

Incidence and management of Ziv-aflibercept related toxicities in colorectal cancer

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common side effects were diarrhea, stomatitis, fatigue, hypertension, weight loss, loss of appetite, abdominal pain, and headache. As the use of Ziv has become more widespread in oncology practices, familiarity with the toxicity profile of the drug and the use of practice guidelines for their treatment has become increasingly important. This review will address the toxicities noted in trials using Ziv for the treatment of mCRC, and will provide recommendations for toxicity management.

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Key words: Ziv-aflibercept; Colon cancer; Metastatic; Bleeding; Hypertension

Core tip: Ziv is an anti-angiogenic agent which has shown survival benefit in colorectal cancer. Side effects of this drug include hypertension, bleeding, perforation and delayed wound healing among others. In this paper, we review the side effects of Ziv and discuss how to manage those toxicities.

Abstract

Ziv-aflibercept (Zaltrap, Ziv) is a humanized fusion protein constructed by joining the vascular endothelial growth factor (VEGF) binding portions of human VEGF receptors 1 and 2 to the Fc portion of human immunoglobulin IgG1. Recently, a randomized, open-label, phase III study compared 5-fluorouracil, leucovorin, irinotecan (FOLFIRI)/Ziv with FOLFIRI/placebo in patients who had been previously treated with oxaliplatin based chemotherapy for metastatic colon cancer (mCRC). Patients who had received prior bevacizumab therapy were also eligible. This study showed that the addition of Ziv improved overall survival with median survival time of 13.5 mo *vs* 12.06 mo in ziv *vs* placebo arm. Ziv also improved progression free survival from 4.67 mo to 6.9 mo with a response rate of 19.8% in the Ziv/FOLFIRI group *vs* 11.1% in FOLFIRI alone group. This led to the approval of Ziv in combination with FOLFIRI in metastatic colon cancer patients treated with prior oxaliplatin regimens. The most

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INTRODUCTION

Angiogenesis is critical for tumor proliferation and metastasis for several malignant tumors^[1]. Vascular endothelial growth factor (VEGF) is a homodimeric protein that binds to and activates receptors VEGFR1 and VEGFR2, located on the vascular endothelium^[2]. This leads in stimulation of downstream signaling leading to inhibition of apoptosis, stimulation of mitosis and cytoskeletal changes associated with motility^[3]. The family of VEGF

proteins binds to several different VEGFRs with distinct binding and signaling properties. VEGFR-1, VEGFR-2, and VEGFR-3 have similar structural features and form homodimers upon ligand binding. VEGFR-1 interacts with placental growth factor (PlGF), VEGF-B, and VEGF-A. VEGF has a higher affinity for VEGFR1, but VEGFR1 has relatively weaker tyrosine kinase activity. VEGFR-2 can interact with the processed forms of VEGF-C and D in addition to VEGF. This receptor is the major mediator of the mitogenic and angiogenic effects of VEGF. VEGFR-3 only interacts with VEGF-C and D and is involved in lymphangiogenesis^[2,4,5].

VEGF is an important regulator of angiogenesis and is principally stimulated by hypoxia. VEGF is over-expressed in several malignancies including gastro-intestinal tumors. Over expression has been associated with increased tumor vascularity, proliferation, progression, invasion, and metastasis^[6,7]. VEGF inhibition represents a promising venue for an anticancer approach. Furthermore, VEGF levels are elevated in patients with metastatic colorectal cancer, suggesting that VEGF induced vascular permeability could contribute to the formation of malignant ascites^[8]. VEGF antagonists have also been shown to increase the intratumoral delivery of cytotoxic chemotherapeutic agents thereby improving their anti-tumor efficacy without increasing toxicity^[9]. Previously, bevacizumab had shown promising results in patients with untreated metastatic colorectal cancer (mCRC). Hurwitz *et al.* showed the benefit of adding bevacizumab to standard chemotherapy in this first phase III trial of mCRC^[10].

