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Hemorrhagic events in Hepatocellular Carcinoma patients treated with anti-angiogenic therapies

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Abstract

Background—The presence of cirrhosis increases the potential risk of hemorrhage for patients with hepatocellular carcinoma (HCC). We evaluated the relative risk for hemorrhage in patients with HCC treated with anti-angiogenic agents.

Patients and Methods—We performed a systematic review and meta-analysis of anti-angiogenic studies in HCC from 1995 to 2011. For non-randomized studies we compared bleeding risk with other HCC single-arm studies which did not include an anti-angiogenic agent. To separate disease-specific factors we also performed a comparison analysis with renal cancer studies which evaluated sorafenib.

Results—Sorafenib was associated with increased bleeding risk compared to control for all grade bleeding events (OR 1.77; 95% CI 1.04, 3.0) but not grade 3–5 events in both HCC and RCC ((OR 1.46 95% CI 0.9, 2.36 [p=0.45])). When comparing the risk of bleeding in single-arm phase 2 studies evaluating anti-angiogenic agents, this risk for all events (OR 4.34; 95% CI 2.16, 8.73) was increased compared to control.

Conclusions—This analysis of both randomized and non-randomized studies evaluating an anti-angiogenic agent in HCC showed that whilst the use of sorafenib was associated with an increased risk of bleeding in HCC, this was primarily for lower grade events and similar in magnitude to the risk encountered in RCC.

Introduction

Until recently the role of systemic therapy in the management of hepatocellular carcinoma (HCC) was minimal. This changed with the publication of the landmark SHARP study in 2008, which resulted in sorafenib becoming the standard of care option for disease that is not amenable to surgery, ablation or chemoembolization (1). While it is true that the median survival advantage in this study was 3 months, its major importance arguably lay in the momentum that it gave to the field, and in particular to the development of so-called ‘anti-angiogenic’ therapies in HCC. However, anti-angiogenic therapies carry their own particular risk profile – including bleeding, hypertension, proteinuria and thrombotic events – and this profile has been further and better defined in the time since the first major study demonstrated proof of principle for their efficacy(2).

In any HCC clinical trial the majority of patients will have underlying cirrhosis and this serves as an additional co-morbidity that must be accounted for in the eligibility criteria and

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risk assessment. It also increases the baseline risk for a patient entering a study, with a greater potential for overlap between the cirrhosis-related risk and the toxicities of the agent under study. Of particular concern is the risk of bleeding in this patient population, who frequently suffer from portal hypertension and thrombocytopenia. However, there are no standardized eligibility criteria across HCC studies – as regards for example acceptable platelet count and coagulation parameters or mandated endoscopy to detect varices – to safeguard against this added risk of bleeding while at the same time taking into account the fact that HCC patients have baseline parameters that would ordinarily be exclusionary.

We sought to investigate fully the incidence and relative risk of bleeding events in patients with HCC who have been treated with an anti-angiogenic agent, mainly sorafenib, as part of a clinical trial. Our major aim was to ascertain whether in fact the bleeding risk is increased in this patient population being treated with this class of drug. Because the majority of randomized studies in HCC have evaluated sorafenib the greater part of our analysis pertained to this drug. To separate disease-specific factors from potential drug class effect we compared the risk of bleeding in HCC studies with that of randomized studies also evaluating sorafenib in renal carcinoma. We also set out to describe the considerable heterogeneity, which exists with regard to the eligibility criteria for study entry in HCC.

Patients and Methods

Selection of studies

We performed a systematic review of published studies evaluating an anti-angiogenic agent in patients with HCC. The term ‘anti-angiogenic’ was defined as any therapy whose putative mode of action was either wholly or partly directed against the tumor vasculature. To identify relevant clinical trials we conducted a PubMed search of citations from January 1995 to December 31 2011. The search terms employed in our literature search included: ‘hepatocellular carcinoma’, ‘anti-angiogenic’, ‘sorafenib’, ‘sunitinib’, ‘bevacizumab’. For the randomized studies we used the non-treatment groups as control and for the non-randomized single-arm phase 2 studies, which accounted for the majority of the studies, we compared bleeding risk with other HCC single-arm studies not including an anti-angiogenic agent. To separate disease-specific effects we also performed a comparison analysis with renal cancer studies which evaluated sorafenib. We confined our analysis to prospective studies which have been published in manuscript form.

