ORIGINAL PAPERS

Adv Clin Exp Med 2011, **20**, 3, 335–342
ISSN 1230-025X

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Examining the Efficacy of Sorafenib – a Meta-Analysis

Ocena skuteczności sorafenibu – metaanaliza

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Abstract

Objectives. The recently approved drug sorafenib has been found to be effective against renal cell carcinoma and hepatocellular carcinoma. A meta-analysis to examine the extent to which this drug is effective in comparison to a placebo-based therapy regimen was conducted.
Material and Methods. We performed a literature survey and recognized randomized controlled trials that had judged the efficacy of sorafenib in comparison to placebos in preventing renal cell carcinoma or hepatocellular carcinoma. The authors have evaluated the data separately.
Results. This analysis contains data from 3,659 patients. The percentage of patients who responded either completely or partially to a sorafenib-based therapy regimen was 6.5% as compared to 2.2% from a placebo-based therapy regimen (log odds ratio = 0.48, 95% CI = 2.893, –1.933). It has also been found that the mean time for progression free survival (PFS) is 5 months for the sorafenib-based therapy regimen as compared to 2.88 months, which is the mean time for progression free survival with a placebo-based therapy regimen.
Conclusions. It was concluded that a sorafenib-based therapy regimen yields a better response and more time for progression free survival in patients with renal cell carcinoma or hepatocellular carcinoma as compared to a placebo-based therapy regimen (**Adv Clin Exp Med 2011, 20, 3, 335–342**).

Key words: carcinoma management, placebo, randomized controlled trials, progression free survival.

Streszczenie

Cel pracy. Niedawno zatwierdzony lek sorafenib okazał się skuteczny w leczeniu raka miąższu nerki i raka wątrobowokomórkowego. Przeprowadzono metaanalizę, aby ocenić zakres skuteczności leku w porównaniu ze schematem leczenia opartym na placebo.
Materiał i metody. Autorzy przeprowadzili przegląd literatury i uznanych randomizowanych badań klinicznych, które miały ocenić skuteczność sorafenibu w porównaniu z placebo w zapobieganiu rakowi nerki lub rakowi wątrobowokomórkowemu. Autorzy dokonali oceny danych oddzielnie.
Wyniki. Analiza zawiera dane 3659 pacjentów. Całkowita liczba pacjentów, u których stwierdzono odpowiedź całkowitą lub częściową na leczenie za pomocą sorafenibu to 6,5% w porównaniu z 2,2% pacjentów, którym podawano placebo (logarytm ilorazu szans = 0,48; 95% CI = 2,893; –1,933). Stwierdzono również, że średni czas przeżycia bez progresji choroby (PFS) wynosi 5 miesięcy w grupie leczonej sorafenibem w porównaniu z 2,88 miesiąca średniego czasu przeżycia wolnego od progresji choroby w grupie otrzymującej placebo.
Wnioski. Stwierdzono, że leczenie za pomocą sorafenibu daje lepsze odpowiedzi i dłuższy czas przeżycia bez progresji choroby u pacjentów z rakiem nerki lub rakiem wątroby w porównaniu z podawaniem placebo (**Adv Clin Exp Med 2011, 20, 3, 335–342**).

Słowa kluczowe: leczenie raka, placebo, randomizowane badania kliniczne, przeżycie bez progresji choroby.

Sorafenib tosylate (BAY43-9006) was approved by the Food and Drug Administration (FDA) on November 16, 2007 [1]. The development of the drug and testing of the success of sorafenib against cancer took about 11 years. After the approval of sorafenib against advanced renal cell carcinoma (RCC), it became the first new treatment in more than ten years [17]. Moreover, it is also recommended for the treatment of unresectable hepatocellular carcinoma [1].

It is an oral multikinase inhibitor [1, 3] for the

treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma [4]. It has two distinct aspects of inhibition as it is not only an inhibitor of Raf but also causes inhibition of vascular endothelial growth factor receptor (VEGFR). It has shown preclinical anti-cancer effects against a wide range of human cancers [5]. The Raf is a form of protein which is of prime importance as an effector of the Ras, which is a small GTPase protein which sends activating signals from growth factors to Raf and from there to mitogen-activated protein kinase (MAPK). There are three structurally protected serine-threonine kinases i.e. A-Raf, B-Raf and C-Raf (Raf-1) [4]. Sorafenib was found to work well in a dose of 400 mg twice daily [6].