Ziv-Aflibercept (Ziv) is a novel antiangiogenic agent which is a fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG₁). It contains sequences encoding IGg domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG₁ Fc domain. Ziv complexes with VEGF in the blood and extravascular space and prevents VEGF from interacting with its receptors on endothelial cells. The VEGF trap binds with high affinity to soluble VEGF but also binds to the proangiogenic factors VEGF-B and PlGF 1 and 2. The combination of these actions may lead to the increased activity of Ziv as an antiangiogenic agent.

CLINICAL EFFICACY OF ZIV-AFLIBERCEPT

A phase I, dose escalation study of Ziv in combination with infusional fluorouracil, leucovorin and oxaliplatin, (FOLFOX4) was studied in 32 patients with advanced solid tumors^[11]. The types of cancer of these 32 patients were as follows: 8 pancreatic, 3 cholangiocarcinoma, 3 gastric, 5 breast, 4 ovarian and 7 other malignancies. In this study, 5 partial responses were noted in the pancreatic, cholangiocarcinoma and colorectal cancers while 10 patients had stable disease. Given the study results, Ziv 4

mg/kg combined with FOLFOX4 was selected for further investigations.

Another Japanese phase I study assessed the use of Ziv with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) in metastatic colorectal cancer^[12]. Ziv, at two dose levels, was administered in combination with FOLFIRI in 16 patients who had received prior chemotherapy and the combination was found to be well tolerated. A phase III, randomized study published recently evaluated Ziv in combination with FOLFIRI in metastatic colorectal cancer patients^[13]. Six hundred and twelve patients were randomized to Ziv or placebo in combination with FOLFIRI with the primary endpoint of overall survival (OS). This study showed that the addition of Ziv to FOLFIRI significantly improved OS and progression free survival as compared to placebo. Response rates were also better in the Ziv group with the main side effects being anti-VEGF related effects.

ZIV-AFLIBERCEPT RELATED TOXICITIES

In the phase III trial of Ziv in colorectal cancer, grade 3 and 4 toxicities were increased in the Ziv arm as compared to the control arm. These included bleeding (2.9% *vs* 1.7%), arterial thromboembolic events (1.8% *vs* 0.5%) and venous thrombotic events (7.9% *vs* 6.3%) (Table 1). Grade 3 hypertension was seen in 19.1% of patients receiving Ziv *vs* 1.5% of patients in the control arm. Grade 4 hypertension was seen in only 1 patient (0.2%) in the Ziv arm. There was no difference in the development of gastrointestinal (GI) fistulae, other fistulae, or GI perforation between the groups. Acute infusion related reactions, grade 3 or 4, were no different and were reported to be 0.5% in both arms. The development of grade 3 or 4 proteinuria was found in the 7.9% of patients in the Ziv arm as compared to 1.2% in control arm. Two of the patients with grade 3 or 4 proteinuria in the Ziv arm developed nephrotic syndrome.

The incidence of chemotherapy related toxicities was also found to be increased with the addition of Ziv. The toxicities included diarrhea (19.3% *vs* 7.8%), asthenia (16.9% *vs* 10.6%), stomatitis and ulceration (13.7% *vs* 5%), infections (12.3% *vs* 6.9%) and palmar plantar erythrodysesthesias (2.8% *vs* 0.5%). Hematologic toxicity was seen more commonly with this agent. Grade 3 or 4 neutropenia occurring in 36.7% of the patients in Ziv arm *vs* 29.5% in the control arm; complicated neutropenia also occurred more frequently in the Ziv arm (0.7% *vs* 2.8%). Thrombocytopenia was also seen more commonly in Ziv arm (3.3% *vs* 1.7%). Permanent discontinuation of chemotherapy due to adverse events was also seen more commonly in the Ziv arm (26.8% *vs* 12.1%). The toxicities most frequently leading to discontinuation of chemotherapy in the study *vs* control arm were asthenic conditions (3.8% *vs* 1.3%), infections (3.4% *vs* 1.7%), diarrhea (2.3% *vs* 0.7%) and hypertension (2.3% *vs* 0%) (Table 2).

