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Overall Survival in Patients with Hepatocellular Carcinoma Treated with Sorafenib: A Polish Experience

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Background: The mortality caused by hepatocellular carcinoma is expected to rise in the upcoming decade. Sorafenib has become the preferred systemic treatment option in patients with unresectable HCC. This study aimed to present the median overall survival (OS) in a group of patients with advanced HCC, treated with sorafenib in Poland between 2011 and 2019.

Material/Methods: The analyzed group of patients was qualified for treatment with sorafenib, financed by the National Health Fund, based on the guidelines of the Polish Drug Program.
Kaplan-Meier method was used to plot the OS curves, and the log-rank test was used for testing. Multivariate assessment of factors (sex and age) related to the time to death of the patient was done using Cox regression.

Results: Of the 2072 treated patients, 75% were men (1556) and 25% were women (516). The minimum age of patients in the trial group was 18 years and the maximum age was 90 years.
Among the 1556 analyzed cases in males, 27.44% (427) did not end with death (by the date of completing the analysis). The percentage of one-year survival for this population was 58.16%, and the 2-, 3-, and 5-year survival rates were 34.45%, 21.81%, and 9.72%, respectively.
The percentage of censored cases in the 516 females was 25.78% (133). The 1-2-, 3-, and 5-year survival for this population was 59.30%, 36.27%, 22.47%, and 11.34%, respectively. Statistical tests did not reveal a significant difference in the curve profiles by sex. There were no associations between OS and age.

Conclusions: Systemic treatment with sorafenib in accordance with the presented criteria allows for very good results, comparable to the results of selected groups of patients presented by other authors.

Keywords: Carcinoma, Hepatocellular • Sorafenib • Survival Rate

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Background

Hepatocellular carcinoma (HCC) is the most common primary hepatic cancer in the world and the sixth most common cancer in the world. In 2018 it was ranked as the fourth leading cause of death among all cancer types [1,2]. The frequency of its occurrence has been increasing in the USA, Europe, and Asia, and the mortality caused by this type of cancer is expected to rise in the upcoming decade [3]. The incidence of liver cancer is also increasing in Poland, reaching about 2000 new cases annually [4].

Since the majority of cases are diagnosed when the disease is highly advanced, the 5-year survival rate of patients with HCC does not exceed 20% [5]. According to the current recommendations, O and A grade patients are classified according to the Barcelona Clinic Liver Cancer (BCLC) system for potentially curative therapies for liver resection or transplantation or thermal ablation (radiofrequency ablation [RFA]) [5]. In patients not eligible for the treatments (eg, with a more advanced tumor, B or C grade according to BCLC classification system), who constitute 46% to 62% of all patients with HCC, loco-regional therapies such as transarterial chemoembolization (TACE) should be considered as a part of the strategy to downstage the patients to treatments that have a curative intent, or to systemic treatment [5,6]. In 2007, the SHARP randomized controlled trial demonstrated the superior efficacy of the tyrosine kinase inhibitor sorafenib versus placebo in patients with advanced HCC, with median overall survival (OS) of 10.7 versus 7.9 months. Similar benefits of sorafenib versus placebo were reported in a phase III study conducted on patients from the Asia-Pacific region (6.5 versus 4.2 months) [7,8]. Based on the data, sorafenib has become the preferred systemic treatment option in patients with unresectable HCC [5,6]. In over 10 years of using sorafenib, there were numerous research analyses carried out on the impact of various predictive factors on OS [5,10-16]. An analysis of the factors affecting OS will help to forecast the effectiveness of sorafenib treatment with greater accuracy. Analyzing the use of sorafenib in patients as part of actual clinical practice allows us to confirm and supplement the results of studies obtained in clinical trials.

Material and Methods

Purpose

This study aimed to present the median OS in a group of patients with advanced HCC treated with sorafenib in Poland between 2011 and 2019. The analyzed group of patients was qualified for treatment with sorafenib, financed by the National Health Fund, based on the guidelines of the Polish Drug Program (DP). Criteria for inclusion in the DP of sorafenib treatment were as follows: histologically or radiologically diagnosed HCC, unresectable tumor or failure of loco-regional therapy, performance status according to WHO 0-1, Child-Pugh A patients only, no extrahepatic spread, and no prior systemic therapy.