RCC is considered as the 14th most common form of cancer throughout the world [7]. It has been found that of all new cancer cases, 2% belong to RCC [8]. More than 20% of the cases of RCC are either cigarette smokers or obese people [9].

The drug-related adverse effects were mild to moderate in sorafenib treatment, comprising diarrhea, fatigue and skin toxicities in phase I studies [6, 10]. Rashes, fatigue, diarrhea and hand-foot syndrome were found as the most common side effects observed in phase II trials [11]. Work is ongoing in reducing skin toxicity caused by sorafenib [3].

The objective of this study was to illustrate and compare the efficacy of sorafenib in comparison to a placebo from seven different studies.

Material and Methods

Searching

We did search on Pubmedcentral.com, highwire.stanford.edu, sciencedirect.com and scholar.google.com (1990–2009) using the search terms "Sorafenib", "Sorafenib and Placebo", "Sorafenib versus Placebo", "Sorafenib and randomized controlled trial" and "Sorafenib and renal cell carcinoma" studying humans and clinical trials.

Selection

For this meta-analysis, only randomized controlled trials that showed the efficacy of sorafenib as a first-line therapy for RCC either alone or in combination with other chemotherapeutic agents were studied. As we did not have direct contact with the patients, we checked the median age of the patients and included studies only on subjects above 50 years of age. Only articles in English were included.

Validity Assessment

Outcome data was extracted separately.

Data Abstraction

In order to prevent bias in the collection process of data, two observers separately checked out the trials and examined the similarities and differences among the results. The following information was taken from each of the selected articles: number of randomly assigned patients, percentage of male patients, median age of the patients, therapy regimen and median progression free survival. Dacarbazine was used in the trial McDermott et al. [12] as a combination therapy regimen with sorafenib and placebo whereas Paclitaxel and Carboplatin were taken as a combination therapy regimen in the trial of Aggarwala et al. [13].

The data separately taken was examined for coherence and differences were resolved by mutual conversation. For evaluation of the responses, the only trials used contained measurable information about the disease of the patients and were examined with well-accepted criteria.

For the analysis of the data and construction of the graphs, Microsoft Excel version 2007 and the "multcompare" function of Matlab R2007a were used.

Study Characteristics

Quantitative Data Synthesis

In this study, we calculated log odds ratios ($_i$) from odds ratios (ORs) by using 2 × 2 tables for the number of responding patients from the abstracted data. Variances of the log odds ratios for the subjects who received a sorafenib-based therapy regimen relative to that of a placebo-based therapy regimen were calculated from the tables. Moreover, inverse of the variance, standard error for the log odds ratio and 95% confidence interval (CI) for the log odds ratio were also calculated from the tables. The line at "0" is the unity line and a value above "0" shows that a sorafenib-based therapy regimen is better than a placebo-based therapy regimen.

A hazard ratio (HR) was assessed for the progression free survival (PFS) of the sorafenib-based therapy regimen as compared with the placebo-based therapy regimen. An HR value above the unity line shows that the sorafenib-based therapy regimen is better than a placebo-based therapy regimen. Heterogenity was calculated.

Results

Trial Flow

The QUOROM statement flow diagram for our study is shown in Fig. 1. Seven studies [2, 9, 12–16], comprising 3,659 patients, were taken for analysis.