Hypertension

Grade 3 hypertension (HTN), defined as hypertension re-

Table 1 Selected grade 3/4 adverse events (%) with FOLFIRI/ziv-aflibercept in VELOUR study

Adverse event	Grade 3 %	Grade 4 %
Fatigue	11.9	0.7
Asthenia	4.9	0.2
Proteinuria	7.5	0.3
Urinary tract infections	0.8	0.0
Neutropenia	23.1	13.6

quiring the addition or modification of antihypertensive agents, is one of the more common toxicities associated with Ziv treatment. HTN can occur at any time during the course of treatment. There have been no deaths due to HTN reported. In the phase I Japanese study, any grade level of HTN was noted in 8 of 13 patients (61.5%) in 4 mg/kg arm and grade 3/4 in 4 patients (30.8%)^[14]. In the phase II study of Ziv administered at 4 mg/kg, the most common treatment related adverse events were HTN, proteinuria, fatigue and headache^[15]. In another phase I study of Ziv in advanced solid tumors, HTN was observed in 38.3% of patients^[16]. HTN of any grade occurred in 0%, 14.3%, 16.7%, 14.3%, 57.1%, 75.0%, and 61.5% of patients at the increasing dose levels of 0.7, 1, 2, 3, 4, 5 and 7 mg/kg respectively, and hypertension of grades 3 to 4 occurred in 0%, 0%, 16.7%, 0%, 42.9%, 75.0%, and 46.2% of patients respectively. The median time to onset of HTN in this study was 3.5 d.

In the phase III trial by Van Cutsem *et al*^[13], HTN in Ziv/FOLFIRI treatment group for all grades, grade 3 and 4 was 41.4%, 19.1% and 0.2%, respectively. In the FOLFIRI/Placebo group, HTN of all grades and grade 3 was 10.7 and 1.5% respectively. There was no grade 4 HTN in the chemotherapy alone arm^[13].

The variation in rates of higher grade of HTN among all of these trials may be due to several factors, including the differing sample sizes across the studies, differing thresholds among practitioners to initiate anti-hypertensive therapy, or variations in patient population across studies. In general, though, most studies do indicate that Ziv increases the risk of developing HTN.

Proteinuria

The risk of developing proteinuria has been shown in the VEGF inhibition pathway as demonstrated with previous bevacizumab related therapies. In the phase I study of Ziv at 2 dose levels, proteinuria of grade 2 or lower was observed in 3 patients (23.1 %) receiving the 4 mg/kg dose^[14]. In the phase I dose escalation study of Ziv in advanced cancers, proteinuria was observed in 10.6% of patients at different dose levels, but none of them were grade 4^[16]. The median time of onset of proteinuria was 15 d in this study.

In the phase III study, the incidence of proteinuria seen in Ziv/FOLFIRI treatment group in all grades, grade 3 and 4 was 62.2%, 7.5% and 0.3%, respectively. Two patients developed nephrotic syndrome. In the FOLFIRI/Placebo group, proteinuria of all grades and grade 3 was 40.7% and 1.2% respectively. There was no

grade 4 proteinuria reported in the placebo arm. There was no correlation between proteinuria and HTN.

Gastrointestinal perforation

There was no GI perforation noted at different dose levels of Ziv in the phase I study by Lockhart *et al*^[16]. In the phase III trial by Van Cutsem, the incidence of all grades, grade 3 and 4 toxicities were 0.5, 0.2 and 0.3%, respectively in Ziv + FOLFIRI treatment group compared to 0.5, 0.2 and 0.2%, respectively, in placebo + FOLFIRI group. The incidence of grade 3 or 4 GI fistula, other fistulae or GI perforation was less than 2% in both treatment groups^[13]. In the phase II study of recurrent ovarian cancer with malignant ascites, Ziv *vs* placebo showed a higher rate of intestinal perforation (three patients) than placebo (one intestinal fistula)^[17].

