RESEARCH ARTICLE

Efficacy and Toxicity of Anti-VEGF Agents in Patients with Castration-Resistant Prostate Cancer: a Meta-analysis of Prospective Clinical Studies

Wei-Xiang Qi[1], Shen Fu[1,2]*, Qing Zhang[1], Xiao-Mao Guo[1,2]

Abstract

Background: Blocking angiogenesis by targeting vascular endothelial growth factor (VEGF) signaling pathway to inhibit tumor growth has proven to be successful in treating a variety of different metastatic tumor types, including kidney, colon, ovarian, and lung cancers, but its role in castration-resistant prostate cancer (CRPC) is still unknown. We here aimed to determine the efficacy and toxicities of anti-VEGF agents in patients with CRPC. Materials and Methods: The databases of PubMed, Web of Science and abstracts presented at the American Society of Clinical Oncology up to March 31, 2014 were searched for relevant articles. Pooled estimates of the objective response rate (ORR) and prostate-specific antigen (PSA) response rate (decline ≥50%) were calculated using the Comprehensive Meta-Analysis (version 2.2.064) software. Median weighted progression-free survival (PFS) and overall survival (OS) time for anti-VEGF monotherapy and anti-VEGF-based doublets were compared by two-sided Student's t test. Results: A total of 3,841 patients from 19 prospective studies (4 randomized controlled trials and 15 prospective nonrandomized cohort studies) were included for analysis. The pooled ORR was 12.4% with a higher response rate of 26.4% (95%CI, 13.6-44.9%) for anti-VEGF-based combinations *vs.* 6.7% (95%CI, 3.5-12.7%) for anti-VEGF alone (p=0.004). Similarly, the pooled PSA response rate was 32.4% with a higher PSA response rate of 52.8% (95%CI: 40.2-65.1%) for anti-VEGF-based combinations *vs.* 7.3% (95%CI, 3.6-14.2%) for anti-VEGF alone (p<0.001). Median PFS and OS were 6.9 and 22.1 months with weighted median PFS of 5.6 *vs.* 6.9 months (p<0.001) and weighted median OS of 13.1 *vs.* 22.1 months (p<0.001) for anti-VEGF monotherapy *vs.* anti-VEGF-based doublets. Conclusions: With available evidence, this pooled analysis indicates that anti-VEGF monotherapy has a modest effect in patients with CRPC, and clinical benefits gained from anti-VEGF-based doublets appear greater than anti-VEGF monotherapy.

Keywords: VEGF inhibitors - angiogenesis inhibitors - castration-resistant prostate cancer - efficacy

Asian Pac J Cancer Prev, **15 (19)**, 8177-8182

Introduction

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males (Jemal et al, 2011). Although nearly 80% of cases are diagnosed as localized disease which could be curative by radiotherapy or surgery, there is still a relapse rate of 30-60% (Merino et al, 2011). Currently, hormonal treatment with androgen deprivation therapy is a standard approach for the majority of patients with relapsed or metastatic disease, but in most cases the duration of response is limited to 15-20 months (Eisenberger & Walsh, 1999), and the disease will become castration-resistant prostate cancer (CRPC). Although secondary hormonal manipulations (eg, corticosteroids, estrogens, and ketoconazole) can benefit a subset of these patients, this benefit is usually short-lived and until recently there is no evidence that secondary hormonal therapies could improve overall survival (OS) (Ryan & Small, 2003). Eventually, we should consider treatment with chemotherapy once hormonal treatments fail. Docetaxel and prednisone is the standard first line therapy for patients requiring chemotherapy (Berthold et al, 2008; Qi et al, 2011a). However, responses are not durable and almost all will progress, the prognosis of these patients is poor, with median survival no longer than 10 months. As a result, there is a need for identification of better or alternative treatment strategies for improving current standard treatment.

