Glutathione treatment of hepatocellular carcinoma

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Abstract: This prospective study was undertaken to substantiate observations that glutathione (GSH) inhibits or reverses tumor growth in humans with hepatocellular carcinoma (HCC), a neoplasm with an extremely poor prognosis. Eight patients with biopsy-proven HCC not amenable to surgery were given 5 g of GSH daily from the time of diagnosis. Two patients withdrew shortly after receiving GSH due to intolerable side-effects. Of the six eligible patients, two had mildly advanced tumors and four moderately advanced tumors. At 1–2-month intervals the liver was CT and ultra-sound scanned to assess the growth status of the tumor (progression, stagnation or regression). All the patients, except a male with a fibrolamellar type of HCC, died within 1 year after diagnosis. Two women with moderately advanced tumors survived almost 1 year, tumor growth stopped or regressed and in one of the women an initially abnormal alfa-1-fetoprotein (AFP) returned to normal after GSH treatment. AFP remained normal throughout the treatment period in the other woman. These observations indicate that GSH may have a sex-dependent effect on HCC. However, further studies involving more patients are required to pursue this hypothesis.

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Liver cell cancer or hepatocellular carcinoma (HCC) is a highly malignant human neoplasm with an extremely poor prognosis (1).

Radiation, chemotherapy or tumor devascularization has not improved survival (2, 3). Tumor resection or liver transplantation are so far the best therapeutic alternatives, with 5-year survival rates at 35% (4) and 20–30% (5). However, patients with metastatic HCC are not amenable to these procedures (4).

Reports of regression of HCC in man (6) and in rats (7) after treatment with glutathione (GSH), a tripeptide naturally occurring in mammalian cells, led us to try treatment with GSH in this group of patients who have no other therapeutic alternative.

Material and methods

Eight patients aged 27–63 (5 male and 3 female patients) with biopsy-proven HCC not amenable to surgery agreed to participate in the study after giving written informed consent. GSH (5 g) was given orally daily, dissolved in a glass of orange juice. Two patients withdrew shortly after receiving GSH due to intolerable side-effects (gastro-intestinal irritation and sulphur odour). Two of the six eligible patients were graded as having a stage I (mildly advanced) tumor and four patients were graded as having stage II (moderately advanced) tumor. This stratification of the disease (8) is based on ascites (present or not), tumor size diagnosed by CT (occupying more or less than 50% of the liver), plasma albumin (more or less than 3 g/dl) and plasma bilirubin (more or less than 3 mg/dl). Half of the patients had a well-differentiated (WD) tumor, while the other half had a poorly differentiated (PD) tumor. In three of the patients the tumor developed in a cirrhotic liver, second to viral hepatitis, autoimmune disease or due to an unknown cause. At 1–2-month intervals the liver was CT- and ultrasound-scanned to assess progression, stagnation or regression of the tumor. In addition, liver function tests including alfa-1-fetoprotein were taken regularly.

Results

All the patients died within 1 year after diagnosis of HCC, except patient no. 6 who is still alive and taking GSH. His fibrolamellar tumor has not progressed and his general condition is good. His AFP has not risen (Table 1). Of the remaining five patients, patient no. 1 survived the longest (363 days), the tumor regressed significantly (Fig. 1) and

Table 1. Age, sex, hepatocellular carcinoma (HCC) histology, cirrhosis of the liver (present or not), etiology, tumor stage, duration of GSH treatment, development in tumor growth [CT-, ultrasound scans, alfa-1-fetoprotein (AFP)] in six patients with HCC

No.	Age y	Sex F/M	Tumor type WD/PD[1]	Cirr.	Etiology	Tumor stage[2]	Duration of GSH treatm days	Regresssion or stagnation of tumor[3]	Initial/ last AFP nmol/l
1	63	F	WD pseudoglandular	yes	autoimmune cirrhosis	II	363	yes	496/5
2	58	F	PD trabecular	yes	unknown	II	322	yes	0/0
3	61	M	PD	no	unknown	I	202	no	102/4500
4	53	M	PD clear-cell	yes	B hepatitis	II	124	no	12/43
5	27	F	WD sclerosing	no	unknown	II	119	no	0/1
6	63	M	WD fibro-lamellar	no	unknown	I	820[4]	yes	0/0

[1] Well-differentiated (WD) or poorly differentiated (PD).
[2] Stratification (I, II or III) according to (8) based on ascites, tumor size, plasma albumin and plasma bilirubin.
[3] Assessment of tumor growth by CT- and ultrasound scans.
[4] The patient is still alive (1992.03.31) taking GSH.

an initially high AFP almost normalized. Patient no. 2 survived 322 days, her tumor progressed initially but stabilized shortly after onset of the GSH treatment. Her AFP was normal all the time. Patients no. 3 and 4 (both male) died 7 and 4 months, respectively, after GSH treatment was initiated. Their tumors progressed and AFP increased during treatment. Patients no. 5 with a stage II tumor died after 119 days, AFP was normal and the tumor progressed even though lipiodolization (9) was tried. The last patient (no. 6) who has a fibrolamellar HCC variant is still alive, thriving, with stagnation of the tumor, AFP has been normal throughout the treatment period and the patient is still receiving 5 g of GSH daily.