Thromboembolism

In the phase I study by Lockhart, there were no reported thromboembolic events^[16]. In a phase I dose escalation study of 18 patients treated with Ziv, pemetrexed, and cisplatin, pulmonary embolism was observed in 11% and deep vein thrombosis was seen in 6% of the patients^[18]. In the recent Phase III study, arterial thromboembolic events were seen in 1.8% in the Ziv + FOLFIRI arm compared to 0.5% in the placebo + FOLFIRI arm. Venous thromboembolic events were seen in 7.9% of patients receiving Ziv + FOLFIRI compared to 6.3% receiving placebo + FOLFIRI^[13].

Hemorrhage

In the previous phase III trials of bevacizumab, there was no significant increase in the risk of bleeding with bevacizumab^[10]. In the phase III VELOUR trial of Ziv with FOLFIRI, 37.8% patients had any grade of hemorrhage, 2.8% patients had grade 3 and 0.2% of patients had grade 4 hemorrhage in Ziv arm^[13]. In the chemotherapy only arm, 19% patients had any grade of hemorrhage and 1.7% patients had grade 3 hemorrhage. There was no reported grade 4 hemorrhage. A higher incidence of grade 3 and 4 hemorrhages was observed in the Ziv group (2.9%) as compared to the placebo group (1.7%).

PATHOGENESIS OF TOXICITIES ASSOCIATED WITH ZIV

The exact of mechanism underlying the toxicities related to Ziv is not fully known at this time.

Hypertension

The effect of Ziv on the development of hypertension is not completely understood. The control of blood pressure is complicated and is related to the factors affecting cardiac output and/or total peripheral vascular resistance^[19]. One explanation for Ziv-associated hypertension may be due to its effects on VEGF inhibition. Under normal circumstances VEGF stimulates nitrous oxide release which in turn causes vasodilation. Inhibition

Table 2 General guidelines for Ziv-aflibercept dosing and schedule modification due to adverse events per CTCAE 4.0

Event	Action to be taken
Hypertension	
Grade 3	If not controlled with medication, discontinue Ziv
Grade 4	Discontinue Ziv
Proteinuria	
> 2 g protein/24 h	Hold Ziv until proteinuria improves to < 2 g of protein/ 24 h
	Discontinue Ziv in a patient with > 2 g proteinuria/24 h that does not resolve in 3 mo time after holding Ziv. Work-up for proteinuria such as renal biopsy should be considered
grade 4 proteinuria (nephrotic syndrome)	Discontinue Ziv treatment
Gastrointestinal perforation	
Gastrointestinal perforation or dehiscence	Discontinue Ziv
Thromboembolic events	
Grade 3 venous thromboembolic event	Hold Ziv treatment
or incidentally discovered pulmonary embolus first occurrence	If the planned duration of therapeutic-dose anticoagulant therapy is ≤ 2 wk, Ziv should be held until the period of therapeutic-dose anticoagulant therapy is over
	If the planned duration of therapeutic-dose anticoagulant therapy is > 2 wk, Ziv should be held for 2 wk and then may be resumed during the period of therapeutic-dose anticoagulant therapy as soon as all of the following criteria are met:
	The patient must be on a stable dose of anticoagulant and, if on warfarin, have an INR within the target range (usually between 2 and 3) prior to restarting study drug treatment
	The patient has no history of Grade 3 or 4 hemorrhagic events before starting Ziv
	The patient has no evidence of tumor invading or abutting major blood vessels on any prior CT scan
Any grade arterial thromboembolic event or symptomatic	Discontinue Ziv
Grade 4 venous thromboembolic event first occurrence	
Hemorrhage	
Grade 1 and 2	No dose modification
Grade 3 or 4 (first occurrence)	Discontinue study treatment

of VEGF may reduce the amount of nitrous oxide available in turn causing vasoconstriction^[20]. This vasoconstriction leads to increased peripheral vascular resistance resulting in hypertension^[21]. VEGF may also have effects on the renin-angiotensin system, which plays a part in the regulation of homeostasis and blood pressure^[20]. The exact mechanism of the VEGF and the angiotensin system interaction is not well known at this time.