Angiogenesis, the generation of new blood vessels, is known to play a central role in the progression of CRPC (Folkman, 2002; Folkman, 2006; Weidner et al, 1993). Among the many mediators of new blood vessel formation, vascular endothelial growth factor (VEGF) family of ligands plays a primary role (Borre et al, 1998b; Ferrara & Davis-Smyth, 1997; Hicklin & Ellis, 2005). Inhibition of VEGF signaling pathway has proven an effective strategy for the treatment of several common

[1]*Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center,* [2]*Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China *For correspondence: fushen2014@sina.com*

solid tumors such as colorectal (Hurwitz et al, 2004; Van Cutsem et al, 2012; Grothey et al, 2013), liver (Abou-Alfa et al, 2006), ovarian (Perren et al, 2011), lung (Sandler et al, 2006; Qi et al, 2011b) and kidney cancer (Yang et al, 2003; Motzer et al, 2006; Motzer et al, 2013a; Motzer et al, 2013b). Additionally, a recent meta-analysis conducted by Wang K. (Wang et al, 2012) also demonstrates that high VEGF-expression in prostate cancer is a poor prognostic factor with statistical significance for OS (HR=2.32, 95%CI: 1.40-3.24), which suggests that VEGF might be a potential treatment target for prostate cancer patients. So far, several clinical trials have been conducted to evaluate the effectiveness and adverse effects (AEs) of anti-VEGF agents in patients with CRPC, and some reviews of novel VEGF-targeted therapies available for patients with CRPC have been also reported (Aragon-Ching & Dahut, 2009; ; Merino et al, 2011; Wu et al, 2011; Loblaw et al, 2013; Mukherji et al, 2013). However, to our knowledge, no meta-analysis has been carried out to estimate the pooled efficacy and safety of anti-VEGF agents administered in CRPC patients. Therefore, the current meta-analysis attempts to analyze and combine the results of these clinical trials to increase the statistical power and improve the estimates of the effects.

Materials and Methods

Literature search for identifying related studies

We conducted an independent review of citations from PubMed between January 1, 2000, and March 31, 2014. Key words were bevacizumab, avastin, aflibercept, VEGF-trap, sorafenib, nexavar, BAY43-9006, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, caprelsa, ZD6474, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, brivanib, ramucirumab, clinical trials and cancer. The search was limited to prospective clinical trials published in English. The search strategy also used text terms such as VEGF inhibitors, angiogenesis inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitors to identify relevant information. We also performed independent searches using Web of Science databases between January 1, 2000, and March 31, 2014, to ensure that no clinical trials were overlooked. Additionally, we searched the clinical trial registration website (http://www.ClinicalTrials.gov) to obtain information on the registered prospective trials. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between Jan 2004 and Jan 2014. Reference lists from relevant primary studies and review articles were also examined to find additional publications. Each publication was reviewed and in cases of duplicate publication only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Study selection

Two reviewers (W.X.Q. and S.F.) independently assess the eligibility of each article. After screening all the titles and reading the abstracts, full texts of the selected articles were reviewed to determine their eligibility for inclusion in the study. Disagreement between reviewers was resolved by consensus. Clinical trials that met the following criteria were included: (1) prospective phase II and III trials in patients with CRPC; (2) participants assigned to treatment with anti-VEGF agents (alone or in combination at any dosage or frequency); and (3) studies had to record necessary data about therapy efficacy and safety. Phase I trials were excluded because of inter study variability in drug dosing as well as the small number of patients in these trials.

Data extraction and synthesis

Two authors (W.X.Q. and S.F.) conducted the data extraction independently. It was performed according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement (Moher et al, 1999), and any types of discrepancies were resolved by consensus. The data were extracted for each trial were: first author's name, year of publication, number of enrolled patients, type and class of anti-VEGF agents, median age, objective response rate (ORR), prostate-specific antigen (PSA) response rate (decline ≥50%), median progression free survival (PFS), and median overall survival (OS). The ORR data (our primary endpoint) and PSA response rate were pooled to produce a weighted ORR and PSA response rate. We also calculated the weighted median OS and PFS for all trials. Outcome data were also pooled for the two patient subgroups (anti-VEGF monotherapy *vs*. anti-VEGF-based doublets) to generate a weighted median ORR, PSA response rate, median PFS and OS. Main toxicities were evaluated accordingly.

