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Haematologic toxicities associated with the addition of bevacizumab in cancer patients

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ABSTRACT

Background: Bevacizumab is currently approved for the treatment of several malignancies. Haematologic toxicities are not among the main concerns associated with bevacizumab, but they have been occasionally reported. We performed a meta-analysis to determine the incidence and risk of haematologic toxicities associated with bevacizumab.

Methods: Pubmed databases from 1966 to September 2010 were searched for studies reported, as well as American Society of Clinical Oncology meetings. Bevacizumab randomised clinical trials with adequate safety data profile were included. Statistical analyses were conducted to calculate the summary incidence, relative risk (RR) and 95% confidence intervals (CI).

Results: 15,263 patients were included. The incidence of bevacizumab-associated all-grade and high-grade haematologic toxicities were, respectively: anaemia: 18.7% and 3.9%; neutropenia: 25.0% and 18.5%; and thrombocytopenia: 13.9% and 3.4%. Febrile neutropenia incidence was 3.8%. Compared to placebo/control arms, bevacizumab was associated with a decreased risk of all-grade (RR = 0.81; 95%CI 0.68–0.96; $p = .016$) and high-grade (RR = 0.73; 95%CI 0.60–0.89; $p = .002$) anaemia, and increased risks of all-grade (RR = 1.15; 95%CI 1.01–1.30; $p = .033$) and high-grade (RR = 1.08; 95%CI 1.02–1.13; $p = .005$) neutropenia, all-grade thrombocytopenia (RR = 1.22; 95%CI 1.00–1.48; $p = .047$) and febrile neutropenia (RR = 1.31; 95%CI 1.08–1.58; $p = .006$).

Conclusions: Bevacizumab is associated with a lower risk of anaemia and increased risks of neutropenia, thrombocytopenia and febrile neutropenia.

1. Introduction

Angiogenesis represents an attractive therapeutic target for cancer patients due to its pivotal role in tumour growth and metastasis.[1,2] Because vascular endothelial growth factor (VEGF) is the dominant growth factor related to this process, clinical use of new agents to block VEGF is becoming more common. Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a humanised monoclonal antibody directed against the VEGF-ligand that became the first angiogenesis inhibitor approved for treatment of metastatic colorectal cancer in the United States due to an overall survival benefit.[3] Currently, it is also approved for treatment of advanced renal cell cancer (RCC), high-grade gliomas, metastatic non-small cell lung cancer (NSCLC) and breast cancer.[4–8]

In clinical trials, bevacizumab is administered with interferon-alpha (RCC) or with cytotoxic chemotherapy (other malignancies). Although bevacizumab has been remarkably

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well tolerated, a distinct pattern of adverse effects has emerged and it is thought to be related to the angiogenesis inhibition. The main concerns are hypertension, proteinuria, wound healing, venous and arterial thromboembolic events, gastro-intestinal perforations and more recently congestive heart failure.[9–14] Myelosuppression is a well-known toxicity associated with chemotherapy often leading to treatment delays and interruptions. However, the overall incidence of haematological toxicities associated with bevacizumab varied substantially among clinical trials, and an accurate quantification of this risk remains to be determined.

There are pre-clinical data to consider that bevacizumab may influence the risk of haematologic toxicities. Early precursors in haematopoiesis, including hemangioblast and stem cells express VEGF receptor-2 (VEGFR-2)[15,16] and disruption of this receptor in mice models resulted in an early defect in development of haematopoietic cells.[17,18] In addition, VEGF is suggested to be a negative regulator of hepatic erythropoietin (EPO) synthesis and VEGF blockade could increase EPO production and erythrocytosis.[19]

In order to address this question, we conducted an up-to-date meta-analysis of randomised clinical trials (RCTs) to evaluate the overall incidence and risk of bevacizumab-related haematologic toxicities.

2. Material and methods

2.1. Data source

An independent review of citations from PubMed from January 1966 to September 2010 was conducted. The search key words were *bevacizumab, avastin* and *randomised trials*. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences held between January 2004 and July 2010. An independent search using the citation database Web of Science (developed by the Institute for Scientific Information) also was performed to ensure that no clinical trials were missed. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. The updated manufacture's package insert from bevacizumab was also accessed to identify relevant information.[20]

2.2. Study selection

Only RCTs comparing cancer patients treated with and without bevacizumab were considered for the analysis. Trials that met the following criteria were included in our analysis: articles published in English language, randomised phase 2, phase 3 trials, patients assigned to treatment with bevacizumab in only one of the arms, similar chemotherapy or immunotherapy in both arms and adequate haematologic safety data available.

2.3. Data extraction and clinical end-points

Data extraction was conducted independently by two investigators (FABS and DLFJ) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[21] and any discrepancies between reviewers were resolved by consensus. For each study, we extracted the following information: first author's name, publication year, trial phase, underlying malignancy, number of enrolled patients, treatment arms, number of cases in each randomised arm, drug dose/schedule, and medians age, treatment duration and progression free survival.

To evaluate the haematologic toxicities we collected the number of events of the following adverse events reported in the safety profile section: anaemia, neutropenia, thrombocytopenia and febrile neutropenia. All-grade and high-grade events, according to the National Cancer Institute's common toxicity criteria (NCI-CTC) (version 2 or 3; http://ctep.cancer.gov), were included in the analysis.

2.4. Statistical analysis

For the calculation of incidence, the number of patients for each adverse event and the number of patients receiving bevacizumab were extracted from the selected clinical trials. The proportion of patients with those adverse outcomes was derived from each trial. We also calculated relative risks (RRs) and CIs of each adverse event in patients assigned to bevacizumab versus placebo/controls in the same trial. For studies reporting zero events in any arm, we applied a classic half-integer continuity correction to calculate the RR and variance.[22] We also conducted stratified analyses by the concomitant treatment (chemotherapy versus immunotherapy) and by the bevacizumab dose (2.5 mg/kg/week versus 5 mg/kg/week).

We examined heterogeneity in results across studies using the Cochrane's Q statistic, and inconsistency was quantified with the I^2 statistic $[100\% \times (Q - df)/Q]$, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[23] We considered a *P*-value of less than 0.10 as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian and Laird method that considers both within-study and between-study variations.[24]

Publication bias was evaluated through funnel plots (i.e. plots of study results against precision) and quantified by the Begg and Egger tests.[25,26] A two-tailed *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using Stata/SE version 11.0 software (Stata Corporation, College Station, Texas).