Proteinuria

The pathogenesis of proteinuria may be related to the effects of VEGF on the renal glomerulus. VEGF inhibition induces downregulation of nephrin, sometimes leading to nephritic syndrome or glomerular thrombotic microangiopathy^[22]. In this MEDLINE review, authors found that mild proteinuria ranged from 21%-63% and severe proteinuria in up to 6.5% of renal cell carcinoma patients. In some cases, discontinuation of the anti-VEGF agent induced improvement of proteinuria, but in many cases proteinuria persisted. Thus urinary protein should be checked periodically in these patients and if patients develop proteinuria they should be referred to nephrologists.

Neutropenia

Grade 3-4 neutropenia occurred in 30% of patients in the FOLFIRI arm and 37% of patients in the FOLFIRI + Ziv arm. Complications of grade 3 neutropenia occurred in 1.7% of patients in chemotherapy alone group and 4.4% in Ziv group. Complications of grade 4 neutropenia were seen similarly in both groups.

Wound healing

VEGF is associated with wound healing and VEGF inhibitors can affect dermal-wound angiogenesis causing delayed wound healing.

Gastrointestinal perforation

The mechanism underlying GI perforation is not known. However, it seems to be multi-factorial. The role of GI pathology related to the tumor, such as carcinomatosis, cannot be excluded in addition to the inhibition of VEGF. To date, however, no baseline risk factors for GI perforation have been identified.

Thromboembolism

Malignancies cause a hypercoagulable state from the procoagulant activity of cancer cells associated with tissue factor and fibrin generation^[23]. Thrombosis associated with VEGF inhibition was initially thought to be mainly arterial, but recent data have also reported venous thrombosis^[24]. The pathogenesis of thrombosis could be related to VEGF's role in vascular integrity. VEGF inhibition is speculated to cause apoptosis of endothelial cells thus resulting in the exposure of subendothelial cells which initiate the coagulation cascade causing the thrombosis^[25].

Hemorrhage

The exact mechanism of abnormal hemorrhage from VEGF inhibition is complex and yet not fully understood. The bleeding risk could be from VEGF's effect on the vascular endothelium promoting endothelial cell survival and vasculature integrity. VEGF inhibition may

decrease the renewal capacity of damaged endothelial cells causing bleeding^[26].

MANAGEMENT OF TOXICITIES

Hypertension

Patients receiving Ziv should have baseline documentation of blood pressure and frequent monitoring. Blood pressure should be monitored done at least once every 2 wk while on treatment. It is optimal for the measurement to be done after the patient has been in a resting/seated position for more than 5 min. If the initial reading is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic then a repeat measurement should be taken for verification.

For Grade I hypertension, defined as an asymptomatic, transient (< 24 h) increase by > 20 mmHg (diastolic) or to $> 150/100$ mmHg in a patient previously within normal range, no intervention is indicated. For Grade 2 hypertension, defined as recurrent or persistent (> 24 h) or a symptomatic increase by > 20 mmHg (diastolic) or an increase to $> 150/100$ mmHg if previously within normal range, anti-hypertensive medications such as calcium channel blockers, beta blockers, and/or ACE inhibitors should be considered. One can consider temporary discontinuation of Ziv if the blood pressure is not controlled with anti-hypertensive medications and once hypertension is controlled to $< 150/100$ mmHg, patients may continue on Ziv. For persistent or symptomatic hypertension or Grade 3 hypertension the Ziv should be held. Once the blood pressure is controlled subsequent cycles of Ziv should resume at a dose of 2 mg/kg. This dose should not be re-escalated. If blood pressure cannot be controlled with anti-hypertensive medications then the Ziv should be permanently discontinued.

