Nine Months to Progression Using Fourth-Line Liposomally Encapsulated Paclitaxel against Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the third most common cause of cancer deaths. Difficulties to diagnose HCC at early stages remain the major obstacle to curative (surgical) therapy. Therapy in advanced stages has to be considered palliative. In this situation, a considerable amount of attention should be paid to innovative treatment strategies, e.g. including antiangiogenetic drugs. ***Results:*** We report on the successful treatment of a patient suffering from progressive HCC with a novel drug (EndoTAG®-1, formerly named LipoPac®) currently investigated in phase II studies. This drug consists of liposomally encapsulated paclitaxel. Its liposomal formulation favors the drug's adherence to the tumor neovasculature, in effect starving the tumor. ***Conclusions:*** EndoTAG®-1 stopped tumor progression for 9 months in our patient. This, along with successes observed testing this drug against other indications, makes it a suitable candidate for future clinical trials.

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Introduction

Primary liver cancer is the fifth most common cancer worldwide [1]. As almost every affected individual dies, it is the third most common cause of cancer deaths worldwide [1]. Liver cirrhosis is the strongest predisposing factor for the development of a HCC [2]. On the basis of estimates of the burden of hepatocellular carcinoma (HCC) in the US, fears arise that during the next two decades the incidence in the US might increase to meet the incidence currently observed in Japan [3]. This rise is mainly attributed to the increasing spread of viral hepatitis [4]. Amongst the well-defined major risk factors, alcohol abuse is a further leading cause for the development of HCC. Intake of aflatoxin via contaminated food, too, and different metabolic disorders are associated with an increased risk for this hazard. As vaccination against hepatitis B [5, 6] helped to reduce the prevalence of HCC, prevention of hepatitis C, the most prominent risk factor for the development of HCC in developed countries, or delay of the disease's progress [7], are hoped to further reduce the prevalence of HCC. Novel treatment strategies against HBV might help to lower this diseases burden as well [8]. Patients who are afflicted with an HCC arising from an

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adenoma of the liver survive significantly longer than patients suffering an HCC evolving from a cirrhotic liver [9, 10].

Noteworthy, establishment of a diagnosis is difficult especially in patients with cirrhosis showing only small nodules [11]. In the absence of a definitive pathological statement, an elevated level of alpha fetoprotein together with nodules larger than 2 cm plus arterial hypervascularization in one imaging technique can lead to the establishment of the diagnosis 'HCC'. In 40% of all HCC, however, AFP at diagnosis is normal. Finally, the appearance of these nodules in two independent imaging techniques is considered sufficient for establishing the diagnosis as well [12]. The Barcelona Clinic Liver Cancer Staging Classification of patients with HCC (BCLC) is a staging nomenclature which is recommended by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver Diseases (EASL) [13].

Detection at early stages (BCLC stage A) allows curative treatment by transplantation, resection or percutaneous ablation [2]. The optimum amongst these curative treatments is not established. Adjuvant chemoembolization or chemotherapy have failed to show beneficial effects after resection [2], yet promising results could be obtained using internal radiation with iodine-131-labelled lipiodol and interferon [14], adoptive immunotherapy by activated lymphocytes [15] and retinoids [16]. Percutaneous treatments administering chemical substances to or altering the temperature of the neoplastic cells have long been considered the best option for early detected though unresectable (BCLC stages B or C) HCC [17–20]. The median survival for patients with BCLC stage A, B, C or D tumors is 53, 16, 7 and 3 months, respectively [21]. In a recent phase III study [22], the group of patients receiving the orally available multikinase inhibitor sorafenib (Nexavar®, Bayer) achieved a median time to progression of 5.5 months and an overall survival duration of 10.7 months. Overall survival in the verum group significantly exceeded overall survival in the placebo group (7.9 months). Sorafenib targets the Raf/MEK/ERK pathway at the level of the Raf kinase and blocks proliferation of HCC cells. It furthermore acts antiangiogenetically through the inhibition of the tyrosine kinases vascular endothelial growth factor receptor-2/receptor-3 (VEGFR-2/-3) and platelet-derived growth factor receptor-β (PDGFR-β). Overall survival in this study is not remarkably superior to the overall survival noted in other trials reporting about patients with BCLC stage B or C HCC [23]. The combination of sorafenib or different multikinase inhibitors or other antiangiogenetically active agents with cytotoxic therapy has to be tested against HCC in larger studies [24]. Further options for palliative treatment are (chemo)embolization [25–27], arterial [28] or systemic chemotherapy [27], internal radiation with ^{131}I-lipiodol [29], hormonal compounds [30–38] and immunotherapy [39, 40]. A meta-analysis [2] of hormonal treatments with tamoxifen [30–36] did not show any survival benefit. A meta-analysis [2] of arterial treatments ((chemo)embolization [41–47]) shows a survival benefit for well-selected patients and constitutes their standard treatment. Arterial embolization has been shown to lead to a partial response in 15–55 % [41–47] of patients. Furthermore, has it been shown to delay tumor progression and vascular invasion [43, 47]. Of seven randomized controlled clinical trials comparing chemoembolization with conservative management, survival benefits for chemoembolization could be found in two studies [46, 47]. Chemoembolization seems beneficial for patients with a preserved liver function and asymptomatic nodular tumors without vascular invasion or extrahepatic spread. Liver decompensation or hepatic failure are contraindications against these options [43]. Anthracyclins have recently been published to show efficacy against HCC [48]. There is evidence against the use of paclitaxel in conventional formulations against HCC [49].