Data analysis

We analyzed studies that met the following criteria: phase 1, 2 or 3 trials in HCC; phase 3 studies evaluating sorafenib in RCC; participants assigned to treatment with an agent whose mechanism of action was known to be wholly or partially anti-angiogenic; adequate safety data available for bleeding events. For every study we extracted the following information: author name; year of publication; number of enrolled patients; treatment; eligibility criteria regarding platelet count, coagulation, hepatic function, Child-Pugh status; endoscopic requirements. Although we sought to evaluate cross-study variability in entry criteria we did include studies where the eligibility criteria were incomplete as this was not the primary aim of our analysis. The occurrence of hemorrhagic events of any grade was recorded. We assessed and recorded adverse events according to the National Cancer Institute’s common toxicity criteria (versions 2.0 or 3.0), which were used by all of the clinical trials.

Statistical analysis

To calculate incidence we extracted from the safety profile the number of bleeding events (all grade and grade 3–5) and the number of patients on the study. For every study we derived the proportion (and 95% confidence interval) of patients with adverse outcomes. For

studies which contained a control arm the number of events was entered for both arms and the Mantel-Haenszel method used to calculate an odds ratio and 95% confidence interval. These odds ratios were plotted in a forest plot where they were assigned a weight, based on sample size and variance, and pooled for an overall effect estimate of anti-angiogenesis therapy on bleeding events. Analysis (using the inverse variance method, alpha of 0.05) and forest plots were generated using R statistical software and Review Manager.

Results

Study demographics

To quantify the risk of hemorrhage associated with the use of anti-angiogenic agents in HCC we performed an analysis of i) randomized studies involving sorafenib in both HCC and RCC (to separate disease-specific effects) and ii) non-randomized studies in HCC involving heterogeneous anti-angiogenic therapies, which we compared with similar studies not involving anti-angiogenic therapy. The randomized studies are shown in Table 1 whilst the non-randomized studies involving both angiogenic and non-angiogenic therapies are shown in Table 2 and 3 respectively. Six randomized studies involving a total of N= 2464 patients and which compared sorafenib to control in HCC and RCC were identified. Of the HCC patients, fifty percent were enrolled in either the SHARP study or the Asia-Pacific study. Among the included set of HCC single arm studies, there were 19 treated with anti-angiogenic therapy and 21 treated with non-anti-angiogenic therapy. Eleven of the studies involved sorafenib, four employed bevacizumab and three studies evaluated sunitinib. The remaining studies involved other agents which are reported to have anti-angiogenic effects (brivanib, lenalidomide, TSU68, Linifanib, ramcirumab).

Eligibility criteria

There was marked variability across all the studies with regard to the stated laboratory eligibility criteria for entry onto the study. As illustrated in Table 2, the required platelet count ranged from 40 to 150 and INR from 1 to 2.3. The two largest studies, the SHARP and AP studies, allowed for a platelet count of greater than or equal to 60,000. Six of the studies restricted entry to Childs-Pugh A patients only. No study was identified which mandated endoscopy to exclude patients with varices. However, after the occurrence of gastrointestinal hemorrhage in the course of two studies (3, 4) (in one case, a fatal variceal hemorrhage), the protocol was amended to require screening endoscopy prior to inclusion in the study in patients with any evidence of portal hypertension. Patients found to have esophageal varices on screening examination were eligible for the study following adequate treatment with banding or sclerotherapy and repeat endoscopy showing the varices to be obliterated, minimal, or grade 1.

Effect of Sorafenib on odds of bleeding event as compared to control in HCC randomized studies

There were four HCC randomized studies involving Sorafenib. The forest plot in figure 1A visually depicts the pooled overall estimate of the effect of Sorafenib on all bleeding events within HCC randomized studies. The number of events for the Sorafenib arm was 48/722 (6.65%) and was 22/653 (3.37%) for the control arm, giving an odds ratio of 1.77 (95% CI 1.04, 3.0) for both the fixed and random effects models. This result provides evidence of a significant ($p=0.04$) increase in the odds of bleeding events (all grades) with Sorafenib compared to control. Figure 1B visually depicts the pooled overall estimate of the effect of Sorafenib on grades 3–5 bleeding events within HCC randomized studies. The number of events for the Sorafenib arm was 33/722 (4.57%) and 13/653 (1.99%) for the control arm, giving an odds ratio (95% CI) of 1.76 (0.91, 3.41) for both the fixed and random effects

models. This result provides evidence that Sorafenib did not significantly increase ($p=0.11$) the odds of bleeding events (grades 3–5) as compared to a non-anti-angiogenic control.