Although ACE inhibitors seem more logical as they can control HTN and may also decrease the amount of proteinuria, no data to determine the best anti-hypertensive agent is available. Moreover, caution should be taken when using diuretics as these patients on cytotoxic agents are at risk for diarrhea, dehydration and volume depletion. In the event of grade 4 hypertension or hypertensive crisis or encephalopathy, Ziv should be permanently discontinued.

Proteinuria

Patients should be evaluated for proteinuria prior to starting the treatment and monitored regularly throughout treatment. We recommend a baseline urinalysis (dipstick or microscopic) to assess for protein before initiating Ziv. If the degree of proteinuria is \leq grade 1, Ziv can be given. If proteinuria is \geq grade 2, urinary protein creatinine ratio should be obtained. If protein creatinine ratio is more than 1, a 24-h urine collection to quantify protein should be sent for further evaluation. In a patient with urine protein > 2 g/24 h, as recommended in the package insert, we recommend holding Ziv until proteinuria improves to < 2 g/24 h of protein. If the 24-h urine does not improve within 3 mo, we recommend discontinuing Ziv permanently.

If proteinuria recurs, Ziv should be held till it improves to < 2 g/24 h and consider reducing Ziv dose to 2 mg/kg (rule of 2). Some clinicians elect to continue Ziv therapy until protein levels exceed 3.0 to 3.5 g/24 h. As there is no definitive data at this point, the decision of when to stop Ziv therapy requires clinical judgment. In patients with Grade 4 proteinuria (nephrotic syndrome) or thrombotic microangiopathy, Ziv should be permanently discontinued.

Neutropenia

Complete blood count should be monitored at baseline and prior to each cycle of therapy. If the neutrophil count is less than $1.5 \times 10^9/L$, chemotherapy + Ziv should be delayed until the neutrophil counts recover above $1.5 \times 10^9/L$.

Wound healing complications

Patients who undergo any invasive procedure while receiving Ziv may encounter problems with wound healing as seen previously with other VEGF inhibitors. Thus, we recommend holding Ziv at least 4 wk prior to and after the elective surgery. Ziv should be held until the surgical wound is fully healed. For minor surgeries like tooth extraction, biopsy or port placement, Ziv should be held till the wound is healed. If the wound is not healing well, Ziv should be discontinued permanently. For emergent surgery, the patient, surgeon, and nursing staff should be aware of the possible risks due to Ziv. In general, clear communication of the risks of Ziv should be done with the surgeon.

Gastrointestinal perforations

In the phase III trial of Ziv in colorectal cancer, grade 3 GI perforation was same in the chemotherapy and chemotherapy with Ziv arms^[13]. Grade 4 GI perforation was seen in 0.2% of patients in the FOLIRI arm and 0.3% of patients in the Ziv arm. Since previous VEGF inhibitors, such as bevacizumab, have shown a possible increase in the risk of GI perforation, Ziv should be held for 1-2 mo after surgery and till the surgical wound is completely healed. Patients should be closely monitored for signs and symptoms of GI perforation.

The exact interval for holding Ziv is unknown; however its long elimination half-life of 6 d should be taken into account. For elective operations, Ziv should be discontinued at least 30-60 d prior to a scheduled surgery. Even though Ziv's half-life is shorter than bevacizumab, we recommend holding Ziv for at least 4 wk prior to or after the surgery until more data is available. In cases of emergent procedures, Ziv should be held and patients followed closely for complications. Once patients develop GI perforation, Ziv should be discontinued.

Thrombosis

In patients who develop grade 3 thromboses, Ziv should be held. If a patient has grade 4 thrombosis, Ziv should be discontinued. We recommend that patients with a se-

vere arterial thromboembolic event during Ziv treatment should discontinue treatment permanently. Many patients with a prior arterial thromboembolic event are routinely treated with low dose aspirin. These patients can continue with Ziv. The use of high dose aspirin cannot be recommended due to the lack of safety data. Warfarin treatment during Ziv therapy should be followed very closely with serial INRs. If the INR is therapeutic, Ziv can be resumed as long as there is no history of severe bleeding associated with Ziv.

