Sorafenib in progressive castrate-resistant prostate cancer. Can we talk about a new therapeutic option?

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Abstract

Castrate-resistant prostate cancer represents a significant clinical challenge. Currently, the standard treatment for patients with castrate-resistant prostate cancer is chemotherapy, after which patients only receive symptomatic treatment. The available results of phase II clinical trials of sorafenib in patients with hormone-refractory prostate cancer indicate that, despite a relatively short progression-free survival, the treatment may be associated with good outcomes in terms of overall survival and maintenance of a good quality of life. The study presents the authors' critical opinions and observations about the usefulness of sorafenib in patients with prostate cancer.

Key words: castrate-resistant prostate cancer, angiogenesis inhibitor, sorafenib.

Introduction

Clinical observations show that prostate cancer progression usually occurs after 18-24 months of hormone therapy [1]. Also, nearly all docetaxel-treated patients eventually experience disease progression [2, 3]. The median survival in metastatic hormone-refractory prostate cancer is below 12 months, and less than 10% of patients survive for more than 2 years [4]. The outcome is related to stage of disease, diagnosis usually appear very late, because knowledge regarding symptoms of prostate cancer is still very unsatisfactory [5].

The National Comprehensive Cancer Network (NCCN) guidelines provide no recommendations on prostate cancer treatment following the failure of chemotherapy [6]. In such an advanced stage of disease, symptomatic treatment appeared to be the only choice.

However, an attempt was made to use sorafenib. Sorafenib targets multiple kinases, such as Raf, c-kit, c-Ret, and vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases. Sorafenib inhibits the Raf kinase pathway, thus inhibiting tumour cell proliferation. In addition, it affects VEGF and PDGF receptor tyrosine kinases and their downstream cascades to exert anti-angiogenic effects.

The Raf kinase pathway is impaired in castrate-resistant prostate cancer [7-9]. In prostate cancer, the VEGF-VEGF receptor pathway is important for the growth of primary tumours and for the formation of metastases [10, 11]. The efficacy of docetaxel was increased when administered with the angiogenesis inhibitors bevacizumab and thalidomide [12].

A M S

Table I. Results of phase II studies including patients with castrate-resistant prostate cancer treated with sorafenib

Author	Patient population	End points	Results of treatment

Steinbild *et al.* 2007 [13]	• 57 patients
	• ECOG < 2
	• HGB > 9 g/dl
	• Creatinine ≤ 1.5 × ULN
		Primary objective:
		rate of progression-free survival ≥ 12 weeks
		Secondary end points:
		• Overall response
		• Overall survival
		• Toxicity
			at 12 weeks
			• 4 – stable disease (RECIST)
			• 11 – stable disease (PSA-response)
			• 2 – PSA - responders
			  – The 1 year PFS rate was 13% (95% CI: 6-28%)
			  – The 1-year OS rate: 68% (95% CI: 56-82%)

Chi *et al.* 2008 [14]	• 28 patients • ECOG: 0 or 1 • HGB ≥ 10 g/dl • Creatinine within normal limits • Creatinine clearance ≥ 60 ml/min	**Primary end point:** PSA response defined as a ≥ 50% decrease for ≥ 4 weeks **Secondary end point:** • Measurable disease responses • PFS and OS	• The PSA response rate was 3.6% • 5 patients had stable disease (among 12 with measurable disease) • Time to PSA progression was 2.1 months (95% CI 1.8-6.4) • OS was 12.25 months (95% CI 6.7-16.46)

Dahut *et al.* 2008 [15]	• 22 patients
	• ECOG: 0 to 2
	• HGB – 13.05 g/dl (10.2-15.1)
	• Creatinine < 1.5 × ULN
	• GFR > 60 ml/min/1.73 m^2
	• Life expectancy of ≥ 12 weeks
		Primary end point:
		disease progression (RECIST) or increase in PSA
		Secondary end point:
		• Overall response rate
		• Overall survival
			• No complete or partial response was noted
			• No patient had a PSA decline of > 50%
			• The median progression-free survival duration was 1.8 months:
			  – 7 patients were progression-free by PSA criteria at 4 months
			  – 9 of 14 patients who progressed at or before 4 months progressed only by PSA consensus criteria

Aragon-Ching *et al.* 2009 [16]	• 24 patients • ECOG: 0 or 1 • HGB: 12.4 g/dl (10.4-14.2)	**Primary end point:** progression by RECIST criteria **Secondary end point:** • Pharmacokinetics • Toxicity • Overall survival	• 1 patient had a partial response • 10 patients had stable disease • Median duration 18 weeks (15-48 weeks) • Median PFS was 3.7 months • Median OS was 18.0 months