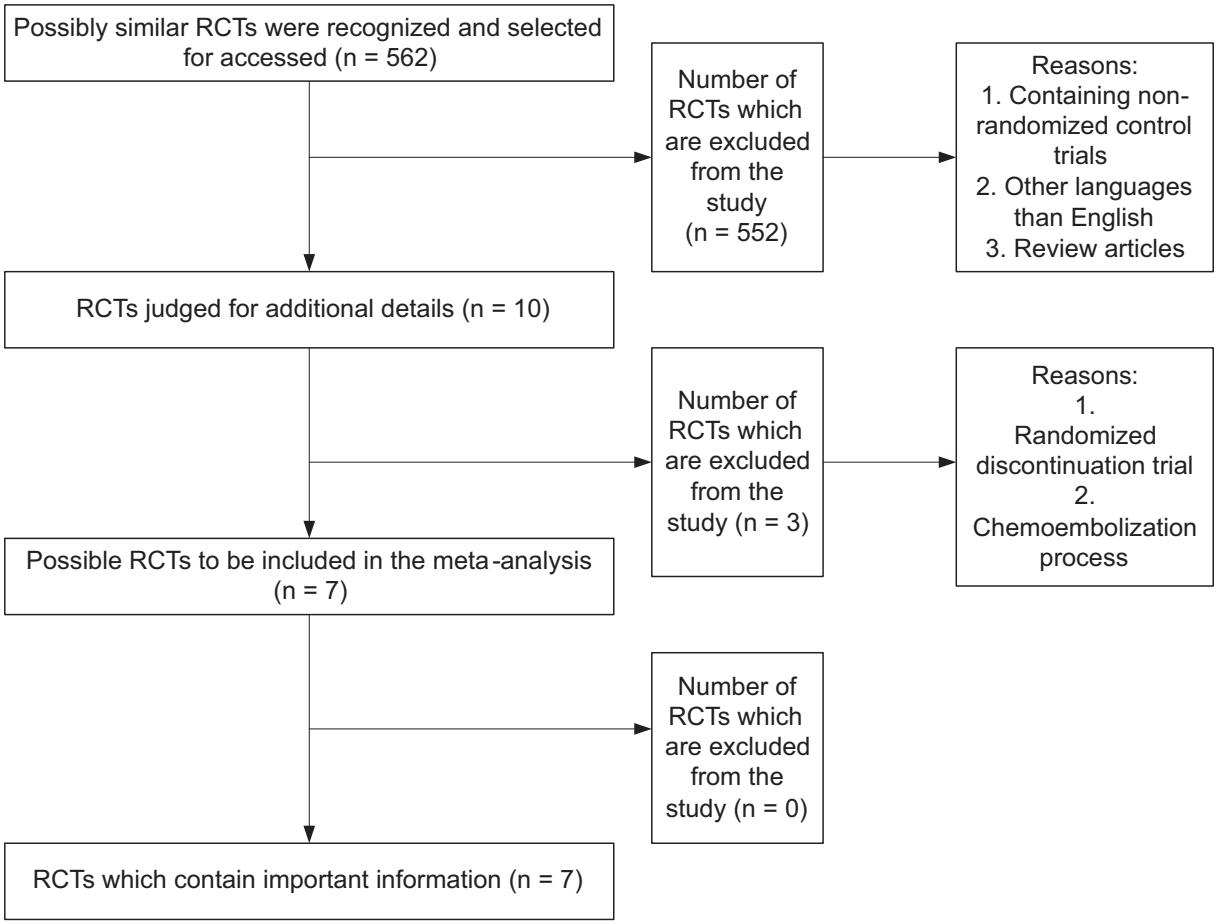


Fig. 1. A QUOROM statement flow diagram presenting the progress of trials through the review. RCT – randomized controlled trials

Ryc. 1. Algorytm QUOROM przedstawiający postęp badań w ramach przeglądu. RCT – randomizowane badania kliniczne

Study Characteristics

The important characteristics of the seven trials are presented in Table 1. Of the total 3,659 patients, 1851 patients were randomly assigned to sorafenib-based chemotherapy whereas 1808 patients were randomly assigned to placebo-based therapy/chemotherapy.

From these trials, six trials [9, 13–17] are randomized trials from phase III whereas one trial [12] was a randomized trial from phase II. These trials were placebo-controlled trials. Furthermore, two trials [12, 13]) contained mixed drug therapy with sorafenib on one arm and placebo on the other arm.

Quantitative Data Synthesis

Number of Responding Patients

The number of responding patients calculated by the sum of complete responses and partial responses was available in all the trials. The total number of responding patients to a sorafenib-based therapy regimen to that of a placebo-based therapy regimen was significantly greater. 6.5% of the patients responded to the sorafenib-based therapy regimen and 2.2% responded to the placebo-based therapy regimen (log odds ratio = 0.48, 95% CI = 2.893, –1.933). The fixed-effects estimate show a log odds ratio of 0.193 (95% CI = 0.597, –0.211). From Table 5, the Q-statistic is somewhat significant ($p = 0.02$) showing some heterogeneity amongst the studies but the overall assessment of the treatment difference shows a salutary effect of the sorafenib therapy regimen (= 0.193) and the U-statistic is not significant ($p = 0.350$). The significant value of the Q-statistic may have arisen due to the trials containing different types of sorafenib-based therapy regimens and placebo-based therapy regimens.