Statistical method

Using a random-effect model, the ORR and PSA response rate to anti-VEGF therapies (all studies and anti-VEGF monotherapy *vs*. anti-VEGF-based studies) treatment was calculated as event rate along with a 95% confidence interval. Significant heterogeneity among the studies employed for this analysis was formally assessed by Cochran's chi-square test and the I^2 index where a p value <0.1 by chi-square test and I^2 value <0.25 indicate a low degree of heterogeneity (Zintzaras & Ioannidis, 2005). ORR, PSA response rate, PFS and OS were calculated for anti-VEGF monotherapy *vs*. anti-VEGF-based doublets. Median pooled PFS and OS were summarized using descriptive statistics. Statistical differences in the weighted median ORR, PSA response rate, PFS and OS for anti-VEGF monotherapy and anti-VEGF doublets were assessed by two-sided t-tests. Publication bias for ORR analysis was assessed by Begg's funnel plot (Begg & Mazumdar, 1994) and Egger's test (Egger et al, 1997). Analyses were performed using the Comprehensive Meta-Analysis (version 2.2.064) and SPSS (version 17.0) programs. GraphPad Prism (version 5.01) was used to generate the graphs (histograms) with horizontal bars for both ORR and outcome values.

Results

Search results

Of the 648 articles retrieved, 53 were eligible after

Table 1. Baseline Characteristics of 19 Included Trials in the Meta-Analysis.

Author/year/phase	Treatment arm	Patients enrolled	Median age	Median PFS/TTP (months)	Median OS (months)	ORR, n	PSA, n response	Patients for analysis, n
Steinbild S. et al/2007/II	Sorafenib 400mg bid po	57	70	1.9	NR	0	2	57
Chi K.N. et al/2008/II	Sorafenib 400mg bid po	28	67	1.8	12.25	0	1	28
Dahut W.L. et al/2008/II	Sorafenib 400mg bid po	22	63.9	1.8	18.3	0	0	22
Aragon-Ching J.B. et al/2009/II	Sorafenib 400mg bid po	24	66	3.7	18	1	0	24
Dror Michaelson M.et al/2009/II	Sunitinib 50mg qd naïve chemotherapy	17	71	NR	NR	0	1	34
	Sunitinib 50mg qd Doc-resistant	17	65	NR	NR	1	1	
Safarinejad M.R. et al/2010/II	Sorafenib 400mg bid po	64	69	2.9	14.6	7	13	64
Sponpavde G. et al/2010/II	Sunitinib 50mg daily	36	69.5	4.52	10.2	0	4	36
Ogita S. et al/2012/II	Bev 20mg/kg	15	70	2.8	NR	NR	0	15
Dahut W.L. et al/2013/II	Cediranib 20mg qd	59	68.9	3.7	10.1	6		59
Di Lorenzo G. et al/2008/II	Bev 10mg/kg+Doc	20	66	4	9	3	11	20
Horti J./2009/II	Vandetanib 100mg qd po+ Doc+ PDN	86	67	7.8	NR	3	17	43
	Placebo +Doc +PDN		67	9.9	NR	8	29	43
Francini F. et al/2011/II	Bev 10mg/kg+Doc	43	74	NR	NR	8	27	43
Picus J. et al/2011/II	Bev10mg/kg+estramustine+Doc	79	69	8	24	23	58	79
Beardsley E.K. et al/2012/II	Sorafenib 400mg bid +bicalutamide	39	75	5.5	26.6	0	12	39
Vaishampayan U.N. et al/2014/II	Bev 10mg/kg+satraplatin	31	67	7	11.2	2	9	31
Kelly W.K. et al/2012/III	Bev 10mg/kg + Doc+ PDN	1050	68.6	9.9	22.6	259	364	524
	Placebo +Doc +PDN		69.3	7.5	21.5	187	305	526
Heath E.I. et al/2013/II	Cediranib 30mg qd +Doc +PDN	57	68	NR	NR	19	15	29
	Placebo +Doc +PDN		68	NR	NR	17	9	28
Michaelson M.D. et al/2014/III	Sunitinib +PDN	873	69	5.6	13.1	35	NR	584
	Placebo +PDN		68	4.1	11.8	6	NR	289
Tannock I.F. et al/2013/III	Aflibercept +Doc +PDN	1224	68	6.9	22.1	NR	NR	612
	Placebo +Doc +PDN		68	6.2	21.2	NR	NR	612