3. Results

3.1. Search results

Our search yielded a total of 222 potentially relevant studies on bevacizumab. After excluding non-randomised trials, non-English studies, trials in patients without cancer and trials without bevacizumab randomisation, a total of 59 trials were selected. We carefully screened each one of the remaining

trials and excluded an additional 36 trials for being duplicates or not reporting an adequate haematological safety profile for the purposes of the study (Fig. 1). Thus, 23 randomised trials with bevacizumab were selected for inclusion in the meta-analysis.[4,6,7,27–46]

3.2. Study quality

All included trials were randomised, with 15 trials being phase-3, and 8 phase-2. Eleven trials had a double-blind placebo-controlled arm. Fifteen trials were published in full manuscripts and eight trials were presented during the ASCO meetings. We attempted to look at differences in incidence or RR of the selected bone marrow events based on (1) the type of report (full publication versus ASCO meeting presentation), (2) the presence or not of a double-blind placebo-controlled arm and (3) the clinical trial's stage (phase-2 versus 3) for quality analyses purposes; and found no statistically significant differences ($P > .05$) (results not shown).

3.3. Patients

The baseline characteristics of each trial are presented in Table 1. A total of 15,263 patients were available for the meta-analysis (bevacizumab: 8,636; controls/placebo: 6,627). Underlying malignancies included breast cancer, RCC, NSCLC, mesothelioma, colorectal, pancreatic, gastric, prostate and ovarian cancers. According to the inclusion criteria of each trial, patients were required to have an adequate renal, hepatic and haematologic function. In all trials, randomisation

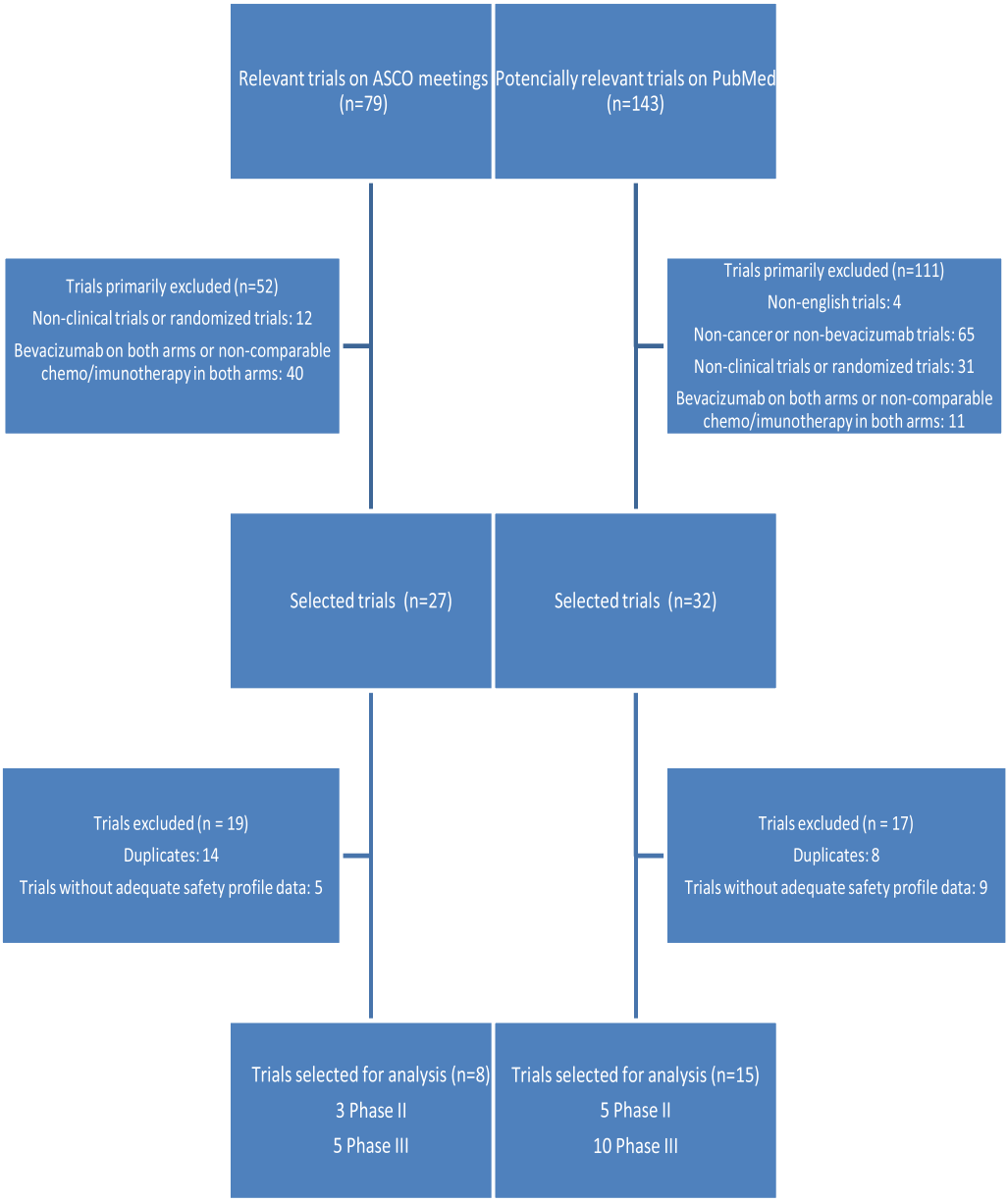


Fig. 1 – Selection process for randomised controlled trials included in the meta-analysis.

Table 1 – Characteristic of randomised-controlled trials included in the meta-analysis.

