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Sorafenib use for recurrent hepatocellular cancer after resection or transplantation: Observations from a US regional analysis of the GIDEON registry

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ABSTRACT

Treatment of unresectable recurrent hepatocellular carcinoma (HCC) in patients who recur after resection or orthotopic liver transplantation (OLT) remains a clinical challenge. One option is sorafenib, although little is known about its safety and tolerance in this unique patient population; therefore, we analyzed patients who underwent prior surgical resection and/or OLT and were treated with sorafenib in US cohort of GIDEON registry. In US, 645 patients were enrolled; 553 for intent to treat and 563 for safety. Data were analyzed in the safety population of 479 patients no surgery and 56 for resection or OLT. Forty-one patients underwent resection prior to the initiation of sorafenib, 15 patients had previously received an OLT, and 6 patients had both resection and OLT. Initial low starting doses (400 mg/day) were observed for more patients with prior OLT (71%) than prior resection (36%), resection and OLT (50%), concomitant OLT (25%), and no surgery (36%). Most AEs occurred in the first 4 weeks of treatment. Drug-related AEs were higher in patients with prior resection (87%), prior OLT (100%), or both (100%) than in patients with concomitant OLT (63%) or no surgery (70%). However, incidence of AEs resulting in permanent discontinuation were similar in all groups (19–38%).

1. Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, yet it is the third leading cause of cancer-related death.[1] Surgical treatments, including resection and orthotopic liver transplant (OLT) are the most definitive treatments for primary HCC. However, approximately 70% of patients will recur

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within 5 years of resection and approximately 20% within 5 years of OLT.[2–4] Treatment of recurrent HCC in the post-surgical population remains a challenge. No consensus regarding a definitive treatment strategy has been reached, and prognosis remains poor.[5] This is particularly true for those who do not meet criteria for repeat resection or for salvage liver transplantation (SLT), defined as the inability to undergo repeat OLT secondary to comorbidities or recurrent disease burden outside of transplant criteria.[6]

Sorafenib, a multi-kinase inhibitor, was approved for use in advanced HCC in 2007.[7] However, experiences using sorafenib for recurrent HCC after resection or OLT is limited. Small retrospective studies suggest a potential benefit and favorable safety profile when used for patients with HCC recurrence after transplant.[6,8–13] GIDEON is a global, prospective, non-interventional study to evaluate sorafenib safety under real-life conditions. The GIDEON registry contains the largest data series collected in US patients treated with sorafenib who have undergone prior surgery for hepatocellular carcinoma. Here we examine disease and treatment characteristics of US patients enrolled in the GIDEON registry who received sorafenib for HCC recurrence after liver resection or OLT. We also assess the safety and tolerance of sorafenib in this unique patient population.

2. Methods

2.1. GIDEON

Patients with unresectable HCC who were candidates for systemic therapy and for whom a decision was made to treat with sorafenib were eligible for inclusion in the GIDEON registry. This report focuses on patients who may have undergone prior or concomitant surgical resection, or OLT, or both. Patient and disease characteristics, dosing, treatment duration, safety, and overall survival were evaluated. Unless otherwise specified, all data were analyzed in the safety population. As GIDEON is an observational study, all results are descriptive. The GIDEON population is non-randomized, and patients are treated at the physician's discretion.

2.2. Literature search

An electronic literature search was conducted using PubMed via EndNote with search criteria that included the phrases “recurrent hepatocellular carcinoma,” “treatment,” “sorafenib,” “mTOR inhibitor,” “calcineurin inhibitor,” and “immunosuppressant” in order to present a comprehensive review of the outcomes of patients with recurrent HCC after resection or OLT. The most commonly used immunosuppressive agents in the post-liver transplant patient were also reviewed for published reports of concurrent sorafenib administration using the search criteria “steroids,” “mycophenolic acid,” “mycophenolate mofetil,” “tacrolimus,” and/or “cyclosporine.”

Articles were chosen based on publication dates from 2007 to 2014, in order to evaluate only the most recent data. Only human studies and English language articles were included. Additionally, only studies with 5 or more subjects were included. Literature reviews were included for reference. Case studies and peer reviews were excluded.

Studies pertaining to sorafenib (n = 19) were reviewed and were included only if they focused on sorafenib as a treatment for recurrent HCC after liver resection and/or OLT and if they presented both sorafenib safety and survival data (n = 13). Additional studies were manually chosen from reference sections when the above criteria were met (n = 1). For simplicity, only studies with 10 or more subjects were included in the summary table (n = 9).

Articles pertaining to other treatment modalities for recurrent HCC after liver resection and/or OLT were reviewed (n = 54). Focus was placed on studies that compared survival data for three or more validated treatment options for the aforementioned target population (repeat resection, SLT, ablation, TACE, sorafenib, chemotherapy, or radiation) (n = 7). Additional articles were manually chosen from reference sections when the above criteria were met (n = 1).

3. Results

3.1. Patient and disease characteristics

In the US, 645 patients were enrolled in GIDEON; 553 were valid for intent to treat (ITT) and 563 for safety (Fig. 1). Unless otherwise specified, data were analyzed in the safety population. Forty-one patients underwent resection prior to the initiation of sorafenib, 15 patients had previously received an OLT, and 6 patients had both. Sixteen patients underwent concomitant/subsequent OLT, defined as OLT after exposure to sorafenib.

All demographic and disease characteristic data reflect the status at the start of sorafenib treatment (Table 1). In the US population in GIDEON, no differences were observed with respect to gender and age between patients who underwent prior resection or OLT and those who did not, with the exception that there were no patients ≥75 years old who underwent prior OLT. A larger proportion of patients who underwent prior resection were Asian than in the overall GIDEON population (23% vs 9%). The populations that had undergone prior resection or OLT tended to have better East Cooperative Oncology Group (ECOG) performance status (PS). The most common disease etiology in patients who underwent prior surgical resection or OLT was chronic hepatitis C virus (HCV) infection.

In the patients who had undergone prior OLT or surgical

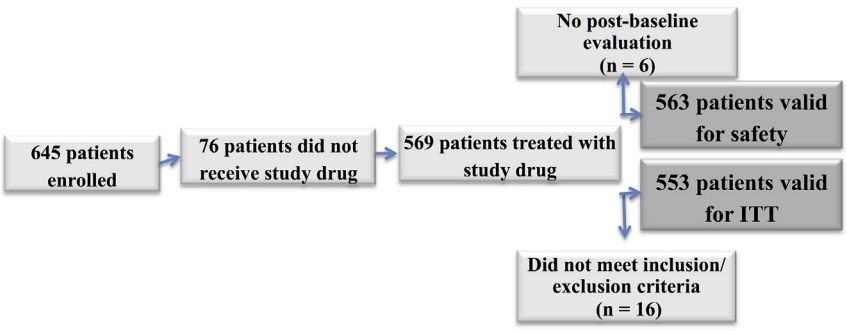

Fig. 1. Patient Disposition for the GIDEON evaluation of Sorafenib use after surgical resection or transplantation.