Abbreviations: PFS, progression-free survival; TTP, time-to-progression; ORR, objective response rate; PSA, Prostate Specific Antigen; Bev, bevacizumab; Doc, docetaxel; PDN, prednisone; NR, not reported

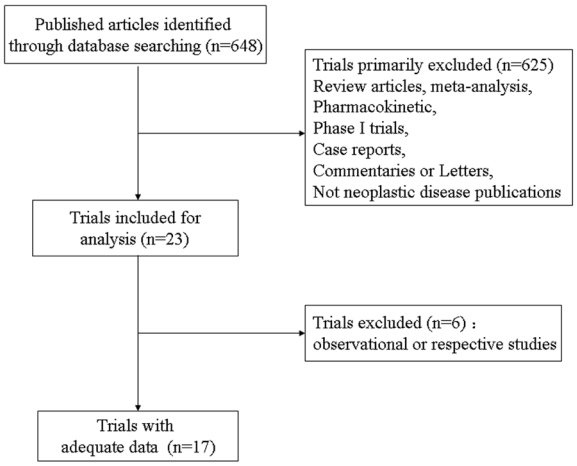

Figure 1. Selection Process for Prospective Clinical Trials Included in the Meta-Analysis

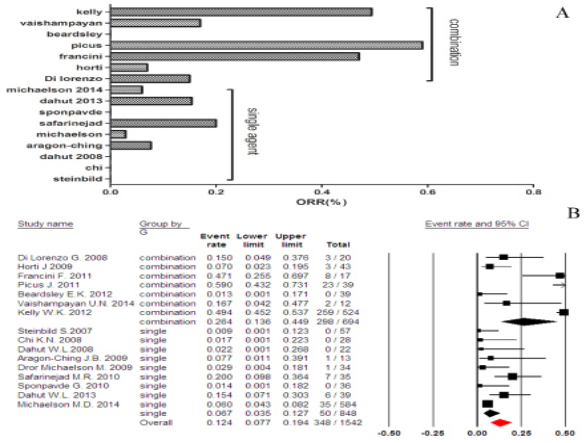

Figure 2. ORR with Anti-VEGF Agents in Patients with CRPC: (A) ORR of All Trials; (B): Pooled ORR of Included Trials

abstract selection (Figure 1). After reading the full texts and abstracts, only 19 studies were considered eligible for this systematic review (Figure 1). Overall, 16 prospective phase II trials and 3 phase III randomized controlled studies were included for this analysis with a total of 3841 patients treated with anti-VEGF agents. The number of patients per trial ranged from 15 to 1224. Details of patient demographics and study designs are included in Table 1.

Efficacy of anti-VEGF agents in CRPC

ORR, PSA response rate, PFS (or time to progression), and OS were available from 16, 16, 17 and 13 studies, respectively. Pooled ORR was 12.4% (95% CI, 7.7%-19.4%, Figure 2) with a higher response rate of 26.4% (95%CI, 13.6-44.9%) for anti-VEGF-based combinations *vs*. 6.7% (95%CI, 3.5-12.7%) for anti-VEGF alone (p=0.004). Heterogeneity was significant (I^2=94%; P<0001) and a random effect model was adopted. Similarly, the pooled PSA response rate was 32.4% with a higher PSA response rate of 52.8% (95%CI: 40.2-65.1%, Figure 3) for anti-VEGF-based combinations *vs*. 7.3% (95%CI, 3.6-14.2%) for anti-VEGF alone (p<0.001).

For PFS, the mean was 7.1 months, and the weighted median PFS was 6.9 months; standard deviation, standard error, and variance were 2.07, 0.34, and 4.29, respectively (Figure 4). When stratifying by treatment regimens, weighted median PFS was 5.6 months for anti-VEGF monotherapy in comparison with 6.9 months for anti-VEGF doublet (p<0.001). For OS, the mean was 19.4 months, and the weighted median OS was 22.1 months; standard deviation, standard error, and variance were 4.55, 0.076, and 20.7, respectively (Figure 4). Again, weighted median OS was higher for anti-VEGF doublet in comparison with anti-VEGF monotherapy (p<0.001).