Author, year	Phase	Histology	Patients enrolled	Treatment arms	Median F/U (months)	Median age (y/o)	Median treatment duration (months)	Median progression free survival (months)	Bevacizumab dose (mg/week)
Brufsky (2010)	3	mBC	684	CT + BEV HD	NR	55	NR	7.2	5.0
				CT + Placebo		55		5.1	–
Burger (2010)	3	Ovarian cancer	1873	CP + BEV HD	17.4	60	8.4	11.2	5.0
				CP + BEV HD + BEV manteinance	17.4	60	9.8	14.1	5.0
				CP + placebo	17.4	60	7.7	10.3	–
Kang (2010)	3	Gastric cancer	774	CAP/FU + CDDP + BEV LD	NR	58	NR	6.7	2.5
				CAP/FU + CDDP		59		5.3	–
Kelly (2010)	3	Prostate cancer	1050	Docetaxel + Prednisone + BEV HD	NR	NR	NR	9.9	5.0
				Docetaxel + Prednisone + Placebo				7.5	–
Kindler (2010)	3	Pancreatic cancer	602	GEM + BEV HD	NR	63.7	4.4	3.8	5
				GEM + Placebo		65	3.9	2.9	–
Miles (2010)	3	mBC	736	Docetaxel + BEV LD	10.2[b]	54	NR	8.7	2.5
				Docetaxel + BEV HD		55		8.8	5.0
				Docetaxel + Placebo		55		8.0	–
Okines (2010)	2/3	Gastric Cancer	104	ECX + BEV LD	NR	64	2.1[a]	NR	2.5
				ECX		63	2.1[a]		–
Rini (2010)	3	RCC	732	INF + BEV HD	NR	61	6	8.5	5
				INF		62	3	5.2	
Tebbutt (2010)	3	CRC	471	CAP + BEV HD	30.8	67	7.0	8.5	5.0
				CAP		69	5.6	5.7	–
Zalcman (2010)	2/3	Mesothelioma	111	PMX + CDDP + BEV HD	6	63.5	6.3	NR	5.0
				PMX + CDDP	6	63.8	4.2		–
Allegra (2009)	3	CRC	2710	mFOLFOX6 + BEV LD	35.6[b]	41.9% (⩾60y/o)	11.5[c]	NR	2.5
				mFOLFOX6		41.7% (⩾60y/o)	6		–
Baar (2009)	2	Neoadj. BC	49	D + BEV HD	NR	48	4[d]	37.2% (60 month)	5.0
				D		46	4[d]	47.3% (60 month)	
Moehler (2009)	2	CRC	46	CAPIRI + BEV LD	17.0	60	6	12.8	2.5
				CAPIRI	19.5	66	6.75	11.4	–
Reck (2009)	3	NSCLC	1043	GC + BEV LD	NR	57	4.9	6.7	2.5
				GC + BEV HD		59	4.4	6.5	5
				GC + Placebo		59	3.5	6.1	–
Robert (2009)	3	1st line mBC	1237	CAP + BEV HD	15.6	NR	NR	8.6	5.0
				CAP + placebo	15.6			5.7	–
				Taxane + BEV HD	19.2			9.2	5.0
				Taxane + placebo	19.2			8.2	–
				Anthra + BEV HD	19.2			9.2	5.0
				Anthra + placebo	19.2			7.9	–

Van Cutsem (2009)	3	Pancreatic cancer	607	GEM + Erlotinib + BEV LD	NR	62	3.79	4.6	2.5
				GEM + Erlotinib + Placebo		61	3.54	3.6	–
Escudier (2007)	3	RCC	649	INF + BEV HD	13.3	61	9.7[c]	10.2	5
				INF + Placebo	12.8	60	5.1	5.4	–
Herbst (2007)	2	NSCLC	122	PMX or DTX + BEV HD	15.8[b]	63.5	NR	4.8	5
				PMX or DTX + Placebo		65		3.0	–
Karrison (2007)	3	Mesothelioma	106	GC + BEV HD	NR	62	5.25	6.9	5
				GC + Placebo		65	4.5	6	–
Miller (2007)	3	mBC	722	Paclitaxel + BEV HD	41.6	56	7.1	11.8	5
				Paclitaxel	43.5	55	5.1	5.9	–
Sandler (2006)	3	NSCLC	878	CP + BEV HD	19	43% (⩾65y/o)	5.25	6.4	5
				CP	19	44% (⩾65y/o)	3.75	4.5	–
Miller (2005)	2	mBC	462	CAP + BEV HD	NR	51	NR	4.86	5
				CAP		52		4.17	–
Johnson (2004)	2	NSCLC	99	CP + BEV LD/HD	NR	NR	6–7.5[c,e]	4.3–7.4[e]	2.5–5[e]
				CP			4.5	4.2	–

mBC, metastatic breast cancer; RCC, renal cell cancer; CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

BEV, bevacizumab; HD, high-dose; LD, low-dose; INF, Interferon; mFOLFOX6, modified FOLFOX6 (fluorouracil, leucovorin and oxaliplatin) regimen; GC, gemcitabine and cisplatin regimen; FOLFOX4, fluorouracil, leucovorin and oxaliplatin regimen; XELOX, capecitabine and oxaliplatin regimen; FU, fluorouracil; LV, leucovorin; IFL, irinotecan, fluorouracil and leucovorin regimen; GEM, gemcitabine; MMC, mytomicin C; PMX, pemetrexed; DTX, docetaxel; CAP, capecitabine; CP, carboplatin and paclitaxel regimen; CAPIRI, capecitabine and irinotecan regimen; CT, investigator choice of chemotherapy; CDDP, cisplatin; ECX, epirrubicin, cisplatin and capecitabine regimen.

[a] Neoadjuvant CT regimen consisted of three cycles of ECX.

[b] Median follow-up reported for the entire cohort.

[c] Median treatment duration reported only for bevacizumab and/or placebo, the chemotherapy and/or immunotherapy had other median treatment durations.

[d] Neoadjuvant chemotherapy (CT) regimen consisted of two cycles of docetaxel 35 mg/m2/week for 6 weeks, followed by a 2 week rest. Bevacizumab was administered every 2 weeks at 10 mg/kg throughout the neoadjuvant CT regimen.

[e] Number of ATE, median treatment duration and median PFS reported for the bevacizumab HD and LD combined cohorts.

Table 2 – Absolute number of all grade and high grade bone marrow toxicities for each trial.