Methods

The study used secondary statistical analysis of the retrospective data on treated patients; the NHF provided the data. Drug Programs (DP) in Poland are carried out as part of separate therapeutic paths financed by the national payer, and the patient treatment protocol is strictly determined. With regard to the patients' explicit inclusion and exclusion criteria, the analyzed population is a highly homogenous group, which corresponds to the criteria of the clinical trial transferred onto real clinical practice. This method of analysis was successfully used in other published works related to disease classification, and medical and environmental issues [17,18].

The information from the period from 7 July 2011 to 31 July 2019 (98.2 months) applying to a population of 2072 treated patients was used for the analysis.

The analyzed group of patients with HCC was qualified for treatment with sorafenib based on the guidelines of the Polish DP, which assumes the following essential criteria for the patient's inclusion for treatment and sorafenib dosing rules:
1) histologically or radiologically diagnosed HCC;
2) unresectable tumor or failure of loco-regional therapy;
3) performance status according to WHO 0-1;
4) Child-Pugh A patients only;
5) no extrahepatic spread (EHS);
6) no prior systemic therapy.

The daily dose of sorafenib is 800 mg (2×200-mg pills twice a day) with no breaks. Should drug-related clinically significant or severe adverse events (AEs) occur, the treatment with the medication shall be stopped until the symptoms are relieved, and reduction in the daily dose of sorafenib to 400 mg a day (2 pills×200 mg once a day) shall be considered. If clinically significant or severe adverse events are not alleviated within 4 weeks, despite a break in the drug administration, the treatment shall be stopped. If despite the dose reduction to 400 mg a day the clinically significant or severe adverse events re-occur, the drug dose shall be reduced to 400 mg administered every other day. It is not possible to further reduce the drug doses (eg, reoccurrence of clinically significant or severe adverse events), the therapy should be stopped.

The investigated aspects included the age and sex of the patients, OS median and percentage of 1-year, 2-year, 3-year, and 5-year survival depending on the sex, as well as the therapy duration.

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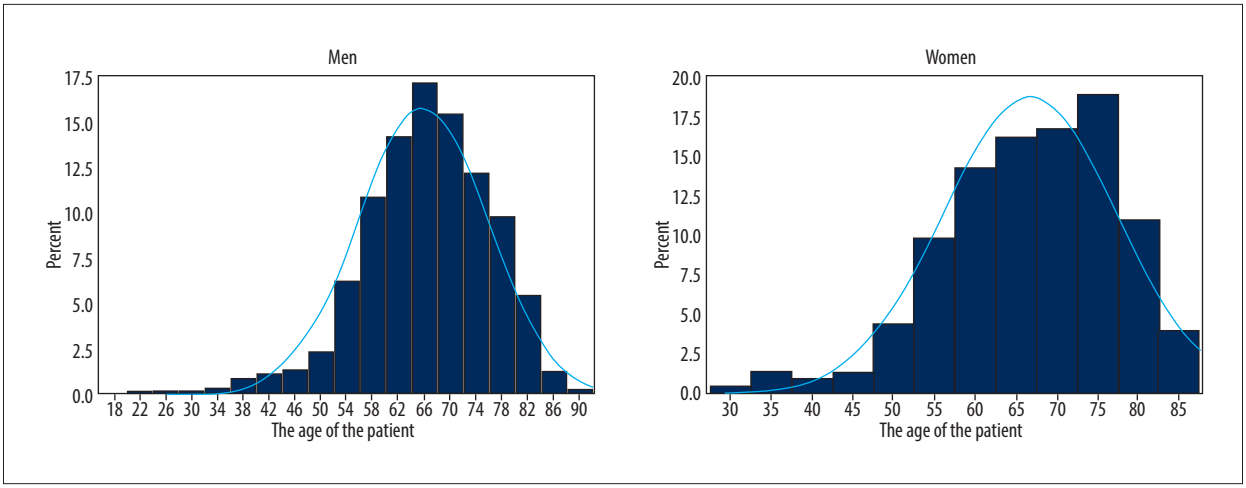

Figure 1. Number of patients involved in the study, divided according to age and sex.

