VALUE IN HEALTH ▮ (2016) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis

Carla Rognoni, PhD[1,*], *Oriana Ciani, PhD*[1,2], *Silvia Sommariva, MSc*[1], *Rosanna Tarricone, PhD*[1,3]

[1]*Centre for Research on Health and Social Care Management (CERGAS), Bocconi University, Milan, Italy;* [2]*Evidence Synthesis and Modelling for Health Improvement (ESMI), University of Exeter Medical School, South Cloisters St Luke's Campus, Exeter, UK;* [3]*Department of Policy Analysis and Public Management, Bocconi University, Milan, Italy*

ABSTRACT

Objectives: To perform a cost-effectiveness analysis comparing the use of transarterial radioembolization (TARE) with that of sorafenib in the treatment of patients with intermediate or advanced hepatocellular carcinoma (HCC) according to the Barcelona Clinic Liver Cancer staging system. **Methods:** Patient-level data were consecutively recorded and collected at three oncology centers in Italy. A propensity score matching was performed to compare patients with similar clinical characteristics who underwent TARE or sorafenib treatment. Clinical data from the matched cohorts were used to populate a Markov model to project, on a lifetime horizon, life years, quality-adjusted life years, and economic outcomes associated with TARE and sorafenib for both intermediate and advanced HCC stages. **Results:** Starting from data covering 389 and 241 patients who underwent TARE and sorafenib treatment, respectively, the propensity score matching yielded a total of 308 matched patients. For intermediate-stage patients, the model estimated for TARE versus sorafenib an incremental cost-utility ratio of €3,302/QALY (incremental cost-effectiveness ratio of €1,865 per life year gained), whereas for patients in advanced stage TARE dominated (lower costs and greater health improvements) compared with sorafenib. **Conclusions:** From an Italian health care service perspective, TARE could be a cost-effective strategy in comparison with sorafenib for patients with intermediate or advanced HCC. The results from forthcoming randomized controlled trials comparing TARE with sorafenib will be able to confirm or reject the validity of this preliminary evaluation. In the meantime, decision makers can use these results to control and coordinate the diffusion of the technology.

Keywords: cost-effectiveness, hepatocellular carcinoma, sorafenib, TARE.

Introduction

Liver cancer is the fifth most common cancer in men and the ninth in women, representing the second most common cause of cancer-related deaths in the world. The highest incidence of liver cancer has been reported for sub-Saharan Africa and Southeast Asia, and the incidence in some of these countries is 10 times higher than reported for United States and Europe [1]. Prognosis of liver cancer is very poor with a mortality-to-incidence ratio of 0.95.

Hepatocellular carcinoma (HCC) represents approximately 75% of primary liver cancers and is a major global health problem. The incidence of HCC increases progressively with age, reaching a peak at 70 years [2].

Clinical guidelines [3–5] support surveillance, diagnostic, and treatment practice for the management of patients with HCC. Disease status is defined through the Barcelona Clinic Liver Cancer (BCLC) classification, which takes into account the size and the extent of the primary tumor, liver function, and physiological factors [6]. This staging system categorizes patients with early (stage A), intermediate (stage B), advanced (stage C), or terminal (stage D) HCC. There is a related treatment plan for each stage, ranging from potentially curative therapies (e.g., resection or transplant for early-stage patients) to best supportive care for end-stage patients.

Interventional locoregional treatments are recommended for nonsurgical patients in the intermediate HCC stage. These treatments include intra-arterial transcatheter embolotherapies through a wide range of devices. Systemic therapy is generally recommended for advanced disease stage (BCLC-C), in which therapies are used with the intention to improve survival and/or maintain quality of life without curative intent.

Transarterial radioembolization (TARE), also known as selective internal radiation therapy, is a liver-directed therapy

* *Address correspondence to*: Carla Rognoni, Centre for Research on Health and Social Care Management (CERGAS), Bocconi University, Via Roentgen 1, Milan 20136, Italy.

E-mail: carla.rognoni@unibocconi.it.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2016.09.2397

presently used in clinical practice in many countries. TARE is not explicitly recommended, and is considered experimental, in HCC clinical guidelines [3–5,7].

TARE plays a potentially leading role in treating advanced HCC accompanied with portal vein thrombosis (PVT) involvement, a clinically relevant scenario occurring in about 40% of patients [8]. TARE is a microembolic procedure causing minimal occlusion of hepatic arteries; therefore, it can be safely used in patients with PVT without compromising blood flow to the hepatic parenchyma [9]. Macrovascular tumor invasion is a shared contraindication to transplantation, ablation, and any kind of chemoembolization technique [3,4]. Treatments for patients with HCC accompanied with PVT are more limited than for those without PVT. Transarterial chemoembolization (TACE) is considered contraindicated in cases of PVT because of its high embolic effect [8], and the alternative to TARE for patients with PVT is only systemic therapy with sorafenib.