Author, year	Treatment arms	Patients for analysis	Anaemia all grade	Anaemia Gr. ⩾3	Neutropenia all grade	Neutropenia Gr. ⩾3	Thrombocytopenia all grade	Thrombocytopenia Gr. ⩾3	Febrile neutropenia Gr. ⩾3
Brufsky (2009)	Chemotherapy[a] + BEV HD	458				81			10
	Chemotherapy[a] + Placebo	221				32			6
Burger (2010)	CP + BEV HD	607				384			30
	CP + BEV HD + BEV manteinance	608				385			26
	CP + placebo	601				347			21
Kang (2010)	CAP/FU + CDDP + BEV LD	386		39		135			19
	CAP/FU + CDDP	381		53		141			15
Kelly (2010)	Docetaxel + Prednisone + BEV HD	524				157			37
	Docetaxel + Prednisone + Placebo	526				126			21
Kindler (2010)	GEM + BEV HD	277		14		91		33	
	GEM + Placebo	263		21		76		32	
Miles (2010)	Docetaxel + BEV LD	250		1		48			38
	Docetaxel + BEV HD	247		3		49			41
	Docetaxel + Placebo	233		6		40			28
Okines (2010)	ECX + BEV LD	53			31	13	6	0	13
	ECX	51			30	14	8	1	14
Rini (2010)	INF + BEV HD	362	59	14	158	33	38	8	0
	INF	347	76	13	124	31	30	2	4
Tebbutt (2010)	CAP + BEV HD	157			19	2	24	0	4
	CAP	156			16	0	15	0	3
Zalcman (2010)	PMX + CDDP + BEV HD	47		4		14		2	1
	PMX + CDDP	47		3		19		6	1
Allegra (2009)	mFOLFOX6 + BEV LD	1326				390		19	16
	mFOLFOX6	1321				431		45	22
Baar (2009)	D + BEV HD	24		2		1			
	D	25		0		1			
Moehler (2009)	CAPIRI + BEV LD	29	4	0	5	2			
	CAPIRI	17	2	1	3	1			
Reck (2009)	GC + BEV LD	330		34		132		89	5
	GC + BEV HD	329		34		117		77	7
	GC + Placebo	327		44		104		76	4
Robert (2009)	Cape + BEV HD	404				5			0
	Cape + placebo	201				2			0
	Taxane + BEV HD	203				19			16
	Taxane + placebo	102				5			2
	Anthra + BEV HD	210				9			8
	Anthra + placebo	100				4			5
Van Cutsem (2009)	GEM + Erlotinib + BEV LD	296	80	21	86	62	89	24	
	GEM + Erlotinib + Placebo	287	95	26	75	49	75	17	

Escudier (2007)	INF + BEV HD	337	33	9	24	15	21	7	
	INF + Placebo	304	41	17	20	7	12	3	
Herbst (2007)	PMX or DTX + BEV HD	39	13	2	12	8	7	1	2
	PMX or DTX + Placebo	42	9	0	10	7	1	0	0
Karrison (2007)	GC + BEV HD	53		2		22		20	2
	GC + Placebo	55		8		22		14	1
Miller (2007)	Paclitaxel + BEV HD	365		1		0		0	3
	Paclitaxel	346		0		1		1	0
Sandler (2006)	CP + BEV HD	420		0		109		7	22
	CP	427		4		74		1	9
Miller (2005)	CAP + BEV HD	229		4				4	
	CAP	215		1				1	
Johnson (2004)	CP + BEV LD	32					2	0	
	CP + BEV HD	34					7	1	
	CP	32					5	0	

[a] Investigator choice of chemotherapy (paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, capecitabine or vinorelbine).

was between placebo/control and bevacizumab. In two studies, both in RCC, bevacizumab was combined to immunotherapy[4,5] and in the rest of the trials to cytotoxic chemotherapy. The bevacizumab dose was 2.5 or 5 mg/kg/week. The number of all-grade and high-grade events for each trial is reported in Table 2. Not all trials consistently reported the four haematologic adverse events of our interest.

3.4. Incidence of bone marrow toxicity events

Among patients receiving bevacizumab the all-grade incidence of anaemia, neutropenia and thrombocytopenia were 18.7% (95%CI, 11.7–28.5%), 25.0% (95%CI, 14.0–40.6%) and 13.9% (95%CI, 8.2–22.6%), respectively. The incidences of high-grade anaemia, neutropenia and thrombocytopenia were 3.9% (95%CI, 2.5–6.0%), 18.5% (95%CI, 13.0–25.5%) and 3.4% (95%CI, 1.6–7.3%), respectively. Febrile neutropenia was present in 3.8% (95%CI, 2.3–6.0%) of bevacizumab-treated patients. Among controls, the all-grade incidence of anaemia, neutropenia and thrombocytopenia were 20.8% (95%CI, 13.6–30.4%), 22.4% (95%CI, 12.7–36.3%) and 10.4% (95%CI, 5.4–19.0%), respectively. The incidences of high-grade anaemia, neutropenia and thrombocytopenia were 5.2% (95%CI, 3.4–7.9%), 17.2% (95%CI, 12.5–23.3%) and 3.0% (95%CI, 1.5–6.0%), respectively. Febrile neutropenia was present in 2.9% (95%CI, 1.7–4.9%) among controls. Table 3 shows the incidences of haematologic toxicities of placebo/control and bevacizumab treated patients.

3.5. Relative risk of bone marrow toxicity events

In order to access the contribution of bevacizumab on the development of haematologic toxicities, we calculated the overall relative risk (RR) for the selected all-grade and high-grade haematologic toxicities. Figs. 2 and 3 show results for the all-grade and high-grade risk of anaemia, neutropenia, thrombocytopenia and febrile neutropenia associated with bevacizumab.

Bevacizumab was associated with a significant increase in the risk of all-grade neutropenia, with RR of 1.15 (95%CI, 1.01–1.30; $p = .03$). Similarly, the risk of high grade neutropenia and febrile neutropenia were also significantly increased in bevacizumab-treated patients: RR of 1.08 (95%CI, 1.02–1.13; $p = .005$) and 1.31 (95%CI, 1.08–1.58; $p = .006$), respectively. The risk of all-grade and high-grade thrombocytopenia were 1.22 (95%CI, 1.00–1.48; $p = .047$) and 1.10 (95%CI, 0.79–1.54; $p = .58$), respectively. On the other hand, bevacizumab combination was associated with a significant decreased risk of all-grade and high-grade anaemia, with RR of 0.81 (95%CI, 0.68–0.96; $p = .02$) and 0.73 (95%CI, 0.60–0.89; $p = .002$), respectively.

3.6. Bone marrow toxicities and bevacizumab dose

We explored the relationship between the dose of bevacizumab (2.5 versus 5 mg/kg/week) and the risk of developing haematologic toxicities. Overall, similar effects were observed for patients treated with both doses, with no significant differences in RRs (all p-values >.05) (Table 4).

Table 3 – Incidence of all-grade and high-grade haematologic toxicities in patients treated with bevacizumab or placebo/control.