Taken together, with the exception of the success from the SHARP study [22], no sound data basis for the recommendation of one or the other palliative treatment option exists for patients not referable to chemoembolization. As is the case for many diseases in this palliative setting, novel treatment strategies are urgently warranted, especially taken into account the rising number of patients suffering from HCC. Strategies currently under observation include antiangiogenetic strategies. Thalidomide [50] and bevacizumab [51] are studied against a variety of neoplasms including HCC in increasing frequency. Data from studies of antiangiogenetic drugs against HCC are scarce and not convincing.

Here, we report encouraging results obtained using an experimental drug as fourth line palliative chemotherapy for a middle-aged European male patient suffering from a large multilocular HCC without extrahepatic spread and without signs of vascular invasion (BCLC stage B). This drug was designed as an antiangiogenic drug and is referred to as EndoTAG®-1, originally named MBT-0206 or Lipopac®. It is a save cationic liposomal formulation incorporating the cytostatic agent paclitaxel and has been developed to treat solid tumors. The drug directly targets

the activated endothelial cells of the tumor vascular system [52]. These activated endothelia exhibit properties differing from the normal tissue vasculature, the most important being a negative surface charge of the endothelial cells as compared to quiescent endothelial cells in normal tissue. This negative charge marks a point of attack and accounts for the specific binding of the positively charged liposomes to endothelial cells in the vasculature of growing tumors. In the amelanotic hamster melanoma A-Mel-3, accumulation of cationic liposomes was preferred and enhanced in tumor vessels, well observed in the tumors and not seen in normal tissue [52, 53]. EndoTAG®-1 effectively prevented melanoma growth and invasiveness, furthermore improved survival of the animals studied in a humanized SCID mouse model [54]. A significant retardation of melanoma growth in Syrian golden hamster by EndoTAG®-1 could be observed even compared to free paclitaxel [55]. The general occurrence of angiogenesis in all solid tumors suggests a broad applicability of this concept. The enrichment of the drug in tumor tissue leads to a reduction of side effects due to the reduced exposure of healthy tissue to cytostatic agents. The manufacturer of EndoTAG®-1, Medigene, has just reported on encouraging interim results from a phase II trial including 200 patients suffering inoperable, locally advanced or metastatic pancreatic carcinoma. In the group receiving the highest dose of EndoTAG®-1 next to gemcitabine, survival exceeded survival of the control group (gemcibatine only) by 30%.

We were encouraged to use EndoTAG®-1 as fourth-line therapy in a patient with progressive HCC.

