

Combination treatment of unresectable hepatomas with chemotherapy, octreotide and antioestrogens: A preliminary study

Research Article

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Summary

Hepatocellular carcinoma (HCC) is a highly malignant tumor with a very high morbidity and mortality, carrying a poor prognosis and presenting considerable management problems. The aim of the study was to estimate if and how much the administration of two drugs regimens chemotherapy together with Sandostatin LAR 30 and tamoxifen improves survival and quality of life in patients with inoperable HCC comparing the results with these of nothing received group patients. 15 patients with HCC were included in the treatment group between 2002 – 2004 (Group A). All patients received: Caelyx 25 mgr/m² – day 1, Gemzar 1000 mgr/m² (d1 + d8), with repeat cycle every 21 days for 6 moths, Sandostatin LAR 30 once a month until progression of disease (PD) and Nolvadex 20 mgr/day. 7 patients with HCC, who refused to received any treatment remain as a control group (Group B). These patients have received medical treatment for pain, nausea or local effects of the disease.

I. Introduction

Hepatocellular carcinoma (HCC) is the most common primary epithelial malignancy occurring in the liver and is characterized by an extremely poor prognosis, and presenting considerable management problems (Johnson, 1996; Alsowmely and Hodgson, 2002).

Surgical resection – either as partial hepatectomy or by orthotopic liver grafting – has traditionally been regarded as the first-choice treatment and the only realistic chance for the cure of HCC.

However only 10% are suitable for curative resections due to many factors: multicentric tumors, vascular invasion, advanced liver cirrhosis, extrahepatic metastases and comorbidities (Hodgson, 1983; Rasmussen and Garden, 1996; Liu and Fan, 1997).

Recently some interesting results have been reported with anti-estrogenic, -anti-androgenic or somatostatin analogues treatment (Farineti et al, 1992; Martinez Cerero et al, 1994; Cascinu et al, 1995; Kouroumalis, 2001) have shown some activity. On the other hand HCC is generally one of the most resistant tumor to chemotherapy (Llovet

and Bruix, 2000). No regimen has proven to be curative in an analysis, no single drug or combination of drugs showed a reproducible response rate of more than 20% (Okuda, 1997).

In this study, a preliminary report is presented of a combination treatment with two chemotherapeutic drugs: liposomal doxorubicin (Caelyx) + gemcitabine (Gemzar) in combination with somatostatin analog (Octreotide) and an antioestrogen (Tamoxifen) with some interesting and promising results.

II. Patients and Methods

Fifteen patients, ten males and five females, median age 70years old (range 62y – 80y) with HCC were included in the therapeutic trial between 2002 and 2004 (Group A). Inclusion criteria were liver biopsy or FNA B diagnosis of HCC, increased levels of a fetoprotein (AFP) with compatible liver ultrasound and CT scan (**Table 1**).

Seven patients, five males and two females with HCC were included as a control group between 2002 and 2004 (Group B). All of these patient with confirmation of HCC with FNA B or liver biopsy refused to received the therapeutic trial and remain

with medical treatment for pain, nausea or local effect of the disease (**Table 2**).

Treatment responses are usually evaluated according to the WHO and response evaluation criteria in solid tumors group criteria (Therasse et al, 2000).

Complete response (CR) is defined as the complete disappearance of all target lesions for more than 4 weeks. In our study two patients (13.3%) presented CR and they are still alive 20 and 17 months retrospectively with median survival rate (MSR) of 18,5 months.

Partial response (PR) is defined as at least 30% reduction in the sum of the longest diameters of target lesions lasting for more than 4 weeks. In our study five patients (33.3%) presented P.R with a MSR of 11,6 months.

Progressive disease (PD) is defined as at least 20% increase in the sum of the longest diameters of target lesions or the appearance of one or more new lesions.

A. Treatment schedule and follow-up

All the patients of Group A received the follow therapeutic schedule:

- Liposomal Doxorunicin (Caelyx) 30mg/m² – day 1
 - Gemcitabine (Gemzar) 1000mg/m² – day 1 + 8
- With repeat cycle every 21 days for 6 cycles
- Sandostatin LAR 30 once a month until PD
 - Tamoxifen (Nolvadex) 20mg/day

Table 1. Patient Characteristics Group A

No	Gender	Age	Tumor diameter	Perf. Status (Karnofsky)	Child
1	Male	62	7 cm	70 %	A
2	Female	64	4 cm	60 %	B
3	Male	78	Multiple	40 %	A
4	Male	74	7 cm	70 %	A
5	Male	80	Diffuse	60 %	B
6	Female	65	5 cm	50 %	A
7	Female	64	9 cm	50 %	C
8	Male	74	6 cm	50 %	A
9	Male	78	4 cm	70 %	A
10	Male	80	Diffuse	40 %	B
11	Female	64	Diffuse	50 %	B
12	Female	62	5 cm	60 %	B
13	Male	70	5 cm	60 %	C
14	Male	67	9 cm	50 %	A
15	Male	66	9 cm	50 %	A

Table 2. Patient Characteristics Group B

No	Gender	Age	Tumor diameter	Perf. Status (Karnofsky)	Child
1	Female	67	9 cm	50 %	A
2	Male	78	5 cm	60 %	A
3	Male	82	Diffuse	40 %	C
4	Female	80	Diffuse	30 %	B
5	Male	73	7 cm	50 %	B
6	Male	76	8 cm	70 %	B
7	Male	77	6 cm	50 %	A

All patients had a monthly follow-up with routine liver biochemical tests and a FP concentrations, liver ultrasound was performed over three months.