Hemorrhage

In patients who experience grade 3 hemorrhage, in the absence of any coagulation disorder that could increase their risk of bleeding, Ziv should be held till the bleeding resolves. Patients with grade 3 hemorrhage on full-dose anticoagulation, Ziv should be discontinued. If the patient experiences a repeat grade 3 or a new grade 4 hemorrhagic event, Ziv should be permanently discontinued. Brain metastases were excluded from the clinical trials and the use of Ziv in these patients could not be recommended.

CONCLUSION

Ziv in combination with FOLFIRI has shown a survival benefit in colorectal cancer^[13]. Ziv has been shown to be associated with the following higher ($\geq 5\%$) grade 3-4 adverse events including neutropenia, diarrhea, hypertension, leucopenia, stomatitis, fatigue, proteinuria and asthenia. Hypertension and proteinuria can occur at any time during treatment, while the risk of GI perforation is increased within 60 d of starting Ziv treatment. While hypertension is the most common adverse event, it is usually managed with oral agents. Wound healing difficulties, while infrequent, are most common when major surgery occurs while the patients are being treated with Ziv. There is potential for GI perforation, and while it is a rare complication, care must be given to patients who require surgery before, during or after Ziv treatment.

This review is mainly focused on Ziv in the treatment (Table 3) of colorectal cancers. Ziv has been studied in other malignancies including lung cancer and with other combinations of chemotherapy. The nature and rate of toxicities was similar in trials with other malignancies. Overall, the risk of grade 3 or 4 hypertension, hemorrhage and thromboembolism with Ziv appears to be low across all studies. In the colorectal cancer studies, GI perforations, while a serious event, have been relatively infrequent. In other malignancies this toxicity may be more of a concern. While the mechanism underlying this increased incidence of GI perforation is unknown, it may be related to the fact that these patients had very advanced disease and many patients had undergone multiple debulking surgeries.

To date, the efficacy and toxicity of Ziv has primarily been evaluated in patients with advanced disease, and the side effects of long-term therapy with Ziv in patients

with less advanced tumors is still unclear. This paper summarizes the guidelines by taking the information from the published data and extrapolating from related drugs like bevacizumab which has similar mechanism of action. As the trial data matures, we will have more clarity on the safety of Ziv. As more data becomes available, specific guidelines for the management of Ziv-related toxicities will become more detailed as well. This will be vital as anti-angiogenic agents become a more integral part of the standard care of patients with colorectal and other malignancies. Overall, though, the clear benefits of anti-angiogenic therapy vastly outweigh the small risks in the majority of patients. The key to administering treatment safely will be through education of patients, nurses and other healthcare providers.

EXPERT OPINION

Ziv is a recombinant fusion protein consisting of VEGF-binding portions from extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of the human IgG1 that is designed to inhibit VEGF, thus inhibiting angiogenesis. Ziv has shown to extend survival in previously treated colorectal cancer. Ziv has provided an increase in median overall survival (13.5 mo *vs* 12.06 mo, $P = 0.0032$) when combined with FOLFIRI *vs* FOLFIRI alone. Clinical benefit, as measured by overall survival, was observed across all patients. Significant improvements in response rate and duration of response in combination with FOLFIRI were also achieved. The overall response rate was also improved in Ziv arm compared to FOLFIRI. Based on these data, Ziv was approved in combination with FOLFIRI by the FDA for the treatment of metastatic CRC, and is currently undergoing vigorous exploration in clinical trials for the treatment of many solid tumors, including non-small cell lung cancer.