Odds Ratios for bleeding event between anti-angiogenic and non- anti-angiogenic single arm studies in HCC

To examine the risk of bleeding event in anti-angiogenic therapy compared to non-anti-angiogenic therapy among single arm studies in HCC, 19 studies incorporating anti-angiogenic therapy and 21-with non-anti-angiogenic therapy (Table 2 and Table 3) were analyzed. Figure 2 shows that, among single arm HCC studies, the odds ratio for any bleeding event with anti-angiogenic therapy is 4.34 (2.16, 8.73; $p<.0001$). The odds ratio of bleeding event grades 3–5 for anti-angiogenic therapy are 2.66 (95% CI 1.03, 6.82; $p=.0425$). This suggests that anti-angiogenic therapy significantly increases the odds of bleeding events (both all grades and grades 3–5) as compared to non-anti-angiogenic therapy in single arm HCC studies.

Effect of Sorafenib on odds of bleeding event as compared to control in renal cell cancer (RCC) and HCC randomized studies

In order to determine if the observed trend towards increased hemorrhagic risk was inherent to HCC or was a class effect we examined the effect of Sorafenib on bleeding events in RCC. Among the RCC randomized studies, treatment with Sorafenib significantly increased the odds of any bleeding event, (OR 1.92; 95% CI 1.30, 2.85) compared to control. The test for subgroup differences showed the effect of Sorafenib on any bleeding event to be similar between the HCC and RCC subgroups [$p=0.75$]. Similar to the HCC result, treatment with Sorafenib did not significantly increase the odds of bleeding events grades 3–5 (OR 1.18 95% CI 0.58 to 2.38) among the RCC randomized studies. The overall pooled estimate of HCC and RCC studies also indicates a non-significant effect of Sorafenib on bleeding events grades 3–5 (OR 1.43 95% CI 0.88, 2.32) which was similar for both HCC and RCC subgroups [$p=0.45$].

Discussion

Worldwide, HCC is the fifth most common malignancy with a median survival of 6–9 months(5). In the United States the incidence of HCC continues to rise, a trend which will likely result in more clinical trials being performed in this disease(6, 7). In addition, after decades of negative studies in HCC the SHARP and AP studies provided an impetus for the investigation of ‘anti-angiogenic’ strategies in HCC in an effort to bolster the relatively small gains made with sorafenib. We have learned however from the experience in other tumor types that anti-VEGF therapies are associated with class toxicities, including bleeding. In one meta-analysis of bevacizumab-related toxicities hemorrhagic events accounted for almost one quarter of the fatal adverse events seen(8). In HCC this is a particular concern because of the almost invariable presence of cirrhosis in this patient population, placing them at an elevated baseline risk of hemorrhage. The main purpose of this analysis was to determine if there was an increased risk of bleeding for a patient with HCC taking part in a study evaluating an anti-angiogenic therapy. For comparison we also performed an analysis of studies evaluating sorafenib in renal cancer. Both analyses show that whilst the use of sorafenib was associated with an increased risk of bleeding in HCC, this was primarily for lower grade events and similar in magnitude to the risk encountered in RCC. Whilst the nature of these low-grade events for the most part were not characterized, they were defined as grade 1 or 2, meaning that by Common Terminology Criteria for Adverse Events (CTCAE) definition they did not require transfusion or endoscopic

intervention. We also set out to describe the heterogeneity with regard to the eligibility criteria employed across HCC trials for study entry as these are reflective of baseline risk and are non-standardized in HCC compared to other solid tumors.

