Research Article

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Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: A case-control study

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Background & Aims: The efficacy of sorafenib in the post-liver transplantation (LT) setting has been scarcely studied. The aim of this study was to evaluate the efficacy of sorafenib, compared to best supportive care (BSC), in two cohorts of patients which presented with hepatocellular carcinoma (HCC) recurrence after LT.

Methods: Data from patients who developed presentation or progression of HCC recurrence after LT not amenable to surgical/locoregional treatments (untreatable presentation/progression, UP) were retrieved. The cohort of patients receiving sorafenib starting from 2007 was compared to that of patients receiving BSC in the previous era. Disease outcome was investigated in terms of survival from recurrence or from UP by means of univariate and multivariate Cox regression models with event times left-truncated at the date of UP.

Results: Of a total of 39 patients, 24 received BSC and 15 sorafenib. The two groups were well matched at baseline, with time-related imbalances regarding mTOR-based immunosuppression and median time from LT to recurrence, significantly higher in the sorafenib group. Patients' outcome in the sorafenib group was significantly improved (median survival from recurrence 21.3 *vs.*11.8 months, HR = 5.2, $p = 0.0009$; median survival from UP 10.6 *vs.* 2.2 months, HR = 21.1, $p < 0.0001$). The only factor associated with survival after HCC recurrence in multivariate analysis was treatment with sorafenib (HR = 4.0; $p = 0.0325$). No severe adverse event was registered in this post-LT setting.

Conclusions: Although the use of historical controls weakens final interpretation, sorafenib seems to be associated with an acceptable safety profile and benefit in survival in HCC patients suffering recurrence after LT.

Keywords: Sorafenib; Liver transplantation; Hepatocellular carcinoma; HCC recurrence.

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Abbreviations: LT, liver transplantation; MC, Milan Criteria; HCC, hepatocellular carcinoma; CNI, calcineurine inhibitor; mTOR, mammalian target of rapamycin; UP, untreatable presentation/progression; BSC, best supportive care; AE, adverse event; CTCAE, common terminology criteria for adverse events; AFP, alpha-fetoprotein; SD, stable disease; PR, partial response; DCR, disease control rate.

Introduction

Ever since its introduction into clinical practice, liver transplantation (LT) appeared to be the ideal cure for both hepatocellular carcinoma (HCC) and cirrhosis, as it eradicates both the seeded tumor and the soiled carcinogenic liver disease. The observation that the probability of tumor recurrence after LT was strictly related to pre-LT tumor stage led to the development of restrictive criteria, such as the Milan Criteria (MC) [1]: the current benchmark and the basis for comparison with other suggested selection criteria [2,3].

Due to the application of stringent selection, the outcome of LT observed nowadays in patients with HCC is similar to that achieved for non-tumoral indications [4]. However, HCC recurrence after LT continues to occur in 8–20% of deceased- and living-donor transplantation, and leads to death in most cases even when aggressive and combined therapeutic approaches are applied [5–7]. In some patients, surgical resection of intra- or extrahepatic tumor deposits has proven to be effective in prolonging survival [5]. Nevertheless once tumor progression goes beyond treatments control, dismal prognosis invariably occurs and this acknowledges for the common experience that any prolonged survival after HCC recurrence in a transplanted patient is exceptional.

Two large randomized control trials (RCTs) in non-transplanted patients have demonstrated that systemic treatment with the multikinase inhibitor agent sorafenib prolongs survival in patients presenting with advanced HCC not amenable to surgical/locoregional treatments [8,9]. Post-transplant status is in most cases an exclusion criteria for RCTs testing molecular target agents in HCC and, therefore, only a few retrospective cohort

studies lacking control arms and isolated case reports have been published so far, investigating both safety and efficacy of sorafenib in the post-LT setting [10–15]. In such a condition, concerns do arise for potential drug interactions and for the course of HCC, with or without specific anticancer treatment, which could be negatively influenced by immunosuppression [16]. The aim of this study was to evaluate the efficacy of sorafenib, compared to best supportive care, in two consecutive cohorts of transplanted patients presenting with HCC recurrence deemed untreatable either at presentation or after tumor progression beyond eligibility to conventional treatments. Such a case-control study was favored by the unicentricity of the experience comparing two different attitudes in management of HCC recurrence after LT. As described below, the sole difference among groups was determined by the availability of sorafenib, being the rest of conventional care equally applied throughout the study periods.

Patients and methods

Patient grouping

Data on consecutive patients with HCC recurrence after LT followed at the Istituto Nazionale Tumori (National Cancer Institute) of Milan between January 1994 and January 2011, were extracted from a prospectively collected database. The following factors were considered: demographics and medical history, etiology of the underlying liver disease, pre-transplant treatments, laboratory results, pre- and post-operative histological and radiological tumor staging, immunosuppressive regimens, type and number of treatments performed for HCC recurrence. Patients were divided into two groups according to differences in treatment introduced when HCC recurrence was deemed untreatable, at first presentation or after disease progression beyond eligibility to conventional surgical or ablative or locoregional treatments (untreatable presentation/progression: UP).

In Group 1 (control arm) best supportive care (BSC) was the sole strategy available, while in Group 2 (treatment arm) sorafenib was added, before or after an immunosuppression switch from calcineurine inhibitor (CNI: cyclosporine or tacrolimus) to an mTOR inhibitor-based regimen (sirolimus or everolimus) was considered. The study aimed at assessing, in patients with HCC recurrence after LT, whether or not sorafenib added to BSC at the time of UP achieves competitive survivals with respect to historic controls that received only BSC. The possible contribution of contemporary mTOR immunosuppression to patient care was also investigated.