Safarinejad *et al.* 2010 [17]	• 64 patients
	• ECOG 0-3
	• HGB ≥ 10 g/dl,
	• Creatinine ≤ 2 mg/dl,
	• Life expectancy > 6 months
		Primary end point:
		PSA response (50% reduction)
		Secondary end point:
		• Objective measurable disease responses
		• Overall survival (OS)
		• Time to progression (TTP)
		• Toxicity
		• Pain response
			Median OS: 14.6 months (CI: 8.2-22.2)
			Partial response:
			• 7/35 patients (20%) with measurable extraosseous disease
			• 13/64 patients (20.3%) achieved ≥ 50% reduction in PSA level after two cycles:
			  – Median response duration: 2.5 months (95% CI: 1.4-4.8),
			  – Median time to progression: 5.9 months (95% CI: 3.6-7.6)

Currently, there are published reports in the literature of phase II clinical trials where the efficacy of sorafenib treatment in advanced prostate cancer has been evaluated [13-17] (Table I). The decision to begin sorafenib treatment may be very difficult. The patient may have many coexisting diseases, and their clinical status may be very bad. Many patients would not have a chance of the treatment in these trials, because exclusion criteria were rigorous. For example, patients with significant anaemia and renal failure were not enrolled in any study; the ECOG performance status of the participants was 0 or 1.

Inclusion criteria

Patients with anaemia and renal failure were not enrolled in any study that evaluated the efficacy of sorafenib treatment. In all such studies, the ECOG performance status of the participants was 0 or 1, and their haemoglobin levels were above 10 g/dl with the exception of one study where the participants had haemoglobin levels above 9 g/dl [13].

In addition, in all studies, the patients exhibited normal renal function, as demonstrated by creatinine levels of < 1.5 × ULN or < 2 mg/dl. In two studies [14, 15], one of the inclusion criteria for the study was that the patients should have a glomerular filtration rate (GFR) > 60 ml/min/1.73 m^2.

Prostate-specific antigen (PSA) reduction

The PSA-based response to treatment has been defined in many different ways. In a study by Safarinejad et al. [17], a complete PSA response was defined as a normalisation of PSA levels to < 4 ng/ml, a partial response was defined as a ≥ 50% reduction in PSA levels, and progression was defined as a ≥ 50% increase in PSA levels when compared to baseline. In that study, none of the patients exhibited a complete response to treatment, and 13 of 64 patients (20.3%) achieved a ≥ 50% decrease in PSA levels after 2 cycles of treatment.

Moreover, PSA levels may be good indicators for a positive clinical and radiological response to sorafenib treatment. For comparison, Chi et al. [14] in their study assumed a PSA reduction of ≥ 50% as the primary end point, and the reported response rate was only 3.6%, and the secondary end point, time to progression, was only 2.1 months.

Similarly, Steinbild et al. [13] reported that only 2 of 57 patients achieved a response to treatment in terms of PSA levels, and 11 other patients achieved disease stabilisation. In another study, Dahut et al. [15] reported that PSA levels may not be a good indicator for the relationship between clinical and radiological responses to sorafenib treatment. In addition, none of the patients who participated in that study achieved a PSA reduction of > 50%, while 21 of 22 experienced disease progression and 13 exhibited increases in PSA levels. In addition, in 9 of 14 patients with progression before 4 months of treatment with sorafenib, the progression status was only determined by PSA levels.

RECIST response

In the field of oncology, assessment of cancer metastases according to the RECIST (Response Evaluation Criteria In Solid Tumors) guidelines [18] is considered the most important. These criteria allow physicians to rule out or confirm the growth of metastatic lesions in solid organs. However, this method has limitations, especially for evaluation of the efficacy of angiogenesis inhibitors such as sorafenib. Inhibition of angiogenesis causes a cytostatic effect (i.e., tumour growth inhibition) and not a cytotoxic effect (i.e., tumour regression). Some of the early results of anti-angiogenic therapy may include oedema around a tumour site. If such a result is misinterpreted, it may suggest tumour progression. Another problem in the assessment of a patient's response to treatment is the issue of whether we should only take into account the largest dimension of the tumour, which is measured on a plane. Measurement of tumour volume would be more precise. Especially, the growth of metastatic lesions in the liver should be assessed carefully.

In a study by Chi et al. [14], only 5 of 12 patients with measurable tumours achieved disease stabilisation. In another study by Steinbild et al. [13], only 4 of 57 patients achieved stabilisation according to the RECIST guidelines. Aragon-Ching et al. [14] reported that out of 24 patients, one achieved a partial response to treatment and 10 had stable disease. The best outcomes were reported in a study by Safarinejad et al. [17] where as many as 7 of 35 patients (20%) with measurable tumours exhibited partial responses to treatment.

Bone metastases and pain

It is worth noting that only one study evaluated the efficacy of sorafenib treatment in terms of pain [16]. In that study, the reduction of PSA levels correlated with pain reduction in 5 patients (7.8%) after two cycles of treatment and in 10 other patients (15.6%) after four cycles of treatment. Among these 15 patients, 8 were receiving high doses of morphine; at follow-up, 3 patients no longer required morphine treatment, and the dose of morphine was reduced by 75% in another 3 patients. The mean duration of pain reduction was 114 days (91-171 days). Our patient reported a significant reduction of pain that has been maintained for at least 8 months, which is significantly longer than previously reported.

