Clinics and Research in Hepatology and Gastroenterology (2018) xxx, xxx.e1—xxx.e3

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

LETTER TO THE EDITOR

Impact of physician experience and multidisciplinary team on clinical outcome in patients receiving sorafenib

KEYWORDS
Sorafenib;
Hepatocellular carcinoma;
TACE;
Chemoembolization;
Multidisciplinary team;
Physician experience

Dear editor,

The experience level of the physician could alter the disease outcome. Tsung-Ming Chen et al [1] have shown that the survival of HCC patients was dependent on the level of experience of the physicians in charge of these patients. Differences in survival was observed in patients with BCLC A and BCLC B stages, not in patients with BCLC C. The study was published before the introduction of sorafenib in clinical practice. In the real world, still few patients with advanced HCC are properly managed by dedicated physicians experienced in HCC management, with still unclear clinical impact on survival. In other oncology diseases several studies have investigated the impact of a multidisciplinary team (MDT) framework and/or multidisciplinary clinic (i.e. multiple consultations with different members of an MDT during a single patient visit) on patient outcome, assessment and management. Results have generally indicated that MDTs and/or multidisciplinary clinics were associated with changes in staging/diagnosis, initial management plans, higher rates of treatment, shorter time to treatment after diagnosis, better survival, and adherence to clinical guidelines. For this reason, we evaluated the prognostic effects in patients cared by physicians with differing experience in HCC management.

We enrolled patients receiving sorafenib for advanced- or intermediate-stage HCC histologically confirmed or diagnosed according to the American Association for the Study of Liver Diseases (AASLD) 2005 guidelines and refractory to or no longer amenable to locoregional therapies were considered for the present study. In this study, we defined ''patients managed by a dedicated physician'' (DP patients) those patients managed by an oncologist dedicated to HCC patients. Dedicated physicians closely cooperated with the MDT, which was composed of an oncologist, a hepatologist, a surgeon, a radiologist, a dermatologist, a pathologist, a biologist and a palliative care physician. We defined ''patients not managed by a dedicated physician'' (nDP patients) those who were managed by an oncologist not dedicated to HCC patients. Non-dedicated physicians did not cooperate with the MDT. This retrospective study was conducted on 77 advanced HCC patients consecutively treated at our institute (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, Meldola, Italy) from 2011 to 2015. Among the entire cohort, 49 patients (63.6%) were managed by one dedicated oncologist, while the remaining 28 patients (36.4%) were managed by three non-dedicated oncologists. Patient characteristics were well balanced between the two groups.

Patients managed by a dedicated physician (DP) had a median PFS of 4.6 months (95% CI 2.8—6.0) compared to 2.0 months (95% CI 1.2—2.5) for those not managed by a dedicated physician (nDP) ($P < 0.0001$) (HR 0.35, 95% CI 0.21—0.58, $P < 0.0001$) (Fig. 1A). DP patients had a median OS of 13.3 months (95% CI 6.8—15.6) compared to 3.1 months (95% CI 2.1—9.7) for nDP patients ($P = 0.002$) (HR 0.44, 95% CI 0.26—0.75, $P = 0.003$) (Fig. 1B). OS was independent of second line-treatment.After adjusting for clinical covariates (BCLC stage, performance status, meld score, basal level of alphafetoprotein, extraepatic vs. hepatic disease, starting dose of sorafenib), the physician dedicated remained independent prognostic factors for PFS (HR = 0.26, 95% CI 0.13—0.52, $P = 0.0001$) and OS (HR = 0.34, 95% CI 0.16—0.73, $P = 0.006$). nDP patients showed a higher percentage of progression at the first CT re-evaluation than nDP patients (79.3% vs. 46.9%, respectively) ($P = 0.008$). We also observed that nDP patients showed a lower percentage of DCR (22.7%) than DP patients (46.2%) at the first CT re-evaluation ($P = 0.030$).Sorafenib was reduced in the first two months of treatment in DP patients compared to nDP patients (51% vs. 85.7%, respectively) ($P = 0.003$). DP

https://doi.org/10.1016/j.clinre.2018.11.005

Please cite this article in press as: Gardini AC, et al. Impact of physician experience and multidisciplinary team on clinical outcome in patients receiving sorafenib. Clin Res Hepatol Gastroenterol (2018), https://doi.org/10.1016/j.clinre.2018.11.005