A major drawback of this analysis is the fact that only four of the HCC studies contained a control arm. When we confined our analysis to randomized studies – all of which involved sorafenib – there was a significant ($p=0.04$) increase in the odds of bleeding events of (OR 1.73; 95% CI 1.02, 2.94) associated with Sorafenib compared to control, although this increased risk appeared to be confined to lower grade events. To ascertain whether this was a disease-specific effect we also analyzed the hemorrhagic risk in studies evaluating sorafenib in RCC and found the risk to be similarly increased (OR 1.92; 95% CI 1.30, 2.85) suggesting that this is not necessarily greater in HCC patients beyond the effect of the drug itself. Given that the majority of studies evaluating an anti-angiogenic agent in HCC are single-arm, non-randomized phase 2 trials it is very difficult to estimate the overall bleeding risk in these studies, especially given the heterogeneity of treatments administered. To address this, at least partially, we performed a comparative analysis with a group of single-arm phase 2 studies which did not include therapy considered to be anti-angiogenic. We acknowledge the limitations of this approach, and certainly one cannot draw conclusions on causal effects from these uncontrolled studies evaluating heterogeneous agents. Since our outcome is one of safety however, we felt that the phase II single arm studies could provide valid additional data. The results were instructive in that patients with HCC taking part in these studies appeared to have a significantly increased the risk of all-grade bleeding compared to non-anti-angiogenic therapy. It must be emphasized however that sorafenib is the only approved agent for HCC. From a biological standpoint although we do not know whether the benefit of sorafenib is predominantly related to its signal transduction inhibition versus its anti-angiogenic properties it seems likely – by association rather than direct proof – that the hemorrhagic risk is related to its anti-VEGF effect(9, 10). It is known that VEGF has an important role in the maintenance of architectural integrity within the endothelial cells of the microvasculature, inhibition of which may induce the increased risk of bleeding.

A related aim of our analysis was also to describe the variability in eligibility criteria used across studies with regard to both laboratory criteria – which are necessarily different from studies in other diseases – and the requirements with regard to allowing for, or out-ruling, known or suspected varices. This is an important practical consideration as we attempt to improve the quality of studies in HCC and minimize risk. None of the studies mandated an upper endoscopy be performed in order to screen for the presence of varices, although two studies did introduce this after the occurrence of a serious hemorrhage. The risk of variceal hemorrhage in patients with cirrhosis is difficult to quantify but has been reported to be as high as 40%(11). In the context of HCC the short to medium-term risk is particularly important to assess given that in the SHARP study the median duration of sorafenib treatment was 5.3 months and the median overall survival for these patients was 10.7 months. The presence of even small varices is a marker of increased bleeding risk as shown by one prospective study where (12) the two-year risk of bleeding was found to be significantly higher in patients with small varices at enrollment compared to those who did not have any varices (12% v 2%). Several factors have been employed to predict the risk of variceal hemorrhage, including the size and location of varices (gastric fundus varices of higher risk(13)), their physical appearance and variceal pressure as measured by endoscopic gauge (14). The NIEC study established a prognostic index - depending on size, presence of red wale marks and Child class - which quantified one-year bleeding risk, a relevant time point for a patient with a diagnosis of advanced HCC(15). According to that study there are "high risk" small varices (those that occur in Child C patients or have red wale marks) that may have the same risk of bleeding than a Child A patient with large varices (and prophylaxis is recommended in these patients). Limiting eligibility in HCC studies to Childs

A patients – as recommended by the American Association for the Study of Liver Diseases (AASLD)(16) – would mitigate some of this risk, but – also consistent with current AASLD guidelines(17) – Child A patients should undergo screening endoscopy unless they have had one in the last 2–3 years (with no varices demonstrated) or last 1–2 years (if small varices had been identified). Five of the studies we reviewed – including both the SHARP and AP studies – were confined to patients with Childs-Pugh grade A cirrhosis. Perhaps the most specific indicator of risk for variceal bleeding is the prior occurrence of a hemorrhagic event with the risk of a subsequent bleeding episode estimated to be 17–40%(18) but also, in older analyses, as high as 70%(19). Seven of the studies in our analysis excluded patients with a history of active bleeding, although the duration of this was variable, ranging from 30 days to 1 year. Given that there are effective therapies to prevent first variceal hemorrhage and also recurrent hemorrhage, patients enrolled in these studies should be screened and treated accordingly, with eligibility being confirmed on subsequent endoscopy – as in the study by Thomas et al. – if the varices are found to be ‘obliterated, minimal, or grade 1.’

While the risk of hemorrhagic event in studies evaluating an anti-angiogenic agent in HCC appears to be not significantly raised for serious (grade 3–5) events, there are no standardized across-study eligibility criteria for this ‘at risk’ population in terms of platelet count, prothrombin time or endoscopic requirements. The eligibility criteria for HCC studies tend to be different from other settings to allow for the hepatic dysfunction that is generally present. For example, the SHARP study required a platelet count of greater than 60,000. Future studies will need to address this issue in more detail, particularly when multiple vascular targeting agents are combined.