Statistical methods

The initial (minimum) date of inclusion into the DP was established as the starting date for the OS analysis in each patient, while 31 July 2019 was the cut-off date. Kaplan-Meier method was applied to plot the OS curves, and the log-rank (Mantel-Cox) test, Gehan-Breslow-Wilcoxon test, and likelihood ratio (-2Log (LR)) test were used for testing. Multivariate assessment of factors (sex and age) related to the time to death of the patient was done using Cox regression. The Cox regression model was applied to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs). Statistical analysis was performed in SAS® Enterprise Guide® ver. 8.2 software. Findings were considered significant with *P* value <0.05.

Ethics Approval

The study did not require the approval of the Bioethical Commission as it was non-invasive and was carried out using data collected by a public institution. The data analyzed in the study were anonymized.

Results

Of the group of 2072 treated patients, 75% were men (1556) and 25% were women (516). The median age of males was 66.0 years (mean age 65.77 years [95% CI: 65.27-66.27]), and the standard deviation was 10.01 years [95% CI: 9.67-10.38]. The minimum age of patients in the trial group was 18 years, and the maximum age was 90 years. The median age of females was 68.0 years (mean age 66.75 years [95% CI: 65.84-67.67]); the standard deviation was 10.60 years [95% CI: 9.99-11.28]. The minimum age of patients in the trial group was 29 years, and the maximum age was 87 years (**Figure 1**).

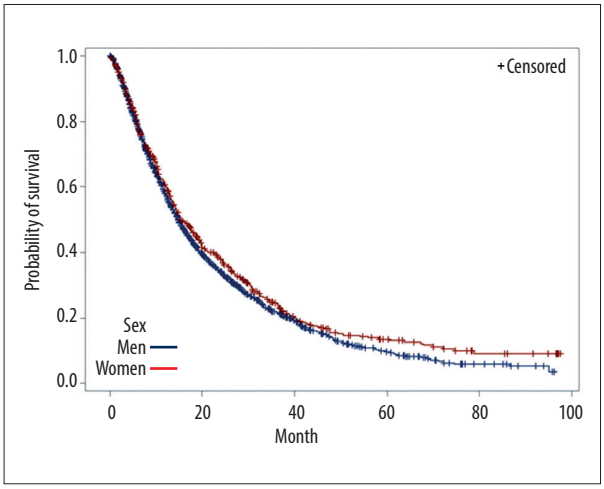

Figure 2. 0Overall survival curves for the patients treated within the Drug Program ("Y" axis is the percentage of the patients who survived).

The overall median survival was 14.86 months (445.8 days) [95% CI: 14.00-16.13] for men, and 15.20 months (456 days) for women [95% CI: 13.57-17.57] (**Figure 2**).

Of the 1556 analyzed cases for males, 27.44% (427) did not end with death by the date of completing the analysis (31 July 2019). The percentage of 1-year survival for this population was 58.16%, the 2-year survival was 34.45%, 3-year survival was 21.81%, and 5-year survival was 9.72%. The percentage of censored cases in the 516 females was 25.78% (133). The percentage of 1-year survival for this population was 59.30%, 2-year survival was 36.27%, 3-year survival was 22.47%, and 5-year survival was 11.34%. Statistical tests did not reveal a statistically significant difference in the curve profiles by sex (log-rank: *P*>0.489; Wilcoxon: *P*>0.559; -2Log (LR): *P*>0.388). There was no association between OS and age (HR=0.996,

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Table 1. Therapy duration summary.

		Comments
Minimum	14 days	
Maximum	2800 days	
Median (50% patients)	111 days	
Mean	225.8 days	95% CL: 207.71-243.97
Observation period	2946 days	

95% CI [0.991; 1.001], *P*=0.125) or sex (HR=0.961, 95% CI [0.856; 1.079], *P*=0.497).

The data on therapy duration (in days) are summarized in **Table 1**.