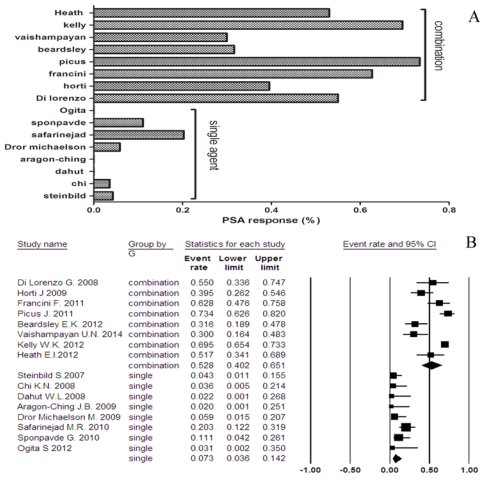

Figure 3. PSA Response with Anti-VEGF Agents in Patients with CRPC: A) PSA Response of All Trials; B): Pooled PSA Response of Included Trials

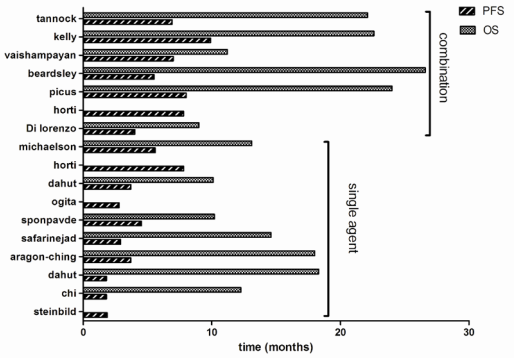

Figure 4. PFS and OS of all Trials (in Horizontal X axis Median Months of PFS and OS Duration, in Vertical Y Axis the Name of First Author)

Toxicities

The hematological and non-hematological toxicities of anti-VEGF monotherapy (grade 3-4) were analysed, where information were available. The pooled incidence of anemia, neutropenia and thrombocytopenia were 3.9% (95%CI: 2.2-6.8%), 5.0% (95%CI: 2.6-9.3%), and 4.4% (95%CI: 2.6-7.6%), respectively. Among non-hematological toxicities the most frequent was fatigue (8.2%, 95%CI: 5.3-12.4%) and hand-foot syndrome 5.2% (95%CI: 3.0-8.6%), with diarrhea, nausea, and rash being rare (<5%).

Publication bias

The Begg's funnel plot showed asymmetry for ORR (p=0.22), while evaluation of publication bias showed that Egger test was significant for ORR (p=0.033). Additionally, the Begg test showed asymmetry for PSA response rate among studies (p=0.22) and Egger test showed that this was significant for PSA response rate (p<0.001). These results indicated a potential publication bias for both ORR and PSA response rate.

Discussion

Despite multiple advanced in prostate cancer therapy, treatment options for castration-resistant prostate cancer (CRPC) remains limited. Preclinical research has established a clear pathogenic role for angiogenesis in the development, maintenance, and progression of CRPC (Gustavsson et al, 2005). And two clinical studies find that VEGF detected in the plasma and urine of patients with CRPC and metastatic prostate cancer is independently associated with decreased survival rates (Duque et al, 1999; Bok et al, 2001). Also, microvessel density has been shown to be prognostically associated with survival and metastasis in multiple studies (Borre et al, 1998a; Borre et al, 1998b). Based on these results, anti-angiogenic therapy with VEGF-targeted drugs is developed as a rational investigational target in prostate cancer. Although several comprehensive and systematic reviews of the literature on novel VEGF-targeted therapies available for patients with CRPC being reported recently (Loblaw et al, 2013; Merino et al, 2011; Mukherji et al, 2013; Wu et al, 2011), this study, to our best knowledge, is the first meta-analysis conducted to estimate the pooled efficacy and safety of anti-VEGF agents in CRPC patients.