In the graph of "log odds ratio of sorafenib therapy regimen relative to placebo therapy regimen", the trial of McDermott et al. [12] shows a difference only from the trials of Escudier et al. [15] and Eisen et al. [9] and the fixed effects estimate and does not show any difference from other studies. The remaining trials were similar to each other.

Table 1. Characteristics of trials of sorafenib vs. placebo

Tabela 1. Charakterystyka badań sorafenibu w porównaniu z placebo

Study (Badanie)	No. of randomly assigned patients (Liczba wylosowanych pacjentów)	Therapy regimen (Schemat terapii)	Male (Płeć) (%)	Median age of the patients (Średni wiek pacjenta)
Kane et al., 2006	384 385	sorafenib placebo	72	< 65 (67%) < 65 (73%)
Escudier et al., 2007	451 452	sorafenib placebo	72.5	58 59
Agarwala et al., 2007	135 135	sorafenib + paclitaxel + carboplatin placebo + paclitaxel + carboplatin	63	57
Llovet et al., 2008	299 303	sorafenib placebo	87	64.9 ± 11.2 66.3 ± 10.2
Eisen et al., 2008	381 407	sorafenib placebo	73.1	57 58
McDermott et al., 2008	51 50	sorafenib + dacarbazine placebo + dacarbazine	70	55 60
Cheng et al., 2009	150 76	sorafenib placebo	85.4	51 (23–86) 52 (25–79)

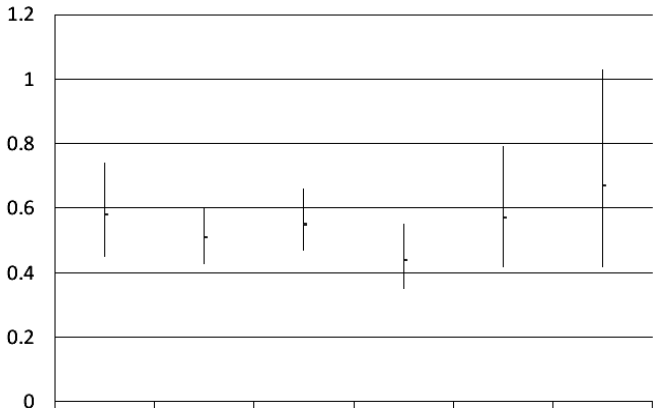
Progression Free Survival

From Table 2, it is clear that progression free survival (PFS) for patients with a sorafenib-based therapy regimen was longer than with patients with a placebo-based therapy regimen. Mean time for PFS in a sorafenib-based therapy regimen was 5 months as compared with a placebo-based therapy regimen which was 2.88 months. Moreover, its graph on hazard ratio shows no significant difference among the different trials.

Table 2. Progression free survival data in the trials of sorafenib vs. placebo

Tabela 2. Dane na temat czasu wolnego od progresji choroby w badaniach sorafenibu w porównaniu z placebo

Study (Badanie)	Therapy regimen (Schemat terapii)	Median progression free survival (Średni czas wolny od rozwoju choroby)		
		time in months	HR (95% CI)	P
Kane et al., 2006	sorafenib placebo	5.6 2.8	0.44 (0.35–0.55)	< 0.000001
Escudier et al., 2007	sorafenib placebo	5.5 2.8	0.51 (0.43–0.60)	< 0.001
Agarwala et al., 2007	sorafenib + paclitaxel + carboplatin placebo + paclitaxel + carboplatin	4.35 4.48	0.906 (N/A)	0.492
Llovet et al., 2008	sorafenib placebo	5.5 2.8	0.58 (0.45–0.74)	< 0.001
Eisen et al., 2008	sorafenib placebo	5.98 2.98	0.55 (0.47–0.66)	N/A
McDermott et al., 2008	sorafenib + dacarbazine placebo + dacarbazine	5.28 2.9	0.665 (0.42–1.03)	0.068
Cheng et al., 2009	sorafenib placebo	2.8 1.4	0.57 (0.42–0.79)	0.0005