Therapy duration in the study population:
1. The patients were taking the medication for 225.8 days (7.5 months) on average;
2. The median (50% of patients) were taking the medication for a period no shorter than 111 days (3.7 months);
3. The minimum therapy duration was 14 days;
4. The maximum therapy duration was 2800 days (93.3 months).

Discussion

The presented analysis results apply to one of the most numerous and relatively homogenous populations of patients of all groups presented in the global literature. Bruix et al and Raoul et al carried out subanalyses of the SHARP trial on 448 and 602 patients, respectively, treated with sorafenib [5,14]. Chinese authors described 338 subjects [12], while Italian authors analyzed a group of 398 patients based on 10-year multicenter studies [9]. Japanese authors from different centers presented the results of research based on the material covering 1065 [11], 524 [18], and 508 [12] patients. Researchers from the United Kingdom presented the results of studies on a group of 448 subjects [15].

The OS of the patients treated with sorafenib presented in the papers ranges from 7 months [20] to 8.7 months, 9.7 months, 11.5 months [21,22], 15.3 months [18], 15.8 months [9], and up to 17.4 months [12]. The results depend on the tumor development stage, liver efficiency, general condition of the patients, and occurrence of portal thrombosis in the analyzed groups. According to different authors, the sorafenib treatment efficacy predictors affecting OS are age, sex, race, general condition, B or C stage of the Barcelona Clinic Liver Cancer (BCLC staging) classification, presence of extrahepatic spread (EHS), macroscopic vascular invasion (MVI), number and size of the tumors, cirrhosis etiology, bilirubin, albumin, ALBI (albumin-bilirubin grade), NLR (neutrophil-to-lymphocyte ratio), Child-Pugh score, AFP, body mass index (BMI), and sorafenib dosage [5,9,10-12,14-16].

In the presented analysis, the therapeutic program inclusion criteria did not take into account all the aforementioned factors because the Polish Drug Program was developed before 2011 when the knowledge of the subject matter was limited. It was also meant to simplify the procedure. In the context of OS and 1-year, 2-year, 3-year, and 5-year survival among the patients in the whole population of 2072 subjects, the presented results are very good. The OS of 14.86 months for the males and 15.2 for the females, which amounts to about 450 days, is comparable only with the results for some selected subgroups of patients with BCLC stage B, Child-Pugh score A, with no extrahepatic spread and macroscopic vascular invasion, analyzed by other authors [5,9,12,16]. The median duration of the treatment for the patients qualified for the Polish therapeutic program was 111 days, and was 30 days longer than the period mentioned by Kaneko based on an analysis of 1065 subjects [11]. In a study on a population of 338 patients carried out by Ye et al, the OS and the median therapy duration were longer than in patients with Child-Pugh score A, as compared to patients in group B, and amounted to 320 and 147 days, respectively, versus 240 and 131.6 days, respectively [13]. The 1-, 3- and 5-year survival rates of the patients with no EHP and MVI treated with sorafenib in China were shorter than in the corresponding data presented in this paper, and were 55.6%, 29.6%, and 4.8%, respectively [10]. Japanese authors also revealed a lower 5-year survival rate than presented in the present study (7.7% vs 9.8% among males and 11.34% among females) [23].

Sorafenib extends the survival as compared to placebo in all patients with unresectable HCC; seeking the factors that improve its efficacy is justified from the clinical and economic point of view. The criteria implemented by the Polish payer, regarded by some as rigorous because they limit the access to treatment for patients with advanced disease, can be approached in different ways. Due to the increasing prices of HCC therapies, most countries carry out studies on the economic effectiveness of such therapies [6,24]. Cost-effectiveness of

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sorafenib treatment is usually confirmed for Child-Pugh score patients and for patients in a good general condition; in more advanced cases, it is generally undetermined [24,25]. This is why the inclusion criteria for sorafenib treatment used in Poland (and in the United Kingdom) should be considered as valid, as the treatment cost is reimbursed by the state [26]. Moreover, the restriction of indications for treatment with sorafenib to the criteria mentioned above gives some assurance of optimal treatment results.

Conclusions

Systemic treatment with sorafenib in accordance with the presented criteria allows for very good results, comparable to the results of selected groups of patients presented by other authors.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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