Case Report

The patient was seeking medical advice in 1998 after experiencing pain under his right rip bow. A routine medical workup yielded multiple hypodensic lesions of the right lobe of the liver in ultrasonography and CT scan. Histology following right hemihepatectomy and resection of a further lesion in segment V which had been dectected intraoperatively confirmed the diagnosis of a large hepatocellular adenoma without any sign of malignancy. The pathologist described fatty degeneration of the liver cells and only partially regressive changes with slight cicatrisation in the adenoma but normal liver tissue without fatty degeneration in physiological liver tissue at the borders of the tumor. Notably, the patient's AFP was slightly elevated at that time. Two years later, in March 2000, the patient experienced a new episode of pain under the right rib bow. Multiple heterogeneous lesions were detected in the patient's liver upon CT scan. They were highly suspicious of malignancy. Exploratory biopsy of these lesions resulted in the diagnosis of a HCC. The consulting surgeons assessed them as unresectable and the liver as nontransplantable. No risk factors

for the development of liver cirrhosis or HCC were present in the patient's medical history. A CT scan 5 months later, a period during which the patient received 20 mg tamoxifen twice daily, revealed progressive disease. The laboratory workup showed a normal AFP. The patient was subsequently referred to our outpatient clinic. First line chemotherapy consisted of intra-arterial regional folinic acid (300 mg, given over 1 h on days 1–5), 5-fluorouracil (600 mg/m², equal to 1,000 mg absolute dose, given over 2 h on days 1–5) and oxaliplatin (110 mg total dose, divided into two intra-arterial 4-hour infusions on days 2 and 4, respectively, of each treatment cycle), with repetition every 3 weeks. Ultrasound controls proved the treatment effective with partial remission. Unfortunately, this effective regional treatment had to be discontinued following occlusion of the hepatic artery after four cycles. Second-line chemotherapy consisted of intravenous oxaliplatin (85 mg/m², equal to 140 mg, given over 2 h) on day 1, folinic acid (500 mg/m², equal to 1,000 mg, given over 2 h) and high dose 5-fluorouracil (2,000 mg/m², equal to 3,000 mg, given over 24 h) on day 1 and day 8. This therapy was repeated every 2 weeks. Two CT scans during this second line treatment revealed 'no change'. A slightly elevated AFP fell back to normal values. Oxaliplatin had to be discontinued in November 2001 following occurrence of severe bone pain. Folinic acid and 5-fluorouracil weekly were continued until a CT scan discovered progressive disease in March 2002. Third-line therapy was initiated: the patient was treated with liposomal adriamycin (Caelyx, 40 mg/m², equal to 70 mg). This had to be halted after four cycles due to progressive disease as observed through computed tomography. After written informed and institutional consent were obtained, the patient was treated as a compassionate use case with liposomally encapsulated paclitaxel (EndoTAG®-1). Treatment started in August 2002. The first dose consisted of 8 mg total lipid per kg bodyweight and 0.29 mg/kg paclitaxel. The cytostatic content was stepwise enlarged up to 1.14 mg/kg paclitaxel, the total lipid content rose to 32 mg/kg. In 39 doses of monotherapy, the infusion was started slowly and accelerated every 10 min. Each application was preceded by intravenous administration of 20 mg dexamethasone and histamine-blocking agents (H1 and H2 antagonists). The first application was carried out in an intensive care unit to ensure maximal safety measurements. With only few exceptions, EndoTAG-1 was repeated weekly.

Results

Safety
During the first application no adverse effect occurred. Yet during the following days, the patient experienced fever for more than 1 day. His clinical status worsened slightly. After these symptoms had ceased, the administration of EndoTAG®-1 was continued on the same dose level as during the first application and was as well tolerated as during the following 38 doses monotherapy. A dose escalation was performed as described above.
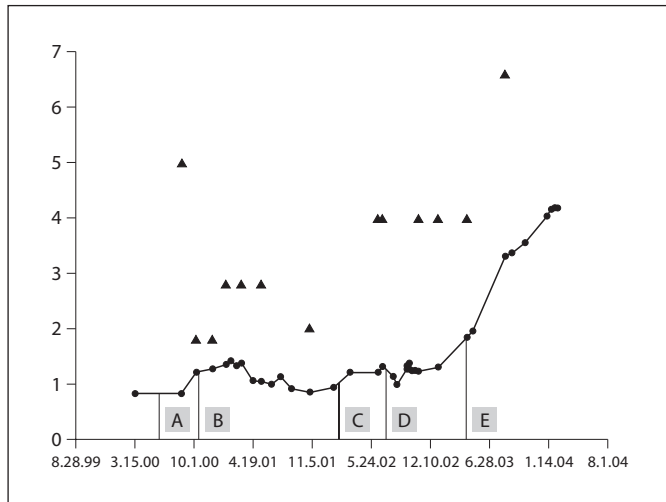
Fig. 1. Tumor marker (alpha-feto protein, AFP, logarithmic value, indicated by ●) and tumor size (diameter of one lesion in centimeters, indicated by ▲) plotted against time. Chemotherapy given during the respective time is: A: intra-arterial folinic acid + 5-FU + oxaliplatin; B: intravenous folinic acid + HD 5-FU + oxaliplatin; C: caelyx; D: EndoTAG®-1; E: EndoTAG®-1 + carboplatin, later EndoTAG®-1 + DTIC.