Our study includes a total of 3,841 patients from 19 prospective studies for analysis. The pooled ORR and PSA response rate is 12.4% and 32.4%, with the weighted median PFS and OS for all trials 6.9 and 22.1 months, respectively. As there is a distinct lack of homogeneity among the trials in many respects, we perform sub-group analysis according to treatment regimens. In general, our results indicate that anti-VEGF monotherapy has modest efficacy in comparison with anti-VEGF combinations. Seven out of 10 trials that reported median OS in our systematic reported are greater than those reported in anti-VEGF monotherapy trials. This is particularly remarkable for the combination of anti-VEGF agents with bicalutamide with an overall survival reaching 20 months. However, the result of this particular study needs to be taken with caution because the PFS in study is only 5.5 months (Beardsley et al, 2012), which is shorter than the combination of anti-VEGF agents with docetaxel. Interestingly, among the seven studies of anti-VEGF doublets that reported median OS, the study by Di Lorenzo G. et al (Di Lorenzo et al, 2008) has the lowest (9 months), this might be explained that bevacizumab and docetaxel doublet is used as second-line therapy for patients with docetaxel-pretreated CRPC in that study. Additionally, the pooled objective response rate (ORR) was 26.4% in 9 out of 10 anti-VEGF combinations studies that reported ORR in our systematic review and 6.7% in 8 out of 9 anti-VEGF monotherapy studies. Similarly, the pooled PSA response rate for anti-VEGF-based combinations was higher than that of anti-VEGF monotherapy (52.8% *vs*. 7.3%, p<0.001). Taken together, these finding are encouraging, and suggest that anti-VEGF agents in combination with some agents may prove to be a preferred synergistic treatment option for CRPC.

Anti-VEGF agents are known to be associated with a number of severe toxicities (grade 3-4), including hematologic toxicities (Schutz et al, 2011a; Schutz et al, 2011b; Funakoshi et al, 2013), hand foot skin reaction (Balagula et al, 2011; Belum et al, 2013; Chu et al, 2009; Fischer et al, 2013), diarrhea (Santoni et al, 2013), rash (Jia et al, 2009), hemorrhage (Je et al, 2009; Qi et al, 2013e),

thrombosis (Scappaticci et al, 2007; Nalluri et al, 2008; Choueiri et al, 2010; Qi et al, 2013c;) and hypertension (Qi et al, 2013a; Qi et al, 2013b; Qi et al, 2013d; Qi et al, 2014). Our results show that the most frequent severe toxicities associated with anti-VEGF agents are fatigue (8.2%) and hand-foot syndrome 5.2%, with hematologic toxicities, diarrhea, nausea, and rash being rare (≤5%).

There are several limitations needed to be considered. First, some of the trials included are randomized controlled trials while the others were not. Hence, the evidence from some of these studies is not of the highest possible quality. Second, there are potentially important differences among included studies, including differing anti-VEGF agents, dosage and administration schedule of anti-VEGF agents, periods of study conduct and study investigators. All of these would increase the clinical heterogeneity among included trials, which also make the interpretation of a meta-analysis more problematic. Additionally, our study includes a mixed population of patients treated anti-VEGF agents-based combination therapy or anti-VEGF agents alone. Therefore, the treatment design is not the same in all arms, and it might be another source of heterogeneity. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects publication bias using Egger test but not for Begg test.

In conclusion, this meta-analysis indicates that anti-VEGF monotherapy has a modest effect in patients with CRPC and clinical benefits gained from anti-VEGF-based doublets appear greater than anti-VEGF monotherapy. Though the use of anti-VEGF agents in the treatment of CRPC patients is considered promising by many physicians, several large phase III trials investigating bevacizumab, aflibercept and sunitinib in patients with CRPC have produced disappointing results. As prostate cancer is a clinically and molecularly heterogeneous disease, further studies are still needed to identify subgroups of patients more likely to benefit from these targeted therapies.

