alone, consisting of itching pigmented maculopapular eruptions that were observed in one quarter of patients.

Three reports are available (one as abstract only) on the use of progestins (Table 2). In the first one, published in 1982 by Friedman and associates [70], 5 patients were treated and two partial responses were reported, lasting 6 and 10 months, respectively. Megestrol acetate (160 mg/day) was given by Colleoni and associates [71] and Chao and associates [72] to patients with unresectable and unembolisable HCC. In the first study, 11 patients were treated with no response. Similarly, in the second study (reported as abstract only), no response was reported in 32 evaluable patients out of 46 treated. In this last study, however, most patients experienced improved appetite and feelings of well-being; no significant toxicity was reported.

Anti-androgens

Five reports are available on anti-androgens, using four different compounds (Table 3). A measurable but low activity

Table 3. Summary of studies on anti-androgens

Author [Ref]	Study arms	Number of patients	Stage of disease	Responses (%)	Median survival (months)	*P*
Single-arm studies						
Forbes [73]	CPA	25	unresectable	3 (12%)	3	
Gupta [74]	Ketoconazole	8	unresectable	—	NR	
Nagasue [57]	CPA	16	unresectable or recurrent	3 (19%)	NR	
Chao [75]	Flutamide	32	unresectable	—	< 3	
Comparative studies						
Bleiberg [76]	Nilutamide: yes versus no	238	advanced	NR	3.9 versus 5.5	NS

CPA, cyproterone acetate; NR, not reported; NS, not significant.

was reported with cyproterone acetate (CPA), a steroidal anti-androgenic compound with progestogenic activity [57, 73]. In the first series [73], three radiological partial responses (according to WHO criteria for response evaluation) out of 25 treated patients (12%) were reported. In the second one [57], three responses were recorded out of 16 treated patients (19%), although the result is given in the discussion of the paper without any other detail or comment. In 1988, Gupta and Korula [74] observed no response in 8 patients with unresectable HCC treated with ketoconazole (an antimycotic drug with androgen antagonist properties). More recently, Chao and associates [75] showed that flutamide (a pure non-steroidal anti-androgen) had no activity in advanced HCC with no response observed in 32 treated patients. The largest trial on anti-androgens is an EORTC study, reported by Bleiberg and associates only as an abstract [76]. In a randomised factorial design, two questions were addressed: the role of a pure anti-androgen (nilutamide) and the role of LHRH analogues (goserelin or triptoreline); overall 238 eligible patients were randomised. The analysis for the first factor effect (nilutamide) showed no benefit for patients receiving the drug, with a very poor median survival (3.9 months), even shorter than in the control group (5.5 months).

LHRH superagonist analogues

Three studies have examined the use of chemically-induced castration as single-agent treatment for advanced HCC (Table 4). Falkson and Ansell [77] reported no response in 14 patients treated with buserelin. In a study primarily devoted to describing the effect of triptorelin on plasma levels of sexual steroids, Guéchot and associates [78] reported no response in 17 patients treated with this drug. Bleiberg and associates [76], in the above-reported factorial EORTC trial, also showed no benefit for patients receiving an LHRH analogue (either goserelin or triptorelin) with a non-significantly shorter median survival than in the control arm (3.4 and 5.5 months, respectively).

The combination of LHRH analogues with tamoxifen or anti-androgens was tested by Manesis and associates [79] in a three-arm randomised study (Table 4). Compared treatments were placebo (29 patients), tamoxifen (30 mg/day) + long-acting triptorelin (33 patients) and flutamide (750 mg/day) + long-acting triptorelin (23 patients). Although median survival was similar in the three arms of the study (4 versus 4 versus 3 months), the authors found a statistically significant ($P = 0.02$) survival advantage for patients receiving tamoxifen + triptorelin that prompted them to stop the trial at an interim analysis. They also claimed that the tamoxifen + triptorelin effect was more pronounced in female than in male patients and was independent of the suppression of serum hormone levels. In addition, a possible association of flutamide treatment with increased bilirubin levels was suggested.

DISCUSSION

Despite a number of suggestions given by biological studies, clinical research on the role of sex hormones in HCC has produced conflicting results and appears overall inadequate because of methodological flaws. Some of the possible confounding variables of published studies deserve more comments.

Stage of disease

Although the wide range of reported median survivals (from 2 to 17 months) indicates that a notable variability of prognostic factors distribution exists in published clinical series, all the studies included only patients with very advanced disease. This contrasts with data from biological studies which indicated that ER levels decrease during progression from benign to malignant tumours and that ERs

Table 4. Summary of studies on LHRH analogues and combinations

Author [Ref]	Study arms	Number of patients	Stage of disease	Responses (%)	Median survival (months)	*P*
Single-arm studies						
Falkson [77]	Buserelin	14	advanced	—	3	
Guéchot [78]	Triptorelin	17	unresectable	—	< 3	
Comparative studies						
Bleiberg [76]	Triptorelin: yes versus no	238	advanced	NR	3.4 versus 5.5	NS
Manesis [79]	TAM (30 mg/day) + Triptorelin versus Flutamide + Triptorelin versus Placebo	85	advanced	—	4 versus 3 versus 4	NS

TAM, tamoxifen; NR, not reported; NS, not significant.

expressed in HCC may be functionally inactivated because of pathological post-transcriptional events. In contrast, AR levels do not seem to correlate with the stage of disease. Thus, it is not surprising that objective tumour shrinkage has been reported only in some trials with anti-androgens, while no response has been observed with tamoxifen.