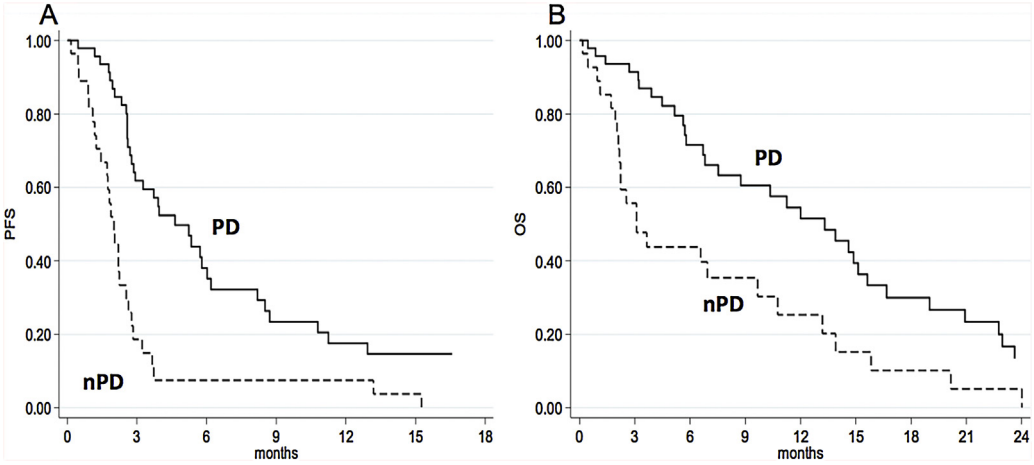

Figure 1

patients were seen more frequently in the first two months than nDP patients [median 3 consultations (range 1—5) vs. 2 (range 1—4), $P = 0.0002$; average 2.98 (standard deviation 1.05) vs. 2.03 (standard deviation 0.82), $P < 0.0001$].A dermatologist saw 28.5% of nDP patients against 100% of DP patients for dermal toxicity ($P = 0.001$). In our study, we found that DP patients had a better outcome than nDP patients. In our opinion, there are two reasons for this result: better management of sorafenib-related adverse events (AEs) and the presence of an MDT (19—20).

AEs include hand—foot skin reaction, rash, upper and lower gastrointestinal distress (i.e. diarrhea), fatigue, and hypertension. These AEs commonly range from grade 1 to 3, according to the Common Terminology Criteria for Adverse Events, and often occur early in treatment. The goal of AEs management is to prevent, treat, and/or minimize their effect, thereby enabling patients to remain on treatment and improve their quality of life. Our study showed that PD patients have a smaller dose reduction of sorafenib in the first two months of therapy, thanks to a better control of the AEs by the dedicated physician.

For example, HSFR lesions are sharply demarcated, erythematous, edematous, painful, highly tender blisters that make walking difficulty. HSFR is dose-dependent and very characteristically localized in areas of pressure or friction on the skin, adjacent to the calluses. An appropriate management of skin toxicity by an expert dermatologist, would increase patient compliance to treatment and improve quality of life.

To optimize care, the patients with HCC should be managed by an MDT [2]. The MDT must be performed by: medical oncologist, hepatologist, hepatobiliary surgeon, diagnostic radiologist and/or an interventional radiologist, pathologist, biologist and palliative care physician [2].

According to the American Association for the Study of Liver Diseases Practice Guidelines for the management of HCC, the complexity of HCC suggests that it should be managed in a multidisciplinary setting [3]. Unfortunately, multidisciplinary management is not fully implemented. A recent survey in the United States found that only 44% of physicians regularly adopt a multidisciplinary approach to treat HCC [4].

