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Case report

Complete remission of unresectable hepatocellular carcinoma on healthy liver by the combination of aggressive surgery and high-dose-intensity chemotherapy by CPT-11

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Hepatocellular carcinoma (HCC) is one of the most frequent cancers. The only curative treatment is liver transplantation or complete surgical resection; however, most patients have inoperable disease at diagnosis. To date, no cytotoxic agent has demonstrated a clinical impact on time-related parameters, especially survival. The development of new treatments of inoperable HCC patients is highly desirable. Among the new cytotoxic agents, DNA topoisomerase I poisons are those with the widest spectrum of antitumor activity. However, few data are available in HCC patients. One of the main obstacles to the use of irinotecan in HCC is the frequent alterations of liver function at diagnosis. A 48-year-old patient with a HCC that had developed within a normal liver but of very poor prognosis because of a multifocal primary tumor with a large nodule measuring 10 cm of diameter, associated with a portal thrombosis, could tolerate very intensive treatment with irinotecan using doses up to 700 mg/m^2 every 2 weeks and was responsive to treatment as measured by α-fetoprotein levels. Despite initial criteria of inoperability, the absence of disease progression under therapy with a follow-up of 1 year invited us to propose a liver transplant. The patient is still in post-surgical complete remission and has consolidation chemotherapy with irinotecan. This result invites us to consider the evaluation of the efficacy of topoisomerase I poisons in HCC patients and to escalate the dose of irinotecan in patients with less than grade 4 neutropenia. [© 2000 Lippincott Williams & Wilkins.]

Key words: CPT-11, hepatectomy, hepatocellular carcinoma, liver transplantation, topoisomerase I poisons.

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent cancers with a world-wide incidence higher than 2.5×10^5 new patients per year.[1] HCC is mainly associated with chronic hepatitis B and hepatitis C virus infections. The only curative treatment is liver transplantation or complete surgical resection. However, 75% of the patients are not suitable for radical surgery.[2] The majority of patients with inoperable disease at diagnosis have a dismal prognosis with a median survival of 4 months.[3] Locoregional palliative strategies have been developed, such as percutaneous ethanol injection or intra-arterial embolization. No non-surgical procedure has demonstrated efficacy on survival.[4] Several chemotherapeutic agents have exhibited a response rate of 15–25%.[5] Among the cytotoxic agents evaluated in phase II clinical trials, none of them has shown an impact on time-related parameters.[4,5] Hence, the evaluation of the antitumor activity of new chemotherapeutic agents with an original mechanism of action is worthwhile in HCC.

DNA topoisomerase I poisons are active anticancer agents for the treatment of a large variety of solid tumors, including colorectal, gastric, pancreatic, cervix and non-small cell lung cancers.[6,7] Camptothecin is a DNA topoisomerase I poison[8] which led to the development of several derivatives, including irinotecan and topotecan. Irinotecan acts as a prodrug; the hydrolysis of the bulky piperidino side chain by carboxylesterase enzymes produces SN-38, a more potent topoisomerase I poison.[6,9]

A trend for a relation between dose and antitumor activity was suggested during phase I studies.[10] A multicenter phase II study has evaluated the efficacy in colorectal cancer patients of every 3 weeks administration of 500 mg/m^2 of CPT-11 in patients who well tolerated a first administration at the dose of 350 mg/m^2.[11]

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Conversion of irinotecan to SN-38 occurs predominantly in the liver, which has the highest carboxylesterase activity. Furthermore, the glucuroconjugation capability impacts on the clearance of SN-38, the active metabolite of irinotecan.[6] SN-38 is glucuronidated by uridine glucuronosyl-transferase (UGT1.1), the same isoenzyme responsible for glucuroconjugation of bilirubin. Severe irinotecan-related toxicity has been reported in patients deficient in UGT1.1 activity (Gilbert's syndrome).[12] Following conjugation, SN-38 glucuronide is secreted into the bile.

As a consequence, the use of irinotecan in the treatment of HCC may be compromised by the frequent alterations of liver functions at the time of diagnosis. This may explain in part why, to date, no data are available concerning the antitumor efficacy of irinotecan in HCC.

We report here a case which is remarkable in that the evidence shows that not only did the HCC patient get benefit from conventional doses of irinotecan but also improved with the dose escalation of irinotecan up to 700 mg/m^2. The results invite us to generate more information on the efficacy of irinotecan in HCC, which currently remains a disease of very poor prognosis and without standard active systemic treatment. We show in this clinical observation that: (i) irinotecan may be used in certain categories of HCC patients, especially in patients with HCC developing within a normal liver, (ii) the optimal efficacy of irinotecan might be obtained by increasing the dose in patients having less than grade 4 hematotoxicity, and (iii) the kinetics of α-fetoprotein (AFP) and the follow-up suggest antitumor activity, and invites us to initiate a phase II clinical trial of irinotecan in HCC.