	No. of studies	Bevacizumab arm			Placebo/control arm		
		No. of patients			No. of patients		
		No. of events	Total	% Incidence (95%CI)	No. of events	Total	% Incidence (95%CI)
All-grade							
Anaemia	5	189	1063	18.7 (11.7–28.5)	223	997	20.8 (13.6–30.4)
Neutropenia	7	335	1273	25.0 (14.0–40.6)	278	1204	22.4 (12.7–36.3)
Thrombocytopenia	7	194	1310	13.9 (8.2–22.6)	146	1219	10.4 (5.4–19.0)
High-grade							
Anaemia	15	184	4020	3.9 (2.5–6.0)	197	3316	5.2 (3.4–7.9)
Neutropenia	21	2283	8341	18.5 (13.0–25.5)	1534	6380	17.2 (12.5–23.3)
Thrombocytopenia	15	292	4686	3.4 (1.6–7.3)	199	4220	3.0 (1.5–6.0)
Febrile neutropenia	16	300	7378	3.8 (2.3–6.0)	156	5484	2.9 (1.7–4.9)

3.7. *Risk of bone marrow toxicities and concurrent antineoplastic treatment*

We conducted stratified analysis to evaluate the risk of haematologic toxicities when bevacizumab is added to immunotherapy or chemotherapy. Regarding immunotherapy, the analysis showed an increased risk of all-grade neutropenia and reduced risk of all-grade anaemia for bevacizumab-treated patients. Considering the trials that used concomitant chemotherapy, the analysis confirmed a statistically significant effect of bevacizumab in lowering the risk of high-grade anaemia and increasing the risk of high-grade neutropenia and febrile neutropenia. Overall, no significant differences were observed when comparing the RR from trials that used immunotherapy or chemotherapy (all p-values >.05) (Table 4).

3.8. *Publication bias*

For high-grade incidence of anaemia, neutropenia and thrombocytopenia, the Egger regression asymmetry test suggested some evidence of publication bias, but this evidence was not shown in the Begg's test (p-values for bias >.05). The difference in the results obtained from the two methods may be due to a greater statistical power of the regression method.[47]

4. Discussion

To our knowledge this is the first meta-analysis focusing specifically on haematologic toxicities associated with bevacizumab. We were able to demonstrate that bevacizumab is associated with a significant increase of 15% and 8% in the risk of all-grade and high-grade neutropenia, respectively; a 31% significant increase in the risk of febrile neutropenia; and a 22% significant increase in the risk of all-grade thrombocytopenia. In addition, we also found an intriguing significant 19% and 27% decrease in the risk of all-grade and high-grade anaemia, respectively. The overall effects observed in the stratified sub-groups according to the concomitant treatment (immunotherapy versus chemotherapy) did not show any significant difference, with similar trends in lowering the risk of anaemia and increasing the risk of neutropenia and thrombocytopenia.

Unlike cytotoxic chemotherapies, the package insert of bevacizumab does not mention any specific measures on dose modifications regarding haematological toxicities. Our results have shown that the reduction of bevacizumab dose will have little effect on haematological toxicities, since there was no difference between low- and high-dose of bevacizumab.

Pre-clinical data shows that inhibition of VEGF receptor blocks haematopoietic stem cells cycling, differentiation and haematopoietic recovery after bone marrow suppression. A feedback increase in the levels of placental growth factor, a member of VEGF family, is responsible for restoring haematopoiesis following a bone marrow insult.[48,49] Recently, a study demonstrated a significant impaired repopulation of the haematopoietic compartment after treatment with cytotoxic chemotherapy in a mouse model in which VEGF receptors 1 and 2 were blocked. The risk of myelosuppression and delayed bone marrow recovery was additive when VEGF blockade was used with cytotoxic agents, such as 5-fluorouracil, carboplatin and adriamycin.[50] These findings were noted in several forms of anti-VEGF blockade, including the inhibition of the tyrosine-kinase (TK) domain of the receptor or through antibodies directed to the VEGF ligand, such as bevacizumab. Our results are consistent with these pre-clinical observations and corroborate the hypothesis that VEGF blockade *in vivo* increases the risk of myelosuppression.

We also observed a consistent effect of bevacizumab in lowering the risk of both all grade and high grade anaemia. This result might be in part explained by differences in transfusions rates and support growth factors between the arms of trials but this question was not addressed due to a lack of individual data. Compelling data suggest a protective role of VEGF inhibition in the development of anaemia. Preclinical data indicates that VEGF overexpression can impair red blood cell production mainly through GATA1 modulation.[51] VEGF blockade leads to an increase in hepatic erythropoietin (EPO) production and red blood cell content, which is not observed for the myeloid or megakaryocytic lineages.[19] Erythrocytosis after repression of VEGF pathway has been observed *in vitro*[52] and also in small series with VEGFR TK inhibitors.[53] However, the meaning of this EPO rebound production is not completely understood. The increase in EPO levels could help the target tissue to overcome vessel pruning and hypoxia related to VEGF inhibitors.[54]