An MDT can take into consideration all the available therapies, giving the patients the possibility to be treated in the most aggressive and effective way. In the present study, patients evaluated in an MDT received significantly more associated therapies than nPD patients with a remarkable outcome improvement.

A close interaction between the hepatologist, oncologist, radiologist and surgeon is necessary to strictly monitor the underlying liver disease, optimize the clinical outcomes and choose the most effective treatment. Among the oncologist's responsibilities is the management of AEs induced by systemic drugs.

As the MDT presides over the entire management of HCC patients, it is the ideal setting for observational and translational research. For this reason the figure of the biologist is very important within the MDT. Translational research projects aim to identify novel prognostic predictors and molecular targets, and to facilitate their implementation in the routine clinical management of patients [5—10].

Our results showed that the survival of patients with advanced HCC was dependent on both the experience of the physician and the multidisciplinary approach.

Disclosure of interest

The author has not supplied his declaration of competing interest.

References

[1] Chen TM, et al. Management and patient survival in hepatocellular carcinoma: does the physician's level of experience matter? J Gastroenterol Hepatol 2008;23:179—88.
[2] Sherman M, et al. Multidisciplinary Canadian consensus recommendations for the management and treatment of hepatocellularcarcinoma. Curr Oncol 2011;18:228—40.
[3] Bruix J, Sherman M. Management of hepatocellular carcinoma:an update. Hepatology 2011;53:1020—2.
[4] Abou-Alfa G, Colombo M. Shaping the future management of hepatocellular carcinoma. Semin Liver Dis 2013;33(Suppl 1):S20—3.

Please cite this article in press as: Gardini AC, et al. Impact of physician experience and multidisciplinary team on clinical outcome in patients receiving sorafenib. Clin Res Hepatol Gastroenterol (2018), https://doi.org/10.1016/j.clinre.2018.11.005

[5] Casadei Gardini A, et al. eNOS polymorphisms and clinical outcome in advanced HCC atients receiving sorafenib: final results of the ePHAS study. Oncotarget 2016 [epub ahead of print].
[6] Casadei Gardini A, et al. Early onset of hypertension and serum electrolyte changes as potential predictive factors of activity in advanced HCC patients treated with sorafenib: results from a retrospective analysis of the HCC-AVR group. Oncotarget 2016;7:15243—51.
[7] Casadei Gardini A, et al. Metformin and insulin impact on clinical outcome in patients with advanced hepatocellular carcinoma receiving sorafenib: validation study and biological rationale. Eur J Cancer 2017;86:106—14.
[8] Casadei Gardini A, et al. Efficacy of sorafenib in BRAF-mutated non-small-cell lung cancer (NSCLC) and no response in synchronous BRAF wild type-hepatocellular carcinoma: a case report. BMC Cancer 2016;7(16):429, http://dx.doi.org/10.1186/s12885-016-2463-2.
[9] Casadei Gardini A, et al. Immune inflammation indicators and implication for immune modulation strategies in advanced hepatocellular carcinoma patients receiving sorafenib. Oncotarget 2016, http://dx.doi.org/10.18632/oncotarget.1156.
[10] Casadei Gardini A. et al. Multicenter Prospective Study of Angiogenesis Polymorphism Validation in HCC Patients Treated with Sorafenib. An INNOVATE Study Protocol.Tumori. 2017 Dec 1:tj5000704.

Andrea Casadei Gardini[a,*]
Emanuela Scarpi[b]
Francesco Giuseppe Foschi[c]
Giorgia Marisi[d]
Marco Maltoni[e]
Giovanni Luca Frassineti[a]

[a] *Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[b] *Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[c] *Department of Internal Medicine, Faenza Hospital, AUSL Romagna, Faenza, Italy*
[d] *Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[e] *Palliative Care Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

* Corresponding author.
E-mail address: andrea.casadei@irst.emr.it
(A.C. Gardini)

Please cite this article in press as: Gardini AC, et al. Impact of physician experience and multidisciplinary team on clinical outcome in patients receiving sorafenib. Clin Res Hepatol Gastroenterol (2018), https://doi.org/10.1016/j.clinre.2018.11.005