It is worth emphasising that in the study by Chi et al. [14], the use of high-dose narcotic analgesics, such as > 30 mg/day morphine, was considered as a criterion for exclusion from the study.

Progression-free and overall survival

From the phase II clinical trials that have evaluated the efficacy of sorafenib, we conclude that hormone-refractory prostate cancer is characterised by a short progression-free survival (PFS) with rather good overall survival (OS). Steinbild et al. [13] reported that the probability of 1-year PFS in prostate cancer patients was only 13% (95% CI: 6-28%) but that the chances of surviving 1 year were as high as 68% (95% CI: 56-82%). Aragon-Ching et al. [16] reported that the median PFS in these patients was 3.7 months, and the median OS was 18 months. In contrast, Dahut et al. [15] found that median PFS was only 1.8 months. In addition, Safarinejad et al. [17] reported that the median PFS was 5.9 months (95% CI: 3.6-7.6) and the median OS was 14.6 months (95% CI: 8.2-22.2), whereas

Chi *et al.* [14] reported a PSA-based PFS of 2.1 months (95% CI: 1.8-6.4) and an OS of 12.25 months (95% CI: 6.7-16.46).

Sorafenib toxicity

Sorafenib is well tolerated by patients. The toxicity of sorafenib has only been evaluated in three phase II clinical trials [13, 16, 17]. The results of these studies show that some complications could impair the patients' quality of life. In the study conducted by Safarinejad *et al.* [17], the most common adverse events experienced by the patients were diarrhoea (40.6%), rash/desquamation (39.1%), fatigue (35.9%), hand-foot syndrome (32.8%), alopecia (31.3%) and nausea (26.6%). Hypertension only occurred in 3.1% of the patients. In the study conducted by Aragon-Ching *et al.* [16], adverse effects were reported by more than 10% of the patients. These adverse effects included hand-foot syndrome (3 grade 3 cases and 9 grade 2 cases in 24 patients), rash/desquamation (11 grade 1 cases and 3 grade 2 cases) and fatigue (12 grade 1 or 2 cases and 2 grade 3 cases). Steinbild *et al.* [13] reported that the most common adverse events experienced by the patients were skin lesions (16 of 57 patients), fatigue (13 patients), diarrhoea (10 patients) and hypertension (9 patients).

Hypertension seems to be a class effect of angiogenesis inhibitors. It is a safe complication of sorafenib treatment that can be very efficiently treated. We should remember some cardiologic drugs are cytochrome P450 inhibitors and they can significantly reduce the efficacy of sorafenib [19, 20].

Own critical observations

In everyday clinical practice there are many young men with advanced castrate-resistant prostate adenocarcinoma, who experienced progression of disease during docetaxel-based chemotherapy. Researchers and experts discuss the use of angiogenesis inhibitors in such patients. The authors observed significant positive clinical and biochemical changes related to sorafenib, this improvement being correlated with the results of the radiological examinations, which according to the RECIST guidelines indicates that the patient was cancer progression-free. At baseline, the patient had an ECOG 3 clinical condition, was diagnosed with steroid therapy-induced diabetes and stage 3 chronic kidney disease, had recurring urosepsis and a right nephrostomy, and was placed on intensive analgesic treatment. During 8 months of treatment with sorafenib, we observed a significant improvement in the patient's biochemical response; he had a 14% reduction in PSA levels after 4 weeks of treatment and a 57.35% reduction after 3 months, after which the PSA levels remained relatively constant.

At the same time, we observed a significant improvement in blood cell counts, the haemoglobin levels remained constant, and blood transfusions were no longer required. As a result of sorafenib treatment, the patient's renal function significantly improved. Therefore, the right nephrostomy was removed, and it was replaced with a double-J urethral catheter. Over the course of 8 months of treatment with sorafenib, the patient had only had one episode of urinary tract infection. The stabilisation of the metastatic lesions in his skeletal system significantly reduced his bone pain. This patient has already achieved a significantly better PFS and quality of life.

In general, remarkable results can be seen with every drug if used for a non-approved indication. If 100 patients are treated there will be 1 or 2 responding just by chance. We would like to add real knowledge to the already existing literature. Therefore we would like to perform Polish multicentre research in this area of interest. This paper would be a first step to discuss which subgroup of patients with castrate-resistant prostate cancer can achieve a real advantage from treatment with sorafenib.

Conclusions

The phase II clinical trials with sorafenib in prostate cancer did not give spectacular results. We believe that sorafenib could be one of some new options following the failure of chemotherapy in this disease. Additional well-designed studies are necessary to evaluate a subgroup of patients with prostate cancer who may experience significant improvement after sorafenib therapy.

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