III. Results

A. Kaplan Meier survival

At the time of the final analysis (May 2004) only two patients (both from the treatment group) were alive.

The overall mean survival was 11.2 months for group A vs 4.3 months ($p < 0.003$) for group B.

There was a significant difference of survival in six months (80% vs 28.5) and in one year (26.6% vs 0%). The treatment schedule was well tolerated with mild complications due to chemotherapeutic drugs. Complete and partial response rates were observed in 46.6% of our patients and all patients reported improvement in the feeling well being.

Figure 1 shows the overall survival between the two groups. There is a significant survival difference ($p < 0.003$) between those who under went treatment and those who did not.

Table 3 shows the percentage of patients surviving three, six, nine, twelve and eighteen months.

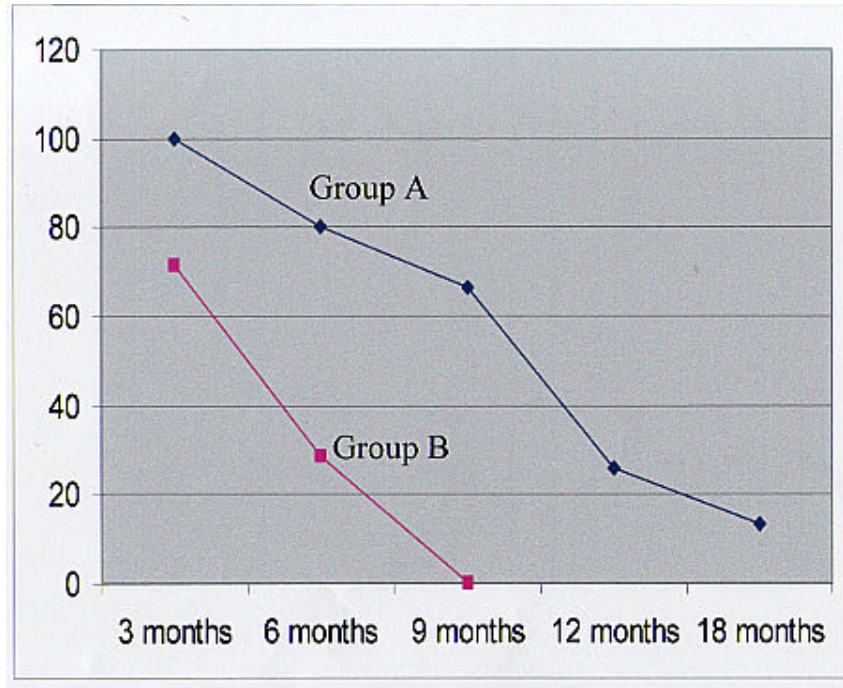


Figure 1. Kaplan-Meier survival

Table 3. Cumulative survival in 3 / 6 / 9 / 12 / 18 months

Characteristics	Survival				
	3 months	6 months	9 months	12 months	18 months
Group A	100% (15/15)	80% (12/15)	66.6% (10/15)	26.6% (4/15)	13.3% (2/15)
Group B	71.4% (5/7)	28.5% (2/7)	0	0	0

B. Drugs tolerate

The treatment schedule was well tolerated. Hematologic toxicity with anemia and Neutropenia was observed in nine patients (60%) and they were treated with G-CSF and EPO.

Diffuse abdominal pain and mild diarrhea was observed in four patients (27%) due to caelyx administration.

In two patients a Hand-foot-syndrome was observed and alopecia was observed in five patients (34%).

C. Quality of life

In this study two patients (13.3%) presented CR and they are still alive 20 and 17 months retrospectively with MSR of 18.5 months, seven patients (33.3%) presented with PR with a MSR of 11.6 months and seven patients (46.6%) presented PD with a MSR of 6.3 months.

Appetite, body weight pain and the general feeling as well being were used as criteria of quality of life. An increase in appetite was reported in twelve patients (80%). All patients reported improvement in the feeling of well being and four patients (40%) gained weight.

V. Discussion

HCC is generally one of the most resistant tumors to chemotherapy (Llovet and Bruix, 2000). A wide variety of chemotherapeutic agents have been tried and are in use. No regimen has proven to be curative. Often the response rate and prolongation of survival are minimal and there is a significant morbidity associated with poor treatment effects (Okuda, 1997).

On the other hand recently, promising results for the treatment of HCC have been reported with somatostatin analog octreotide (Raderer et al, 1999). In addition Kouroumalis et al, have reported the first study to demonstrate a survival benefit with application of octreotide in patients with advanced HCC as compared to untreated controls (Kouroumalis et al, 1998). All this outcome together with the controversial beneficial effect of anti-oestrogens (tamoxifen) suggesting our group to use the combination of chemotherapy and hormonal manipulations with octreotide and tamoxifen in patients with advanced HCC.

There are important large randomized studies with chemembolization-radiotherapy or intra arterial radiotherapy (Kaneto et al, 2000; Lygidakis et al, 2000) providing really promising results of advanced hepatocellular carcinoma.

Our results confirms a prolongation of survival 80% in six months as compared with 28.7% to untreated controls, and a 27% one year survival in treatment group vs 0% of untreated patients. The results of our study were similar with some others recently published studies using octreotide only and more promising with some others using tamoxifen only (Elba et al, 1994; Samonakis et al, 2002)

The treatment schedule with combination of systemic chemotherapy and octreotide and tamoxifen improves survival of patients with HCC and is an alternative for inoperable HCC.

On the other hand before embracing this warm recommendation it seems prudent in the future to requiring confirmation of this out-come with large-scale trials as the drugs although expensive, are well tolerated.

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