In summary, this analysis of both randomized and non-randomized studies evaluating an anti-angiogenic agent in HCC showed that whilst the use of sorafenib was associated with an increased risk of bleeding in HCC, this was primarily for lower grade events and similar in magnitude to the risk encountered in RCC.

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Figure 1.

A: Overall hemorrhagic risk for randomized HCC studies. The forest plot visually depicts the pooled overall estimate of the effect of Sorafenib on all-grade bleeding events within HCC randomized studies.

B: Grade 3–5 bleeding events for HCC studies containing control arm. The forest plot visually depicts the pooled overall estimate of the effect of Sorafenib on grade 3–5 bleeding events within HCC randomized studies.

Figure 2.

Effect of anti-angiogenic therapy on hemorrhagic risk in single arm HCC studies. Using a logistic regression to model the odds of any bleeding event the forest plot below indicates the odds ratio of all grade and grade 3–5 bleeding event for antiangiogenic therapy compared to non-antiangiogenic therapy among single arm HCC studies. This estimate is significant as the 95% confidence interval excludes 1 ($p < .0001$).

Figure 3.

A: Overall pooled effect estimate of all bleeding events in the HCC subgroup and RCC subgroup combined. To examine the effect of Sorafenib on bleeding events in RCC and to compare it with the effect in HCC, data was analyzed for all grade bleeding events with HCC and RCC as distinct subgroups. Individual study level effects, pooled subgroup estimates (within each cancer type) and the overall effect were determined and plotted for the RCC subgroup along with results from the tests for subgroup differences which compare the effect of Sorafenib in HCC with the effect of Sorafenib in RCC.

B: Overall pooled effect estimate of bleeding events grades 3–5 in the HCC subgroup and RCC subgroup combined. To examine the effect of Sorafenib on bleeding events in RCC and to compare it with the effect in HCC, data was analyzed for grade 3–5 bleeding events with HCC and RCC as distinct subgroups. Individual study level effects, pooled subgroup estimates (within each cancer type) and the overall effect were determined and plotted for the RCC subgroup along with results from the tests for subgroup differences which compare the effect of Sorafenib in HCC with the effect of Sorafenib in RCC.

Table 1

Randomized sorafenib studies in RCC and HCC

Author	Year	Cancer	Interventions	ID	Study
Abou-Alfa(20)	2010	HCC	Sorafenib+Doxorubicin vs. Placebo+Doxorubicin	NCT00108953	A Randomized Controlled Study of BAY43-9006 in Combination With Doxorubicin Versus Doxorubicin in Patients With Advanced Hepatocellular Carcinoma.
Cheng (21)	2010	HCC	Sorafenib vs. Placebo	NCT00492752	A Randomized, Double-blinded, Placebo-controlled Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma.
Escudier (22)	2007	RCC	Sorafenib vs. Placebo	NCT00073307	Phase III randomized, double-blind, placebo-controlled trial of sorafenib in patients with advanced clear-cell renal cell carcinoma (RCC).
Escudier (23)	2009	RCC	Sorafenib vs. Interferon	NCT00117637	A Randomised, Open-label, Multi-centre Phase II Study of BAY43-9006 (Sorafenib) Versus Standard Treatment With Interferon Alpha-2a in Patients With Unresectable and/or Metastatic Renal Cell Carcinoma
Kudo (24)	2011	HCC	Sorafenib vs. Placebo	NCT00494299	Phase III Study of BAY43-9006 in Patients With Advanced Hepatocellular Carcinoma (HCC) Treated After Transcatheter Arterial Chemoembolization (TACE).
Llovet(1)	2008	HCC	Sorafenib vs. Placebo	NCT00105443	A Phase III Randomized, Placebo-controlled Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma.

Table 2

Eligibility criteria and bleeding experience in HCC studies involving anti-angiogenic therapy.