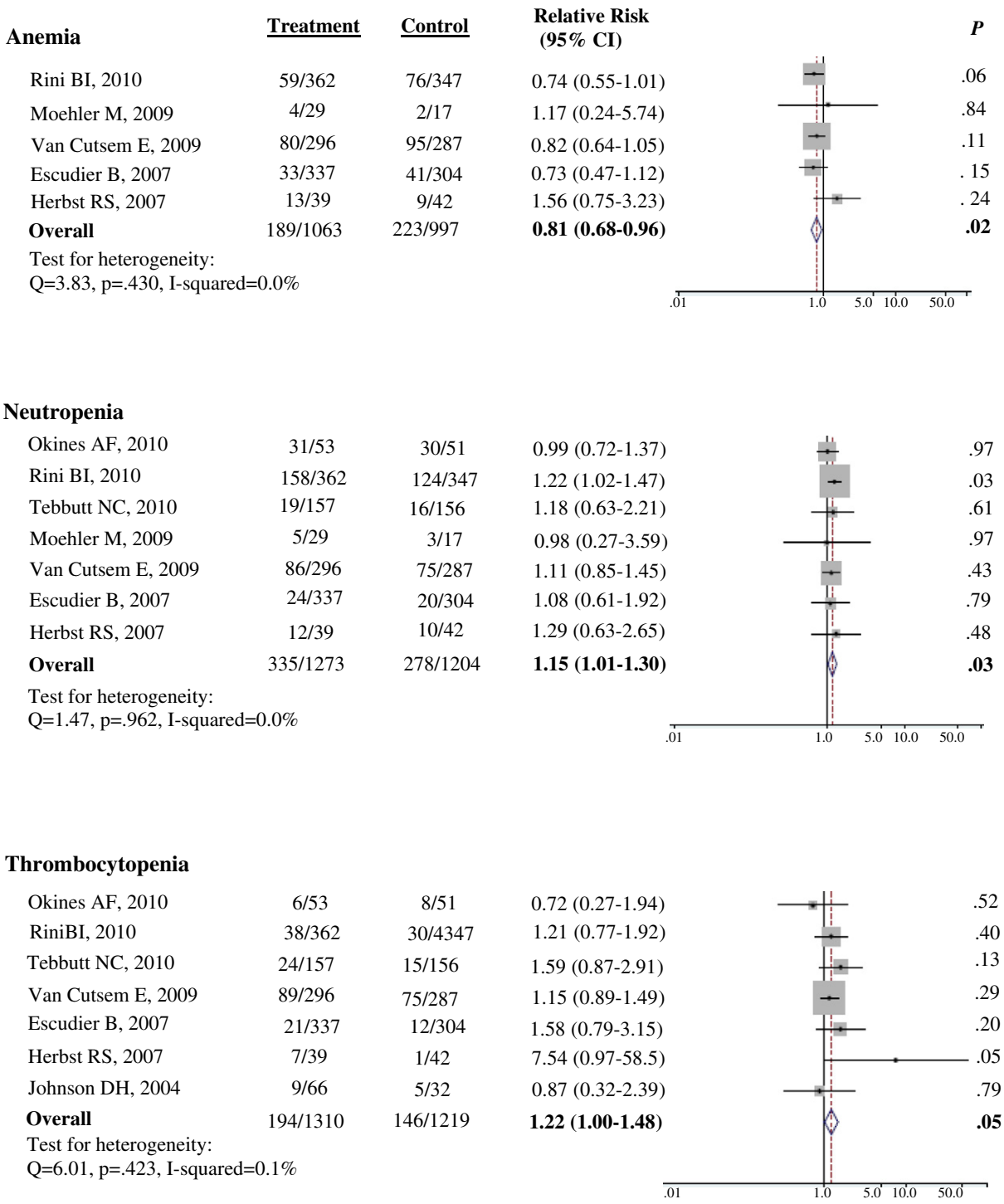


Fig. 2 – Relative risk of all-grade of bone marrow toxicity associated with bevacizumab versus control.

Furthermore, increases in plasma levels of placental growth factor (PGF) were observed during bevacizumab treatment.[55] In a previous report, PGF attenuated the interferon-induced suppression of erythroid colony formation of sickle cell patients.[56] Our results showed that there was a trend towards a lower risk of INF-induced anaemia in RCC patients receiving bevacizumab, which may be in part due to elevation in PGF levels.

Interestingly, our results are similar to the ones observed with sorafenib, a small molecule tyrosine kinase inhibitor of VEGFR. Using a meta-analysis design, sorafenib was also associated with increased risks of neutropenia and thrombocytopenia, and a decreased risk of anaemia.[57] These results corroborate our meta-analysis and support the importance of the VEGF pathway in haematopoiesis.

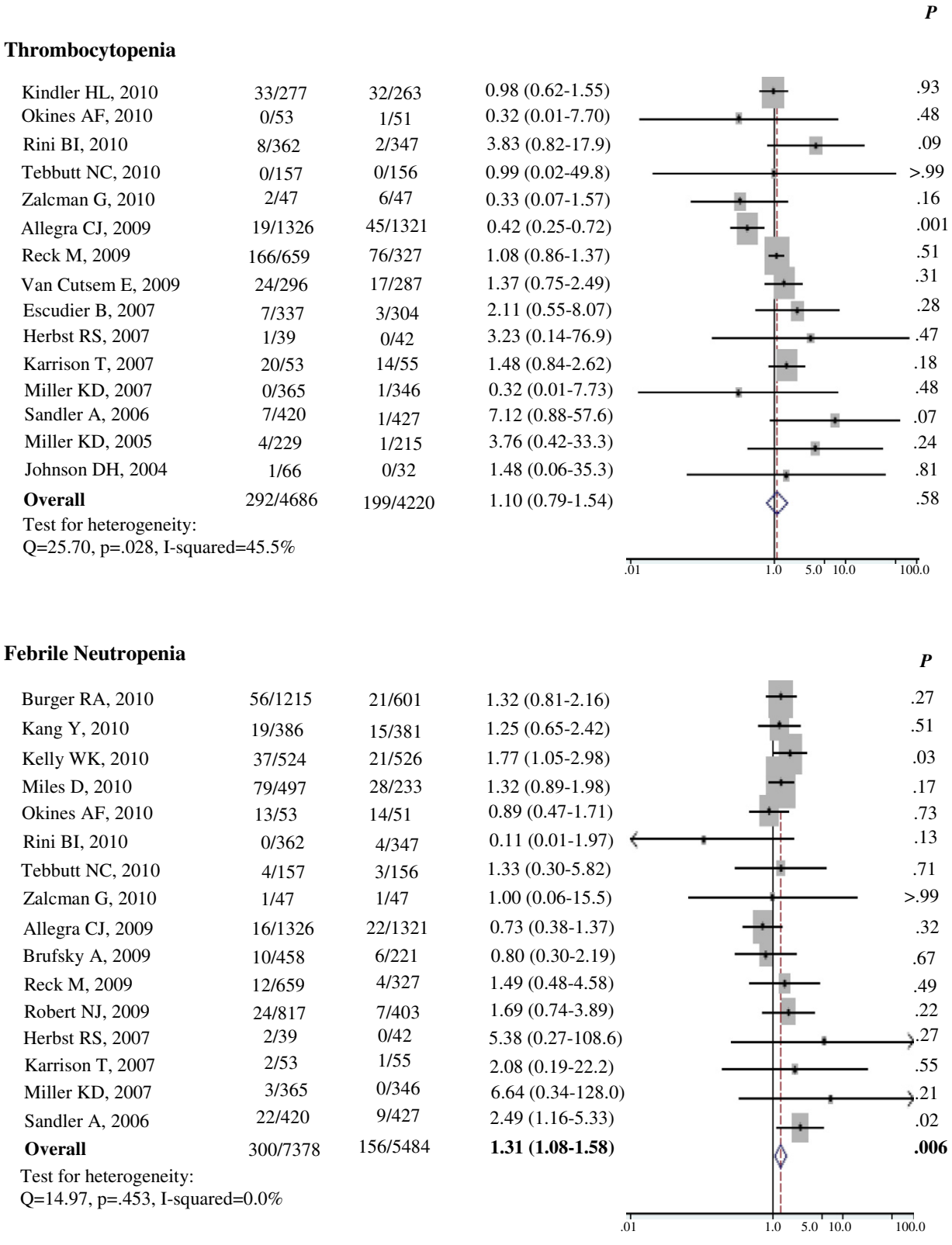
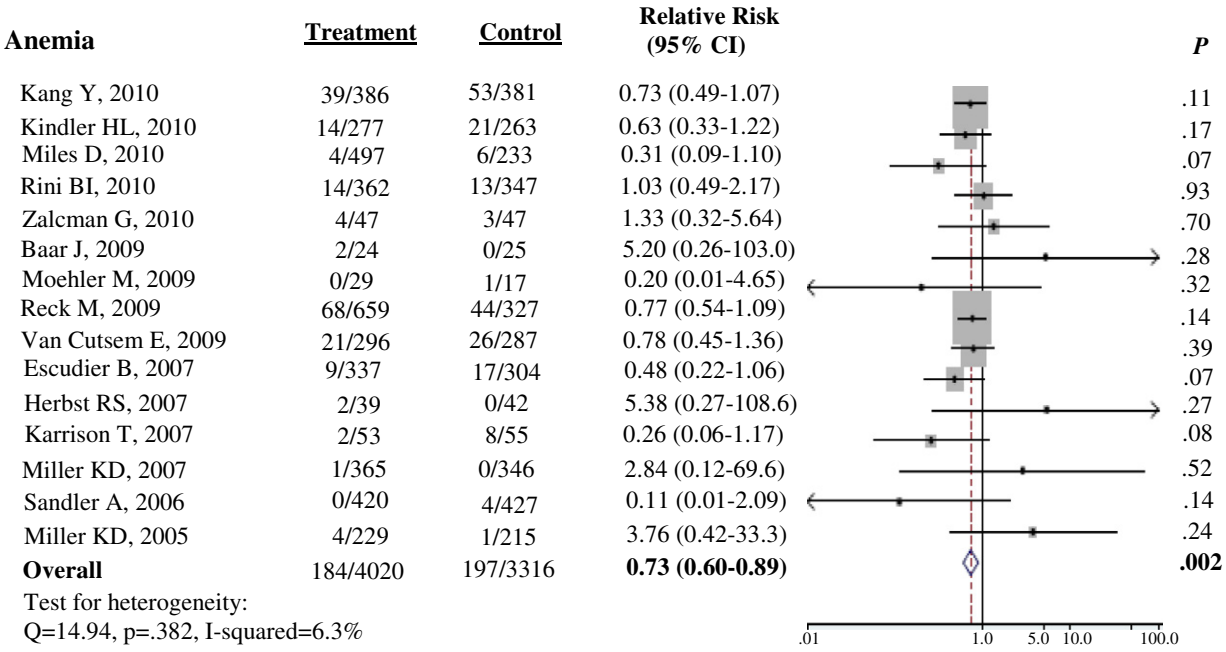