Effects

Surprisingly and most encouragingly, this drug arrested tumor growth as seen in computed tomography for 9 months until a massive progression was observed. The progression was evidenced through the worsening of the patient's clinical status and through CT scanning. Concomitantly, the AFP rose to values above 2,300 ng/ml. The addition of carboplatin to the therapy had to be interrupted due to an acute adverse reaction and due to increased hematotoxicity in November 2003. The patient then was subdued to a combination of EndoTAG®-1 and DTIC. After 3 months, the patient's tumor was progressive again in February 2004. One week later, the patient died. The time course is depicted in figure 1.

Of note, none of the drugs used is approved for use against HCC. There is no evidence for an optimal treatment against intermediate or advanced (BLCL stages B, C) HCC. Treatment in the case presented followed expert opinion.

Conclusion

Intermediate or advanced primary HCC is a disease without curative treatment options. Current therapeutic concepts consisting of chemotherapy, immunotherapy,

local interventions or combinations of those fail to achieve convincing results. Novel interventions at BCLC stages B or C include kinase inhibitors like sorafenib and antiangiogenic strategies. Using this option, a median time to progression of 5.5 months and an overall survival of 10.7 months was achieved in a recent phase III study [22]. We successfully treated a patient with intermediate (BCLC stage B) and progressive HCC with paclitaxel encapsulated in cationic liposomes and achieved a time to progression of 9 months, exceeding the survival time achieved in the SHARP study of sorafenib monotherapy against HCC. It is believed that the specific formulation of this drug leads to specific adherence to the tumor's vasculature through physicochemical interactions, delivering the drug specifically to the tumor, furthermore starving the tumor through antiangiogenic actions. Paclitaxel itself has been studied without success against HCC [49]. Yet, in this situation the specific formulation of this drug and the drug itself showed efficacy.

Both options, the inhibition of many kinases in the tumor and the antiangiogenetic approach, we report on warrant studies in combinations with further cytostatic drugs and with each other. Notably, sorafenib is also reported to act against the formation of neovasculature. HCC are tumors showing a high degree of (neo)vasculature. Transcatheter arterial chemoembolization (TACE) is reported to further enhance this vascularization [56]. If combined with antiangiogenetic approaches, this might lead to an even higher degree of tumor starvation.

Albeit that HCC arising in the noncirrhotic liver, e.g. from an adenoma after a metabolic disease as in the case presented here, has a better survival compared to HCC arising in a cirrhotic liver [9, 10], the time to progression was measured starting at a very advanced stage of the disease where previous therapies failed to achieve a response. In general, low remission rates and usually rapid disease progression are observed with all drugs tested against intermediate and advanced HCC. Thus, a time to progression of 9 months even as fourth-line therapy is highly remarkable. This warrants phase II studies of EndoTAG®-1 in HCC as well as in other solid tumors. The drug is currently tested in phase II trials against various types of solid tumors. Medigene, the manufacturer of EndoTAG®-1, recently announced the interim results of EndoTAG®-1 against inoperable, locally advanced or metastasized pancreatic cancer. In this study, gemcitabine monotherapy was randomized against different doses of EndoTAG®-1 in combination with gemcitabine. Median survival in the group receiving the highest dose of EndoTAG®-1 exceeded median survival of the control

group by 30%. Survival was even higher in patients who received EndoTAG®-1 over a longer period and repeatedly. Results from a phase II study against hormone refractory breast cancer will be reported in 2009. In summary, the approach we present here should be tested early in the course of the disease in controlled studies against intermediate and advanced HCC.

Conflict of Interest Statement

K.B. and K.N. were employees of the former M.B.T. who developed the drug.

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