Study	Therapy	N	Eligibility Criteria				Prior bleeding or anticoagulation restriction	Bleeding experience	Endoscopy
			Child-Pugh (CP) status/ liver function or ALT/AST	Platelet	INR				
Llovet et al. (1)	Sorafenib v Placebo	602	CP A albumin, 3 2.8 bilirubin, 3 ALT/AST 5× ULN ²	>60	<2.3	No stated restriction	Sorafenib v placebo: 9% v 13% serious hemorrhagic event; 2% v 4% variceal bleeding; 0% v 2% peritoneal hem; 1% v 2% upper GI hem	-	
Abou-alfa et al. (20)	Sorafenib + doxorubicin v doxorubicin	96	CP A bilirubin 3 mg/dL; ALT/ AST 5 × ULN	>75	NS ¹	No stated restriction	doxorubicin-sorafenib v doxorubicin 19.1% v 10.2% any-grade. N=2 G3/ 4 GI bleeding in the doxorubicin-sorafenib group.	-	
AP study (21)	Sorafenib v Placebo	271	CP A albumin 28 g/L; total bilirubin 51.3 μmol/L; ALT 5 × ULN	>60	<2.3	Bleeding in previous 30 days excluded.	4(2.7%) v 3(4%) upper GI hemorrhage– all G1 or G2. No G3/4 hemorrhage	-	
Abou-alfa et al. (25)	Sorafenib	137	CP A/B 72%/ 28%; minimal other details given;	NS	NS	No comment on ex criteria re: varices or bleeding.	1 death from intracranial hemorrhage No other bleeding events reported	-	
Siegel et al. (3)	Bevacizumab	46	CP A/ compensated B, bilirubin .3 mg/dL; albumin 2.5	>75	<1.5	Excluded anticoagulation or antiplatelet tx	Major bleeding in 11% ie G3/4. Protocol amended after 1 st bleed. There was also one G 4 hemoperitoneum, and one G3 intraumoral hemorrhage.	If prior varices or evidence of varices on CT/MRI	
Thomas et al.(4)	Bevacizumab + erlotinib	40	CP A/B; PT 3s above institutional norm; albumin 2.5 Bili 2gm/dL ALT 5 × ULN	>40	3s above ULN	no active GI bleeding in previous 3months	72% G1/2 pulmonary hemorrhage, nose bleeds. No G3/4. 17.5% G1/2 GI bleeding and 12.5% G3/4/5 bleeding.	Pillcam in patients with any evidence of portal hypertension.	
Koeberle et al. (26)	Sunitinib	45	CP A/B; Bili 2gm/dL ALT 7 × ULN No	>75	NS	no documented variceal bleeding in last 3months	3 patients with variceal bleed.	-	

Study	Therapy	N	Eligibility Criteria				Prior bleeding or anticoagulation restriction	Bleeding experience	Endoscopy
			Child-Pugh (CP) status/ liver function or ALT/AST	Platelet	INR				
			ascites of any grade.						
Dufour et al. (27)	Sorafenib + TACE	14	CP A/B ALT, AST 5 × ULN	>60	INR 1.5	No anticoagulation	None reported	-	
Kanai et al. (28)	TSU68	35	CP A/B; bilirubin 2.5 mg/dl; AST and ALT 200U/l; albumin 3 g/dl	>75	PT >40s	Need for ligation/sclerotherapy excluded.	No bleeding events reported.	-	
Zhu et al. (29)	Sunitinib	34	CLIP 3	NS	NS	'history of bleeding'.	2(6%) G3 upper GI bleeding. 6(18%) G 1/2 epistaxis.	-	
Faivre et al. (30)	Sunitinib	37	CP A/B bilirubin <1.25 ULN ALT/AST 2.5×ULN	NS	-	grade-3 haemorrhage less than 4 weeks before	N=3 G3/4 bleeding: epistaxis, bleeding ascites, varices. N=1 G5 variceal bleed.	-	
Zhu et al. (31)	Gemcitabine/oxaliplatin/bevacizumab	33	CLIP 3; Bili 3mg/dL AST ×7 ULN	>75	NS	'history of active bleeding' excluded.	N=2 esophageal variceal bleed. N=2 G3 epistaxis, hematochezia	-	
Hsu et al. (32)	Bevacizumab + capecitabine	45	CP A, Bili 1.2mg/dL ALT ×5 ULN	>150	NS	NS	n=4 (9%) GI bleeding (including three patients with oesophageal variceal bleeding)	history of GI bleeding <1 yr or known varices required to undergo EGD.	
Funuse et al. (33)	Sorafenib (phase I)	27	CP A/B Bili 3mg/dL AST/ALT ×5 ULN	>75	PT/APTT ×1.5uln	NS	No bleeding events reported	-	
Worns et al. (34)	Sorafenib in consecutive patients.	34	CP A/B/C. Advanced population with 12%C and 44%B	NS	NS	NS	2 variceal hemorrhages	-	
Yau et al. (35)	PTK787 (VEGF tki) + doxorubicin	30	CP A/B, bili< ×2ULN, AST/ALT <<5uln.	>100	NS	NS	2 bleeding complications: 1 death from GI bleed and 1 cerebellar bleed.	-	
Santoro et al. (36)	NGR-hTNF	27	CP A/B bilirubin <2-fold ULN, AST/ALT<3-fold ULN	>100	NS	NS	1G1 esophageal variceal hemorrhage, 1G2 hemoptysis	-	