Discussion

Two female patients, with stage two HCC disease, who survived 1 year, exhibited regression or stagnation of their tumor growth and patient no. 1 had in addition a significant decrease in AFP. AFP was normal before and during treatment of patient no. 2. The HCC of these two patients developed in cirrhotic livers in contrast to the HCC in patient no. 5, a young woman, who died 3–4 months after diagnosis. This may indicate a different etiology for tumor activation. The remaining three patients, all male, died as expected within 6 months. The patient with the fibrolamellar type of HCC is still alive, but the prognosis of this tumor is known to be better and a possible beneficial effect of GSH is uncertain.

GSH offers effective protection of biological structures against oxidative attack (10) and evidence that antioxidants can inhibit tumor formation in animals has been presented (11). However, the effect on solid tumors remains an unsolved problem.

Novi found regression of aflatoxin-induced tumors in female rats after GSH treatment (7). This experiment was repeated by Iverson et al. in 1987 (12) who found no effect of GSH. Other investigators have used the same experimental conditions on male rats (13, 14), getting the same negative result as Iverson.

Altogether, the observations indicate that the effect is sex-dependent and is supported by the observation by Kawano et al. (6), who successfully treated a woman with HCC with GSH.

HCC in adult male and female patients has higher androgen receptor titers than the surrounding normal liver (15), suggesting that HCC is an androgen-dependent tumor. Endogenous compounds like sex steroids are conjugated to GSH in the intact liver and excreted in bile or urine (10). Administration of high doses of GSH may raise the capacity of the liver to conjugate androgens, thereby, lowering the supply of the hormone to the tumor, which becomes reduced in size. An investigation of a therapy combining administration of GSH and anti-androgens is theoretically justified.

The reason for using 5 g of GSH daily in the treatment of HCC is arbitrary, but based on animal experiments which indicate that the anti-tumor effect is dose-dependent (16).

Due to the relatively few annual cases of HCC in Denmark, a controlled randomized trial of the

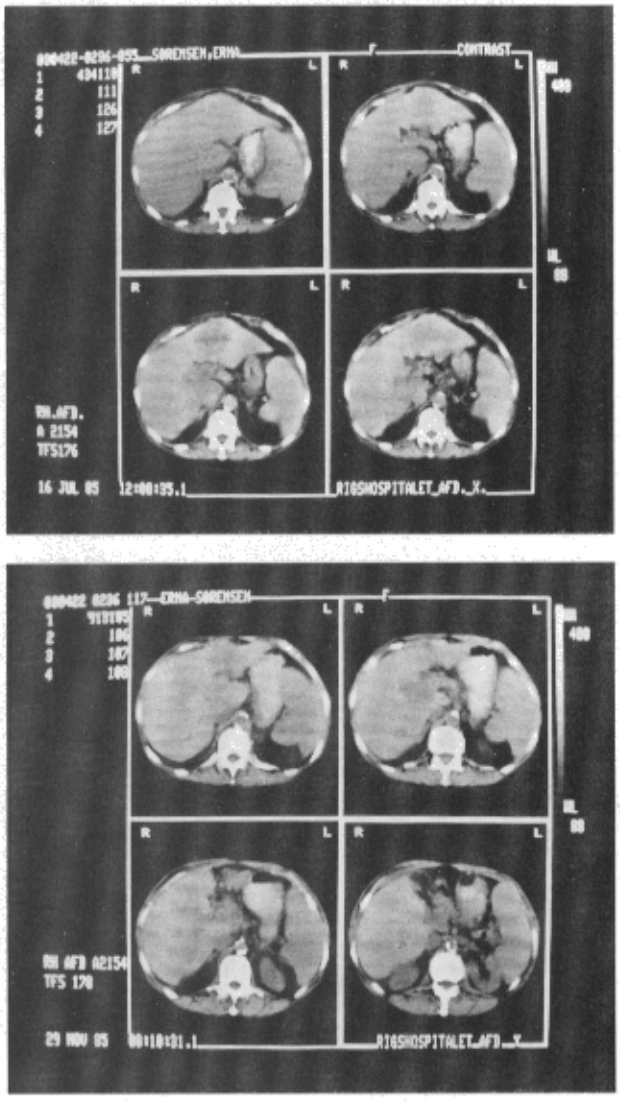

Fig. 1. Abdominal CT-scans of patient no. 1 with hepatocellular carcinoma prior to treatment with glutathione (upper) and 3 months after treatment with glutathione was initiated (lower).

effects of GSH is extremely difficult to carry out. We hope, however, that this study may stimulate others to do a controlled study in female patients with cirrhosis and HCC, a study which could include supplementary treatment with anti-androgens.

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