Fig. 3 – Relative risk of high-grade of bone marrow toxicity associated with bevacizumab versus control.

Despite the size of this meta-analysis, our study has limitations. First, this is a meta-analysis at study level and cofounding variables at the patient level could not be incorporated. Second, the incidence showed significant heterogeneity, and this fact may reflect the different tumour types included, the different concomitant antineoplastic agents used, and differences in sample size. Third, we were not able to define the incidence of haematologic toxicities related to bevacizumab



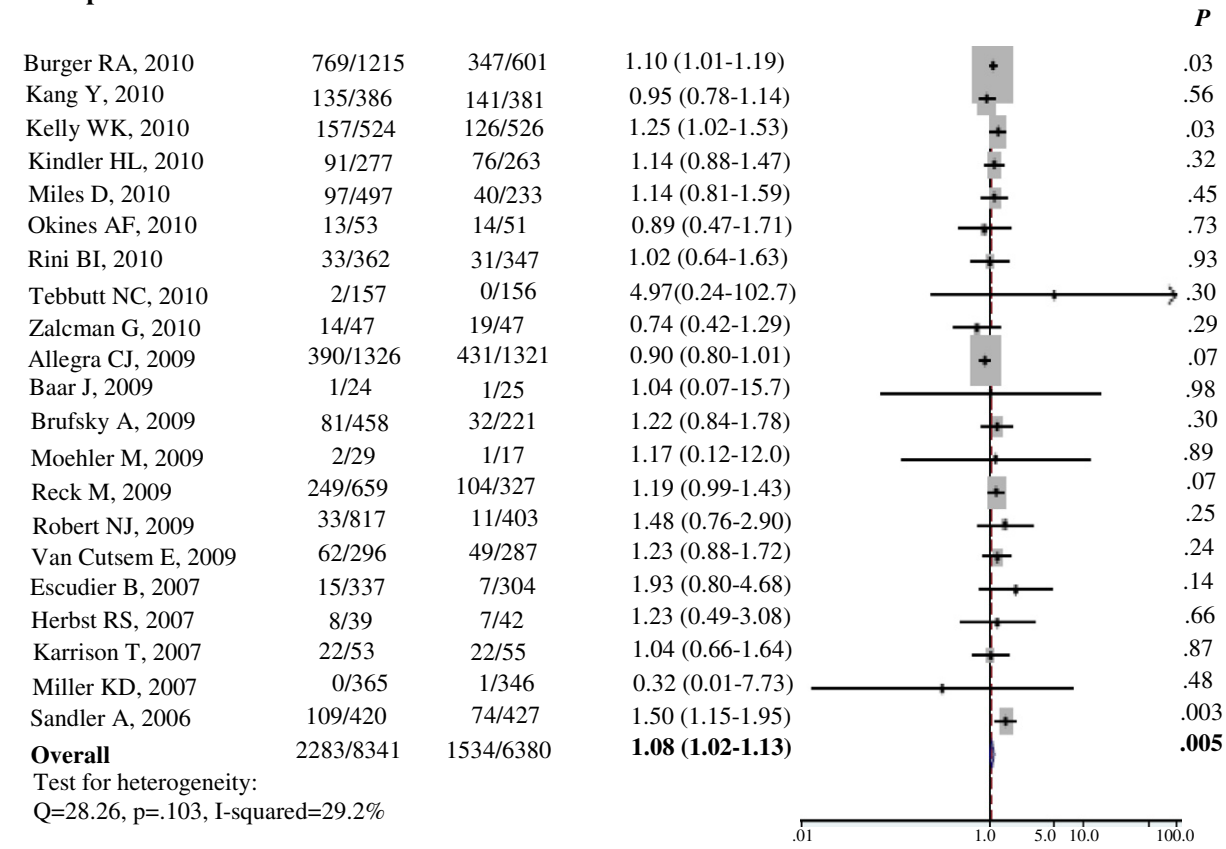


Fig 3. *(continued)*

alone and the reported incidences herein reflect the bevacizumab interaction with different agents. Fourth, we cannot determine the risk of bevacizumab-induced haematologic toxicities in different regimens due to a small number of studies available for each regimen. Fifth, we were not able to correlate our data with dose delays/interruptions or with

Table 4 – Stratified analysis according to bevacizumab dose (2.5 mg/kg/week versus 5.0 mg/kg/week) and concomitant antineoplastic therapy (immunotherapy versus chemotherapy) of all-grade and high-grade haematologic toxicities associated with bevacizumab.