Case report

A 48-year-old woman had abdominal pain and vesperal fever for 1 month. Ultrasound examination revealed a bulky tumoral liver involvement. Tumor biopsy revealed a HCC. There was no histological evidence of cirrhosis or of any underlying chronic liver disease. Viral serology B and C were negative. Liver function was normal. AFP plasma levels were high at 3461 ng/ml (normal below 10 ng/ml) at admission. Curative surgical resection was not possible because the patient had a large (10 cm), multifocal, primary tumor, with intrahepatic portal thrombosis. The initial treatment had been a transcatheter arterial embolization of lipiodol and cisplatin. The chemoembolization failed. A partial right hepatectomy was performed which allowed the resection of up to 90% of the disease. Debulking of this multifocal HCC was justified to increase chemotherapy efficacy. Pathological examination of the liver revealed a well-differentiated HCC with tumoral portal thrombosis. Post-operatively, AFP levels remained elevated at 321 ng/ml and chemotherapy with irinotecan was initiated. The starting dose of irinotecan was 350 mg/m^2 repeated every 3 weeks. Since no dose-limiting clinical toxicity was noted, the dose intensity of the treatment was progressively increased. We previously described that irinotecan can be re-administered every 2 weeks even in the absence of complete recovery of the leukocytes.[13] Based on this observation, the patient received eight administrations of 350 mg/m^2 of irinotecan repeated every 2 weeks with still no significant clinical or hematological toxicity. The evidence of clinical benefit and of a rapid decrease in AFP levels invited us to continue the same every 2-weeks schedule with a dose escalation of irinotecan by steps of 50 mg/m^2 up to a total dose of 700 mg/m^2 at the 17th cycle. Toxicity remained limited to a grade 1 diarrhea and a grade 4 non-febrile neutropenia from cycle 13. Complete alopecia was the main clinical side effect. The measurement of intrahepatic liver volume indicated disease stabilization. At the end of this treatment, AFP levels had return to normal levels (see Figure 1), and no extrahepatic malignant disease was detected by abdominal and thoracic CT scan as well

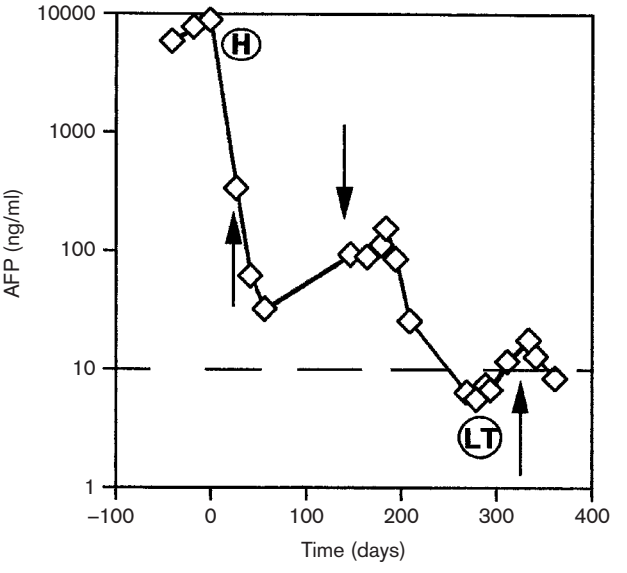

Figure 1. Kinetics of plasmatic AFP levels. H, partial hepatectomy. LT, Liver transplantation. The three arrows, from left to right, indicate the introduction of irinotecan, the increase in dose of irinotecan and the re-introduction of irinotecan.

as by bone scintigraphy. Consequently, liver transplantation was finally performed 7 months after right hepatectomy. Pathological examination of the liver revealed over 50 nodules of well-differentiated HCC on healthy liver. The largest nodule measured 4 cm of diameter, several nodules were totally necrotic. Tacrolimus and prednisolone were given to prevent liver transplant rejection. Liver function was normal. According to the high risk of relapse and the sensitivity to irinotecan, six adjuvant cycles of irinotecan were given using a conventional schedule of 350 mg/m^2 every 3 weeks. The patient is presently in complete remission with normal AFP plasma levels, 7 months after liver transplantation and 20 months after the diagnosis of massive liver involvement by HCC.

Discussion

In this clinical observation, we report evidence that irinotecan, despite the major influence of liver function and cholestasis on its pharmacokinetics and pharmacodynamics, may be safely administered in certain HCC patients. The major dose-limiting toxicities encountered with irinotecan are neutropenia and diarrhea.[14]

There is frequently a discrepancy between a favorable decreasing kinetics of AFP levels and the absence of measurable changes in tumor volume, as measured by CT scan. However, the decrease in AFP seems to correlate with antitumor activity and pathological complete responses could be reproducibly described in patients with a biological response based on AFP levels despite stable or residual disease at CT scan.[15]

Interestingly, within the 20 months following the diagnosis of HCC, despite initially bulky liver disease, no extrahepatic localizations were detected and the patient is still in complete post-surgical remission.

The potential interest of topoisomerase I poisons in HCC patients has been previously tested with topotecan, another camptothecin derivative, in a phase II clinical trial.[16] Topotecan was given at the initial dose of 1.5 mg/m^2/day for 5 consecutive days every 3 weeks. Despite the detection of some antitumor activity with an objective response rate of 13.9% (five partial remissions among 36 patients plus eight patients with stable disease), the authors did not recommend the development of topotecan in this disease because of severe hematotoxicity. In this study, grade 4 neutropenia was frequent (69% of patients) and frequently life threatening. Moreover, severe thrombocytopenia in patients having either esophageal varices, gastritis and/or alterations of hemostasis may become life threatening through the increasing risk of fatal haemorrhage. More recently, we pointed out that topotecan clinical toxicity could be largely predicted by the careful measurement of nutritional and inflammatory status, that we called the biological performance status (BPS).[17] With this tool in our hands, we were able to treat safely HCC patients with the combination of topotecan and oxaliplatin, and we observed evidence of antitumor activity during the phase I clinical trial.[18] Altogether, these preliminary results suggest that topoisomerase I poisons may be active in HCC patients but that the active dose may be difficult to achieve. However, in selected patients, especially those with healthy liver, high dose intensity is achievable with interesting results and acceptable toxicity, as in the case reported herein. Indications of liver transplantation in those patients might be enlarged if efficacy of topoisomerase I poisons will be confirmed.

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