According to the latest release of the European Society for Medical Oncology guidelines, TARE may therefore be competitive with sorafenib in patients in the intermediate stage who failed chemoembolization treatment or in advanced patients with PVT with no extrahepatic spread and good liver function [5]. At present in Italy this treatment is offered to about 4% of patients with intermediate or advanced HCC [10,11].

The evidence that supports the use of TARE in HCC treatment is mainly based on retrospective or prospective observational studies [12–16], and no cost-effectiveness analyses have been performed comparing the use of TARE with that of sorafenib for the treatment of patients with HCC. Two randomized controlled trials (RCTs) comparing TARE with sorafenib are ongoing at present (YES-P: NCT01887717; SARAH: NCT01482442). Although RCTs are the most universally accepted and robust experimental designs to estimate treatment effects, they are often conducted in highly selected populations and may lack external validity [17,18]. Moreover, randomization is not always feasible because of technical or ethical issues, such as insufficient evidence equipoise. In the meantime, however, real-world data are accruing because of the diffusion of this innovative therapy in the clinical practice.

The aim of the present study was to perform a cost-effectiveness analysis comparing TARE with sorafenib in patients with intermediate or advanced HCC using real-world clinical data collected at three major Italian oncology centers. TARE is an established and simultaneously experimental procedure used in Italy for the treatment of intermediate and advanced HCC. The unmet clinical needs for this patient group are substantial, and this study can inform decision makers in Italy regionally and nationally in due course.

Methods

Target Population and Interventions

The study focused on patients with intermediate or advanced HCC treated with TARE (which alongside the TARE procedure includes a bundle of inpatient procedures including diagnostic tests) or sorafenib (target dose, 800 mg/d).

Overall survival (OS) and *progression-free survival* (PFS), defined as the time from the start of the treatment to progression or death, whichever occurred first, were identified as the most important health outcomes.

Patient-level data were prospectively collected from 2005 to 2015 at three oncology centers with the highest volume of TARE procedure use in Italy (National Cancer Institute, Milan; Azienda Ospedaliero-Universitaria Pisana, Pisa; and Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna). Because data from the three centers referred to different index years (Milan, 2007; Bologna, 2005; and Pisa, 2013), we compared the OS and PFS of patients treated in the first 2 years versus patients treated in the following years to check that no learning curve effect was present.

After the exclusion of patients with metastatic disease, early or terminal disease stage, and patients with metastases, a quality check was performed to assess incomplete clinical data (OS or PFS), out-of-range values, and consistency of data (OS and PFS greater than 0, OS greater than or equal to PFS) [19]. Available data have been gathered and merged to build a new data set to populate the cost-effectiveness model. To compare patients with comparable prognostic factors in the TARE and sorafenib groups, a one-to-one nearest neighbor propensity score matching (PSM) procedure [20] was performed. Because a systematic literature review [21] reported PVT, alpha-fetoprotein, Child-Pugh class, and tumor size as the most robust predictors for survival for patients with HCC, these patients' characteristics and prognostic factors were taken into account by the clinical advisors and the modeling team. In particular, Child-Pugh score uses five clinical measures of liver disease (total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy) to classify patients according to different expected survivals (at 2 years: A, 85%; B, 57%; and C, 35%) [22].

Child-Pugh score, PVT status, and a proxy for tumor size (i.e., number of nodules) were judged as the main prognostic factors to be considered in the PSM. A second round of data filtering was performed excluding patients with incomplete data on the PSM variables, and then a logit function of the probability of receiving either treatment for a patient with these baseline characteristics was built. According to Tandon and Garcia-Tsao [21], patients' demographic characteristics were not included in the analysis.

Different simulations were made, varying the radius from 0.001 to 1, to find an adequate balance between bias reduction and common support size. Patients were further classified into being in intermediate and advanced stages according to the BCLC staging system to perform subgroup analyses. STATA 11 software (StataCorp, College Station, TX) and the command psmatch2 [23] were used to perform the PSM.

The Model

A Markov multistate model was selected for this economic evaluation and developed to project lifetime health (life years and quality-adjusted life years [QALYs]) and economic outcomes associated with TARE and sorafenib strategies for both intermediate and advanced HCC stages. Markov models are commonly used in economic evaluations for oncology treatments by health technology assessment bodies internationally. The model structure and problem formulation have been validated during two consecutive focus group meetings by the clinical expert group. In particular, in the first one, an evaluation of face validity of the model's structure and problem formulation was conducted, whereas during the second meeting a discussion on the evidence used to populate the model and on the results obtained was undertaken [24].

The health states in the implemented Markov model include (Fig. 1) stable disease, disease progression, death for disease, and death for other causes. In the intermediate stage, an additional state was included to take into account the possibility of liver transplantation. A hypothetical cohort of patients with HCC starts the Markov process in the stable state, that is, with stable HCC. Patients may stay in the stable state or, in case of disease progression, may move to the progression state. Progressive patients may remain in the progression state or may die from the disease (the model assumes that death for disease affects only progressive patients). Transition probabilities between