	Llovet et al.	Escudier et al.	Eisen et al.	Kane et al.	Cheng et al.	McDermo tt et al.
Upper limit of 95% CI	0.74	0.6	0.66	0.55	0.79	1.03
Lower limit of 95% CI	0.45	0.43	0.47	0.35	0.42	0.42
- Hazard ratio for Median PFS	0.58	0.51	0.55	0.44	0.57	0.67

Fig. 2. Hazard ratio of median PFS along with 95% CI

Ryc. 2. Ryzyko względne mediany PFS wraz z 95% CI

Table 3. Responses in the trials comparing sorafenib vs. placebo therapy regimen

Tabela 3. Odpowiedzi w badaniach sorafenibu w porównaniu z placebo

Study (Badanie)	Therapy regimen (Schemat terapii)	No. of responding patients – complete response + partial response (Liczba pacjentów odpowiadających na terapię – odpowiedź całkowita + odpowiedź częściowa)	No. of patients eligible for evaluation (Liczba pacjentów zakwalifikowanych do oceny)	Objective response (Odpowiedź obiektywna) (%)	Odds ratio (Iloraz szans)	Log odds ratio (Algorytm ilorazu szans) ($_i$)
Kane et al., 2006	sorafenib placebo	7 0	335 337	2.1 0	N/C	
Escudier et al., 2007	sorafenib placebo	44 8	451 452	9.8 1.9	6	0.778
Agarwala et al., 2007	sorafenib + paclitaxel + carboplatin placebo + paclitaxel + carboplatin	15 16	135 135	12 11	0.93	–0.032
Llovet et al., 2008	sorafenib placebo	2 1	299 303	0.7 0.3	2.03	0.307
Eisen et al., 2008	sorafenib placebo	33 6	381 407	8.7 1.5	6.33	0.801
McDermott et al., 2008	sorafenib + dacarbazine placebo + dacarbazine	12 6	51 50	24 12	0.04	–1.398
Cheng et al., 2009	sorafenib placebo	5 1	150 76	3 1	2.59	0.413
Total (Suma)	sorafenib therapy regimen placebo therapy regimen	118 38	1802 1760	6.5 2.2	3.03	0.48

Table 4. 95% CI for log odds ratio

Tabela 4. 95% CI dla logarytmu ilorazu szans

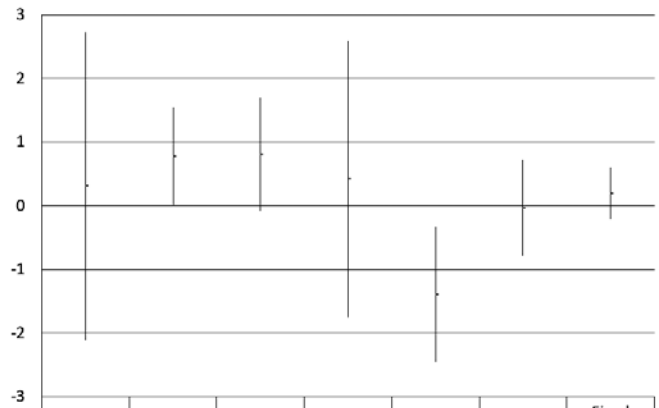
	i	Var $_i$	w_i (=1/ var $_i$)	se ($_i$) (=)	95% CI (= $_i$±1.96/)
Escudier et al., 2007	0.778	0.152	6.58	0.389	1.54, 0.016
Agarwala et al., 2007	–0.032	0.144	6.94	0.378	0.712, –0.776
Llovet et al., 2008	0.307	1.506	0.66	1.227	2.722, –2.106
Eisen et al., 2008	0.801	0.202	4.95	0.449	1.684, –0.082
McDermott et al., 2008	–1.398	0.29	3.45	0.535	–0.345, –2.451
Cheng et al., 2009	0.413	1.22	0.82	1.104	2.578, –1.752
Total (Suma)	0.48	0.036	27.78	0.19	2.893, –1.933

Table 5. Fixed effects meta-analysis of the log-odds ratio of sorafenib therapy regimen relative to placebo therapy regimen