Study	Therapy	N	Eligibility Criteria			Prior bleeding or anticoagulation restriction	Bleeding experience	Endoscopy
			Child-Pugh (CP) status/liver function or ALT/AST	Platelet	INR			
Hsu et al. (37)	Sorafenib + tegafur/uracil	53	CP A AST/ALT <5 ULN, albumin 2.8 g/dl, bilirubin 3 mg/dl	100	INR 2.3	GI bleeding <30 days prior.	N=4 G3/4 GI bleeding (3=esophageal varices, 1=gastric ulcer).	-
Prete et al. (38)	Sorafenib + octreotide	50	Child-Pugh A/B, bilirubin 3 mg/dl, albumin 2.5	60	NS	History of active bleeding excluded	N=3 (6%) G1 bleeding, not specified.	If clinically indicated.
Yau et al. (39)	sorafenib	51	Minimal eligibility Advanced Hep B population	NS	NS	NS	N=3 hemorrhage; (1 epistaxis, 2 upper GI)	-
Richly et al. (40)	Sorafenib + doxorubicin	18	CP status NS bilirubin <1.5 × ULN; ALT/AST 2.5 × ULN	100	PT 1.5 × ULN	NS	N=1 G3 hemorrhage, not specified, 'associated with surgery'	-
Cappa et al. (41)	Thalidomide, megace, IL-2	9	A/B/C Bilirubin 5mg/dl	NS	NS	NS	No bleeding events	-
Petrini et al.(42)	Sorafenib + 5FU	39	Child-Pugh A/B			clinically significant gastrointestinal bleeding within 1 month from the enrollment were not eligible		

Table 3

Single-arm 'non-anti-angiogenic' studies in HCC

Author	cancer	Therapy	Outcome (m)	N
Sanoff(43)	HCC	Cap/Ox/Cetux	3.3 PFS	29
Alberts(44)	HCC	Gem/docetaxel	2.7 PFS	25
O'Neil(45)	HCC	AZD6244	1.4 PFS	19
Lombardi(46)	HCC	Lipos dox/gemcitabine	5.8 TTP	41
Furuse(47)	HCC	S-1	3.7 PFS	26
Kim(48)	HCC	Bortezomib	1.6 TTP	35
Yang(49)	HCC	Pegylated deiminase	2.8 duration disease control	77
Greten(50)	HCC	Telomerase vaccine	1.87 TTP	40
Glazer(51)	HCC	Pegylated deiminase	None	80
Bekaii-Saab(52)	HCC	Lapatinib	1.9 PFS	26
Lin(53)	HCC	Arsenic	4.8 PFS	29
Yen(54)	HCC	Oxaliplatin	2 TTP	36
Uhm(55)	HCC	Oxaliplatin+doxorubicin	7.75 PFS	40
Chia(56)	HCC	Gemcitabine+cisplatin	1.5 TTP	15
Higginbotham(57)	HCC	TAC-101	3.2 PFS	33
Yuan(58)	HCC	Etoposide,cisplatin,doxorubicin,FU/LV	3.3 TTP	66
Kearm(59)	HCC	5FU, cisplatin	2.4 TTP	57
Asnacios(60)	HCC	Gemcitabine,oxaliplatin,cetuximab	4.7 PFS	45
Lin(61)	HCC	Imatinib	1.15 TTP	15
Cohn(62)	HCC	Penetrexed	None	21
Knox(63)	HCC	SB715992	1.6 TTP	15

/ PFS or TTP used as surrogate for period of follow-up evaluation unless stated.