General strategy of clinical trials

A couple of paradoxical situations have been identified. Indeed, the classical sequence phase 2 → phase 3 trials has been ignored both with tamoxifen and with anti-androgens, in different ways. Only one phase 2 trial on tamoxifen has been reported, with negative results [61]. Nevertheless, six randomised studies have been performed and published [62–65, 68, 79]; one large trial has just reached the planned sample size [66] and another large trial is planned by the EORTC [67]. A possible explanation of this could lie in the predicted effect of tamoxifen that is considered not purely cytotoxic, but rather able to reduce the speed of tumour growth, a biological action that can be clinically seen by only analysing survival or time to progression.

The single-arm studies showing measurable although low activity against HCC are those on the steroidal anti-androgen compound CPA [59, 73]. However, in the first paper, two of the five claimed responses were based on the sole reduction of serum AFP levels [73], while, in the second paper, the data on treatment of patients are only reported as an accessory result in the discussion paragraph without any detail on response evaluation and toxicity. CPA has never been tested in a randomised study, presumably because of its hepatic toxicity; in fact, at least 10 cases of acute hepatitis have been described, 4 of which were fatal in patients with prostate cancer treated with this drug [80]. Paradoxically, flutamide and its analogue nilutamide, that are non-steroidal anti-androgens, have been tested in randomised trials with negative results [76, 79] without any previous published evidence of their activity. The first reported single-arm study was published as an extended paper in 1996, with negative results [75].

Selection of patients and sample size

Overall, a predefined statistical plan is lacking in the majority of single-arm studies. Patients dying soon after the start of treatment have been wrongly considered as not evaluable in some reports. Unfortunately, the only study reporting positive results [70] is too small and has never been confirmed. Furthermore, in some studies too many patients have been treated with inactive drugs, raising ethical problems. These problems, however, can be reasonably mitigated by the highly unfavourable prognosis and the absence of any other active treatment for HCC.

All the published phase 3 trials suffer from a small sample size, the effect of a lack of any baseline statistical design in some cases, or of non-realistic hypothetical advantage in survival for the experimental arm in other cases. This is confirmed by the plannings of the two major ongoing trials on tamoxifen. The CLIP-01 trial [66] that we are coordinating was planned on the basis of an expected 1-year survival in the control arm (supportive care) = 50% and an expected difference in the treatment arm (supportive care + tamoxifen) = ± 12%. This would translate, if tamoxifen was effective, into prolongation of median survival from 12 to 17 months. With common statistical constraints, approximately 450 patients would be required. In the EORTC trial that should have begun by the end of 1996 (tamoxifen versus placebo), the recruitment of 414 patients is planned [67]. Nevertheless, by summing up all studies, fewer than 350 patients have been entered in published randomised trials on tamoxifen, and the largest one showed no advantage for tamoxifen-treated patients. The only large randomised trial so far reported [76] can reasonably rule out an advantage due to anti-androgens or LHRH analogues, of the order of a 50% increase in the 6-month median survival of control arm; additional information derives from the factorial design of this study, as the absence of a trend favouring the association of anti-androgens and LHRH analogues makes it reasonable to assume that combined hormonal treatment of HCC has no utility.

CONCLUSIONS

No clear evidence of benefit from endocrine treatment of HCC can be derived from the published literature. Unfortunately, clinical studies on endocrine treatment of HCC have not adequately tested the hypotheses from biological studies. This can be partially ascribed to the fact that much biological evidence has become available only in recent years, while clinical efforts of hormonal manipulation of HCC started at the beginning of the 1980s. No clinical trial has been performed to test the efficacy of endocrine agents in the chemoprevention of HCC in cirrhotic patients or in preventing relapse of patients who underwent radical ablation of primary HCC. Most studies on the treatment of established HCC tested anti-oestrogens that were less promising than anti-androgens. Studies on anti-androgens have produced prevalently negative results, either because of lack of activity or due to excessive toxicity. The use of chemical castration, which theoretically could have enhanced the activity of anti-hormonal compounds, produced no benefit at all. Overall, a definitive demonstration of a significant benefit of endocrine treatment on the outcome of patients with HCC has, as yet, not been shown.

In planning future studies, antihormonal treatment as chemoprevention of HCC in cirrhotic patients should be addressed. This could be more feasible with tamoxifen and non-steroidal anti-androgens, thanks to the lack of significant toxicity. Available anti-androgens do not seem worthy of further studies in advanced disease; phase 2 trials should be conducted to test the activity and tolerability of new compounds as they became available. The results of large trials of tamoxifen treatment are awaited to conclude on its efficacy; these data will be available shortly. If they are positive, tamoxifen should become the standard treatment with which to compare new drugs, but if they were negative, there would be no other reasonable basis to test anti-oestrogens in the treatment of advanced HCC. Nonetheless, every effort should be made to incorporate biological studies (e.g. on the expression of hormone receptors) in future trials, to study prognostic factors and, eventually, to select subgroups of patients who are most likely to benefit from hormonal treatment.

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