Among the comprehensive data collection within each groups, the analysis pointed out at factors related to tumor, immunosuppressive, and anticancer regimens, which are summarized below.

Conventional treatment strategy of post-transplant HCC recurrence

After LT, patients were monitored with thoraco-abdominal CT scan every 6 months for the first 3 years, and then annually, alternating with abdominal US and chest X-ray. Monitoring of AFP was performed every 6 months together with radiological controls. In all patients, the hepatocellular cancer nature of recurrence was confirmed at histology, whilst in case of intrahepatic recurrence, non-invasive radiologic criteria were added [17].

Treatment strategy was thoroughly discussed within the multidisciplinary hepato-oncology board and aimed, whenever possible, at surgical removal of recurrence with no limits in size and number of lesions. Should the patients' condition be marginal or the HCC bulk judged not amenable for removal, radiofrequency ablation (RFA) was performed. For patients with liver-only although non-resectable graft tumor deposits and in those presenting with repeated recurrences after resection or ablation, transarterial chemoembolization (TACE) or ^{90}Yttrium radioembolization was performed according to tumor extension. Tumor response was evaluated after each treatment and every three months with chest-abdominal CT, MRI, and alpha-fetoprotein (AFP) serum level determination; response assessment was performed according to RECIST 1.1 [18] and retrospectively with modified RECIST (mRECIST) criteria [19].

Untreatable progression, best supportive care, and sorafenib treatment

Patients with a first diagnosis of HCC recurrence or with a progression of recurrence deemed not anymore eligible to surgical, ablative or locoregional treatment were defined as having UP. Until 2007 patients presenting with a UP received BSC only, including local radiotherapy for bone or brain metastasis with a palliative intent. This subset (Group 1) accounted for the historical control group for the subsequent cohort of patients receiving sorafenib as a molecular target agent (Group 2).

Considering the lack of data on safety of sorafenib in the post-transplant setting, patients in Group 2 were additionally monitored according to an institutional protocol. Sorafenib was started at the target dose of 400 mg twice daily, to be adjusted in case of grade 1–3 toxicity according to common terminology criteria for adverse events (CTCAE) 3.0 [20] and withdrawn in case of prolonged or serious adverse events. A further reason for sorafenib withdrawal was tumor radiological progression according to RECIST 1.1 criteria. Treatment was re-challenged at full dosage after complete recovery of AEs, or maintained at the same dosage in case of unmanageable toxicity. Clinical visits were performed every four weeks on an outpatient basis, and included physical examination, laboratory analysis, and AE monitoring.

Immunosuppression regimens and mTOR therapy

Single-drug immunosuppression regimen with calcineurine inhibitor (CNI) was followed in all cases, since steroids were tapered within the first post-LT month. Coincidentally with the introduction of sorafenib (Nexavar, Bayer), three patients undergoing LT for HCC received a mammalian target of rapamycin (mTOR) inhibitor (sirolimus: Rapamune, Pfizer; target through level of 4–10 ng/ml) continued at the same dosage in case of HCC recurrence. During the same time interval (2007–2011), four other patients with HCC recurrence during the post-LT follow-up were shifted from CNI inhibitors to the mTOR inhibitor everolimus (Certican, Novartis; target through level of 4–10 ng/ml).

Statistical analysis

We used standard statistics (median and range for continuous variables, percentage for categorical variables) to describe baseline series characteristics and safety data, and non-parametric tests (Kruskal-Wallis for continuous variables, Pearson's Chi-Square test for categorical variables) to compare characteristics distribution in the two identified study groups.

The outcome event of interest was death for any cause. Survival time was computed in two ways: (i) as the interval between tumor recurrence after LT and death (survival after recurrence); (ii) as the interval between assessment of UP and death (survival after UP). Survival time was censored at the date of last contact in living patients. Survival curves were estimated in each treatment arm with the non-parametric Kaplan-Meier method, and statistically compared by means of univariable Cox regression models. Furthermore, considering that the compared study groups were not achieved through randomization, careful search of possible confounders was carried out. The limited number of outcome events recorded hampered confounder investigation within a single joint multivariable model. Therefore, we assessed singly taken confounders with Cox models stratified by received treatment, and finally entered all factors with p <0.10 and treatment into a multivariable Cox model. The 10% p-value threshold chosen in the confounder selection phase yielded a reasonable event per variable ratio of 6.6 (33 deaths/5 variables, considering that time to recurrence (TTR) accounted for 2 variables), in order to limit the risk of model overfit.

Furthermore, in Cox models for the analysis of survival after recurrence, event times were left-truncated at the date of UP. Such an approach was necessary considering that investigated patients were selected as having had UP, and were thus at risk of dying only some known time after the natural time origin of the phenomenon under study (recurrence after LT). In other words, death risk was zero between recurrence and UP, and non-zero thereafter; disregarding such a data structure would imply a less powerful analysis.

Calculations were done using SAS™ version 9.2 (SAS Institute Inc., Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values below the 5% conventional threshold are reported as statistically significant.

Results

Study groups and balancing

The main characteristics of the entire study series, as well as differences between the study groups, are described in Table 1, while study design and patients grouping are reported in Fig. 1.