Tabela 5. Model z efektem stałym metaanalizy logarytmu ilorazu szans w badaniach sorafenibu w porównaniu z placebo

Study (Badanie)	Therapy regimen (Schemat terapii)	No. of responding patients – complete response + partial response (Liczba pacjentów odpowiadających na terapię – odpowiedź całkowita + odpowiedź częściowa)	No. of patients eligible for evaluation (Liczba pacjentów zakwalifikowanych do oceny)	i	w_i (=1/ var $_i$)	$_i w_i$	$_i^2 w_i$
Escudier et al., 2007	sorafenib placebo	44 8	451 452	0.778	6.579	5.12	3.98
Agarwala et al., 2007	sorafenib + paclitaxel + carboplatin placebo + paclitaxel + carboplatin	15 16	135 135	–0.032	6.99	–.224	0.01
Llovet et al., 2008	sorafenib placebo	2 1	299 303	0.307	0.664	0.204	0.06
Eisen et al., 2008	sorafenib placebo	33 6	381 407	0.801	4.95	3.96	3.18
McDermott et al., 2008	sorafenib + dacarbazine placebo + dacarbazine	12 6	51 50	–1.398	3.49	–4.88	6.82
Cheng et al., 2009	sorafenib placebo	5 1	150 76	0.413	0.82	0.34	0.14
Overall (Suma)					23.493	4.523	14.189

U (Model sum of squares) = $(4.523)^2/23.493 = 0.871$; (1df) p = 0.350.
Q (Error sum of squares) = 14.189–0.871 = 13.318; (5df) p = 0.02.
(Fixed effects estimate) = 4.523/23.493 = 0.193; se () = $1/\sqrt{23.493} = 0.21$.
95% CI for fixed effects estimate = $(0.193 \pm 1.96/\sqrt{23.493}) = (0.597,–0.211)$.



	Llovet et al.	Escudier et al.	Eisen et al.	Cheng et al.	McDermott et al.	Agarwala et al.	Fixed effect estimate
Upper value of 95% CI	2.722	1.54	1.684	2.578	–0.345	0.712	0.597
Lower value of 95% CI	–2.106	0.016	–0.082	–1.752	–2.451	–0.776	–0.211
· Log Odds Ratio	0.307	0.778	0.801	0.413	–1.398	–0.032	0.193

Fig. 3. Log odds ratio of sorafenib therapy regimen relative to placebo therapy regimen

Ryc. 3. Logarytm ilorazu szans w badaniach sorafenibu w porównaniu z placebo

Discussion

In this meta-analytic review, we demonstrated the efficacy of sorafenib against cancer in randomized controlled trials. In these trials, we have found a significant response and progression free survival in the patients of a sorafenib-based therapy regimen.

Like all meta-analyses, this meta-analysis does have some technical limitations. The authors are not able to design this review according to individual patients and so the information is based on abstracted data. It is suggested that further studies must be done on individual patient data (IPD) as this will show better results. Moreover, in each of the trials, overall survival rate was not mentioned which could not be written in this review. Heterogeneity among trials can be a limitation notwithstanding that heterogeneity was taken into account for this study.

Considering all the results, it has been concluded that sorafenib (alone or in combination with certain other anti-cancer agents) is an effective new medicine for the treatment of hepatocellular carcinoma. Further assessment and analysis is needed in hepatocellular carcinoma as well as in the issue regarding treatment of other forms of cancer using a sorafenib-based therapy regimen, desirably in combination with other chemotherapeutic agents, so that more data will be available for proper treatment.

Acknowledgement. We wish to thank Dr. G. A. Miana, Rector and Director, Riphah Institute of Pharmaceutical Sciences (RIPS), Islamabad, Rizwan Nasir Paracha, PhD, scholar in Chemistry, Auckland University and Dr. Zahid Iqbal, Assistant Professor, RIPS, Islamabad, for their help in collecting the data. We also wish to thank Mr. Asif Iqbal Paracha, MS Scholar in Computer Science, Muhammad Ali Jinnah University, Islamabad, for his support in data management of the trials.

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Conflict of interest: None declared

Received: 30.11.2010
Revised: 5.01.2011
Accepted: 2.06.2011