			No. of studies	Bevacizumab arm No. of patients			Placebo/control arm No. of patients			RR (95%CI)	*p*-Value for difference in the RR
				No. of events	Total	% Incidence (95% CI)	No. of events	Total	% Incidence (95% CI)		
All-grade events	Anaemia	BEV low-dose	2	84	325	22.2 (11.8–37.9)	97	304	24.1 (8.6–51.7)	0.82 (0.64–1.05)	.88
		BEV high-dose	3	105	738	17.2 (9.5–28.9)	126	693	18.2 (12.5–25.9)	0.80 (0.63–1.01)	
		BEV + immunotherapy	2	92	699	12.8 (7.7–20.7)	117	651	17.4 (10.6–27.3)	0.74 (0.58–0.95)	.39
		BEV + chemotherapy	3	97	364	27.0 (22.6–31.8)	106	346	25.3 (15.1–39.1)	0.88 (0.70–1.11)	
	Neutropenia	BEV low-dose	3	122	378	34.2 (16.6–57.6)	108	355	33.8 (14.7–60.3)	1.06 (0.87–1.30)	.37
		BEV high-dose	4	213	895	19.7 (6.5–46.5)	170	849	16.2 (5.9–37.6)	1.21 (1.03–1.43)	
		BEV + immunotherapy	2	182	699	19.7 (2.4–70.3)	144	651	16.7 (2.5–60.2)	1.21 (1.01–1.44)	.45
		BEV + chemotherapy	5	153	574	27.6 (15.5–44.2)	134	553	25.2 (13.1–43.0)	1.09 (0.90–1.31)	
	Thrombocyto penia	BEV low-dose	3	97	381	15.1 (5.3–36.0)	88	370	24.1 (20.0–28.8)	1.09 (0.85–1.40)	.22
		BEV high-dose	5	97	929	12.3 (8.2–18.1)	63	881	7.6 (4.8–12.0)	1.43 (1.06–1.94)	
		BEV + immunotherapy	2	59	699	8.3 (4.9–13.6)	42	651	6.0 (2.7–12.7)	1.31 (0.90–1.92)	.69
		BEV + chemotherapy	5	135	611	17.6 (11.0–27.1)	104	568	13.9 (7.3–24.8)	1.19 (0.95–1.48)	
High-grade events	Anaemia	BEV low-dose	5	95	1291	7.3 (4.6–11.7)	130	1245	9.1 (5.7–14.1)	0.73 (0.57–0.94)	.93
		BEV high-dose	12	89	2729	3.4 (2.0–5.7)	117	2631	3.9 (2.2–6.9)	0.74 (0.57–0.97)	
		BEV + immunotherapy	2	23	699	3.4 (2.2–4.9)	30	651	4.7 (3.3–6.6)	0.72 (0.42–1.24)	.96
		BEV + chemotherapy	13	161	3321	4.1 (2.5–6.5)	167	2665	5.7 (3.8–8.5)	0.73 (0.59–0.91)	
	Neutropenia	BEV low-dose	7	782	2670	26.9 (21.4–33.2)	780	2617	26.0 (20.2–32.7)	0.99 (0.91–1.07)	.11
		BEV high-dose	16	1501	5671	16.0 (9.5–25.8)	898	4323	14.2 (8.8–22.1)	1.14 (1.07–1.21)	
		BEV + immunotherapy	2	48	699	6.5 (3.2–12.9)	38	651	4.8 (1.2–16.8)	1.17 (0.78–1.77)	.75
		BEV + chemotherapy	19	2235	7642	20.9 (15.0–28.5)	1496	5729	20.1 (14.9–26.6)	1.10 (1.01–1.19)	
	Thrombocyto penia	BEV low-dose	5	132	2037	4.4 (0.9–18.7)	139	2018	5.4 (1.6–16.9)	0.86 (0.47–1.56)	.24
		BEV high-dose	12	160	2649	3.8 (1.7–8.6)	136	2561	2.7 (1.2–6.2)	1.12 (0.91–1.38)	
		BEV + immunotherapy	2	15	699	2.2 (1.3–3.6)	5	651	0.8 (0.3–1.9)	2.73 (0.99–7.51)	.13
		BEV + chemotherapy	13	277	3987	3.8 (1.7–8.4)	194	3569	3.8 (1.9–7.8)	1.01 (0.72–1.41)	
	Febrile neutropenia	BEV low-dose	5	91	2345	5.4 (1.7–16.1)	83	2313	5.2 (1.7–5.2)	1.06 (0.80–1.41)	.08
		BEV high-dose	13	209	5033	3.6 (2.2–5.7)	105	3731	2.4 (1.4–4.0)	1.51 (1.20–1.90)	
		BEV + immunotherapy	1	0	362	0	4	347	1.2 (0.4–3.0)	0.11 (0.006–1.97)	.11
		BEV + chemotherapy	15	300	7016	4.0 (2.4–6.5)	152	5137	3.1 (1.8–5.2)	1.32 (1.09–1.60)	

haematologic support measures used. Finally, all these studies were conducted in patients with adequate organ function and blood tests were performed frequently as part of clinical protocols, so the overall incidences of haematologic toxicities from this study may be overestimated, but not the RRs.

In conclusion, our study has shown that concurrent use of bevacizumab with chemotherapy or immunotherapy is associated with a significantly increased risk of all and high grade neutropenia and neutropenic fever and all grade thrombocytopenia. Physicians and patients should be aware of these risks and frequent haematological monitoring should be emphasised when adding bevacizumab. In addition, bevacizumab-reduced risk of treatment related-anaemia suggests a protective role of VEGF inhibition during erythropoiesis and merits further studies.

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Conflict of interest statement

FABS, DLFJ and YJ: none.

TKC: Advisory board for Bayer/Onyx Pharmaceuticals, Novartis, GlaxoSmithKline, Genentech, Pfizer, Aveo and Agennix. No speaker's bureau.

Contributions of authors

Concept and design: FABS and TKC.

Search and collection of data: FABS and DLFJ.

Analysis of data and interpretation: FABS, DLFJ, YJ and TKC.

Tables and Figures: FABS, DLFJ, YJ and TKC.

Writing the manuscript and review: FABS, DLFJ, YJ and TKC.

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