References

Abou-Alfa GK, Schwartz L, Ricci S, et al (2006). Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol,* **24**, 4293-300

Aragon-Ching JB, Dahut WL (2009). VEGF inhibitors and prostate cancer therapy. *Curr Molec Pharmacol,* **2**, 161-8

Balagula Y, Wu S, Su X, Feldman DR, Lacouture ME (2011). The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: a systematic review of literature and meta-analysis. *Invest New Drugs*

Beardsley EK, Hotte SJ, North S, et al (2012). A phase II study of sorafenib in combination with bicalutamide in patients with chemotherapy-naive castration resistant prostate cancer. *Invest New Drugs*, **30**, 1652-9

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics,* **50**, 1088-101

Belum VR, Wu S, Lacouture ME (2013). Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Invest New Drugs*

Berthold DR, Pond GR, Soban F, et al (2008). Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol,* **26**, 242-5

Bok RA, Halabi S, Fei DT, et al (2001). Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: a cancer and leukemia group B study. *Cancer Res*, **61**, 2533-6

Borre M, Bentzen SM, Nerstrom B, Overgaard J (1998a). Tumor cell proliferation and survival in patients with prostate cancer followed expectantly. *J Urol,* **159**, 1609-14

Borre M, Offersen BV, Nerstrom B, Overgaard J (1998b). Microvessel density predicts survival in prostate cancer patients subjected to watchful waiting. *Br J Cancer*, **78**, 940-4

Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J (2010). Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol*, **28**, 2280-5

Chu D, Lacouture ME, Weiner E, Wu S (2009). Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. *Clin Genitourin Cancer*, **7**, 11-9

Di Lorenzo G, Figg WD, Fossa SD, et la (2008). Combination of bevacizumab and docetaxel in docetaxel-pretreated hormone-refractory prostate cancer: a phase 2 study. *Eur Urol*, **54**, 1089-94

Duque JL, Loughlin KR, Adam RM, et al (1999). Plasma levels of vascular endothelial growth factor are increased in patients with metastatic prostate cancer. *Urology*, **54**, 523-7

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629-34

Eisenberger MA, Walsh PC (1999). Early androgen deprivation for prostate cancer? *N Engl J Med*, **341**, 1837-8

Ferrara N, Davis-Smyth T (1997). The biology of vascular endothelial growth factor. *Endocrine reviews,* **18**, 4-25

Fischer A, Wu S, Ho AL, Lacouture ME (2013). The risk of hand-foot skin reaction to axitinib, a novel VEGF inhibitor: a systematic review of literature and meta-analysis. *Invest New Drugs*

Folkman J (2002). Role of angiogenesis in tumor growth and metastasis. *Seminars in oncology*, **29**, 15-8

Folkman J (2006). Angiogenesis. *Ann Rev Med*, **57**, 1-18

Funakoshi T, Latif A, Galsky MD (2013). Risk of hematologic toxicities in cancer patients treated with sunitinib: A systematic review and meta-analysis. *Cancer Treat Rev*, **39**, 818-30.

Grothey A, Van Cutsem E, Sobrero A, et al (2013). Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*, **381**, 303-12

Gustavsson H, Welen K, Damber JE (2005). Transition of an androgen-dependent human prostate cancer cell line into an androgen-independent subline is associated with increased angiogenesis. *Prostate,* **62**, 364-73

Hicklin DJ, Ellis LM (2005). Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*, **23**, 1011-27

Hurwitz H, Fehrenbacher L, Novotny W, et la (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*, **350**, 2335-42

Je Y, Schutz FA, Choueiri TK (2009). Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and

meta-analysis of clinical trials. *Lancet Oncol*, **10**, 967-74
Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin,* **61**, 69-90
Jia Y, Lacouture ME, Su X, Wu S (2009). Risk of skin rash associated with erlotinib in cancer patients: a meta-analysis. *J Support Oncol*, **7**, 211-7
Loblaw DA, Walker-Dilks C, Winquist E, Hotte SJ (2013). Systemic therapy in men with metastatic castration-resistant prostate cancer: a systematic review. *Clin Oncol*, **25**, 406-30
Merino M, Pinto A, González R, Espinosa E (2011). Antiangiogenic agents and endothelin antagonists in advanced castration resistant prostate cancer. *Eur J Cancer*, **47**, 1846-51
Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF (1999). Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet,* **354**, 1896-900
Motzer RJ, Escudier B, Tomczak P, et al (2013a). Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*, **14**, 552-62
Motzer RJ, Hutson TE, Cella D, et al (2013b). Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*, **369**, 722-31
Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD (2006). Sunitinib in patients with metastatic renal cell carcinoma. *JAMA*, **295**, 2516-24
Mukherji D, Temraz S, Wehbe D, Shamseddine A (2013). Angiogenesis and anti-angiogenic therapy in prostate cancer. *Crit Rev Oncol Hematol*, **87**, 122-31
Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S (2008). Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*, **300**, 2277-85
Perren TJ, Swart AM, Pfisterer J, et al (2011). A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med,* **365**, 2484-96
Qi WX, He AN, Shen Z, Yao Y (2013a). Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis. *Br J Clin Pharmacol*, **76**, 348-57
Qi WX, Lin F, Sun YJ, et al (2013b). Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis. *Cancer Chemother Pharmacol* , **71**, 431-9
Qi WX, Min DL, Shen Z, et al (2013c). Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and meta-analysis. *Int J Cancer*, **132**, 2967-74
Qi WX, Shen Z, Lin F, et al (2013d). Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials. *Br J Clin Pharmacol*, **75**, 919-30
Qi WX, Shen Z, Tang LN, Yao Y (2014). Risk of hypertension in cancer patients treated with aflibercept: a systematic review and meta-analysis. *Clin Drug Investig*, **34**, 231-40
Qi WX, Shen Z, Yao Y (2011a). Docetaxel-based therapy with or without estramustine as first-line chemotherapy for castration-resistant prostate cancer: a meta-analysis of four randomized controlled trials. *J Cancer Res Clin Oncol*, **137**, 1785-90
Qi WX, Tang LN, He AN, Shen Z, Yao Y (2011b). The role of vandetanib in the second-line treatment for advanced non-small-cell-lung cancer: a meta-analysis of four randomized controlled trials. *Lung,* **189**, 437-43
Qi WX, Tang LN, Sun YJ, et al (2013e). Incidence and risk of hemorrhagic events with vascular endothelial growth factor receptor tyrosine-kinase inhibitors: an up-to-date meta-analysis of 27 randomized controlled trials. *Ann Oncol*, **24**, 2943-52
Ryan CJ, Small EJ (2003). Role of secondary hormonal therapy in the management of recurrent prostate cancer. *Urology* , **62**, 87-94
Sandler A, Gray R, Perry MC, et al (2006). Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*, **355**, 2542-50
Santoni M, Conti A, De Giorgi U, et al (2013). Risk of gastrointestinal events with sorafenib, sunitinib and pazopanib in patients with solid tumors: A systematic review and meta-analysis of clinical trials. *Int J Cancer,* **135**, 763-73.
Scappaticci FA, Skillings JR, Holden SN, et al (2007). Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst,* **99**, 1232-9
Schutz FA, Jardim DL, Je Y, Choueiri TK (2011a). Haematologic toxicities associated with the addition of bevacizumab in cancer patients. *Eur J Cancer*, **47**, 1161-74
Schutz FA, Je Y, Choueiri TK (2011b). Hematologic toxicities in cancer patients treated with the multi-tyrosine kinase sorafenib: a meta-analysis of clinical trials. *Crit Rev Oncol Hematol*, **80**, 291-300
Van Cutsem E, Tabernero J, Lakomy R, et al (2012). Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*, **30**, 3499-506
Wang K, Peng HL, Li LK (2012). Prognostic value of vascular endothelial growth factor expression in patients with prostate cancer: a systematic review with meta-analysis. *Asian Pac J Cancer Prev*, **13**, 5665-9
Weidner N, Carroll PR, Flax J, Blumenfeld W, Folkman J (1993). Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol*, **143**, 401-9
Wu Y, Rosenberg JE, Taplin ME (2011). Novel agents and new therapeutics in castration-resistant prostate cancer. *Curr Opin Oncol*, **23**, 290-6
Yang JC, Haworth L, Sherry RM, et al (2003). . A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med,* **349**, 427-34
Zintzaras E, Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*, **28**, 123-37