In trials, Ziv was combined with conventional chemotherapy making it difficult to identify which toxicities are unique to it. However, since the adverse effects of chemotherapy are well characterized it is reasonable to assume that any new or unexpected adverse effects can be attributed to Ziv. It does not appear that any overlapping hematologic or gastrointestinal adverse effects exist between Ziv and conventional chemotherapy. Common adverse events associated with Ziv include HTN, proteinuria, and epistaxis (mainly mild). More patients in the Ziv arm of these studies experienced at least one grade 3 or 4 toxicity compared with chemotherapy alone, primarily attributable to HTN. Other frequent adverse events associated with Ziv are bleeding episodes and thrombotic events. The manufacturer has issued a black box warning regarding the risk of gastrointestinal perforation, wound dehiscence, and fatal hemoptysis.

The overall rate of grade 3-4 hypertension related to Ziv was approximately 19%. HTN can occur at any time during the course of treatment. No deaths from HTN have been reported and $< 1\%$ of patients has discontinued therapy due to HTN. Blood pressure is typically

Table 3 Recommendations for Dose Modification and Treatment Delay for Zaltrap

Discontinue ZALTRAP for:	Severe hemorrhage Gastrointestinal perforation Compromised wound healing Fistula formation Hypertensive crisis or hypertensive encephalopathy Arterial thromboembolic events Nephrotic syndrome or thrombotic microangiopathy (TMA) Reversible posterior leukoencephalopathy syndrome (RPLS)
Temporarily suspend ZALTRAP:	At least 4 wk prior to elective surgery For recurrent or severe hypertension, until controlled. Upon resumption, permanently reduce the ZALTRAP dose to 2 mg per kg For proteinuria of 2 grams per 24 h. Resume when proteinuria is less than 2 grams per 24 h. For recurrent proteinuria, suspend ZALTRAP until proteinuria is less than 2 grams per 24 h and then permanently reduce the ZALTRAP dose to 2 mg per kg (RULE OF 2)

Table 4 Special Situations about Toxicities of Zaltrap

Geriatric Use	The effect of ZALTRAP on overall survival was similar in patients < 65 yr old and ≥ 65 yr old who received ZALTRAP/FOLFIRI. No dose adjustment of ZALTRAP is recommended for patients ≥ 65 yr of age.
Paediatric Use	The safety in paediatric patients has not been established.
Hepatic Impairment	No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ziv-aflibercept.
Renal Impairment	No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of ziv-aflibercept.
Contraception and Nursing Mothers	Females and males of reproductive potential should use highly effective contraception during and up to a minimum of 3 mo after the last dose of treatment.
Overdose	No information on the safety of aflibercept given at doses exceeding 7 mg/kg every 2 wk or 9 mg/kg every 3 wk is present. No specific antidote to ZALTRAP overdose exists. Patients of Zaltrap overdose should be managed with supportive measures.
Infections	The Velour study showed an increased incidence of infections in patients receiving ZALTRAP/FOLFIRI (46%, all grades; 12%, Grade 3-4) than in patients receiving placebo/FOLFIRI (33%, all grades; 7%, Grade 3-4), including urinary tract infection, nasopharyngitis, upper respiratory tract infection, pneumonia, catheter site infection, and tooth infection. Be vigilant about recognizing them. Treat them according to general guidelines.

controlled with an antihypertensive agent(s). The most common bleeding events in clinical trials were grade 1 and 2 epistaxis, which were transient. More serious bleeding events include central nervous system hemorrhage, hemoptysis, and gastrointestinal hemorrhage.

Ziv was associated with 2.6% of arterial thromboembolic events (ATE) including transient ischemic attack, cerebrovascular accident and angina pectoris compared to 1.7% of patients treated with placebo/FOLFIRI. In Ziv patients, grade 3-4 ATE occurred in 1.8% compared to 0.7% in placebo arm. Risk factors for arterial thromboembolic events included a history of prior arterial thromboembolic events such as stroke or heart attack, and age of 65 years or older.

There is paucity of data on drug interaction with other medications. However, based on the available data it is recommended that Ziv be used cautiously with medications that can increase the risk of bleeding, such as non-steroidal anti-inflammatory drugs, aspirin, and warfarin. Caution should be observed with the use of Ziv when administered to patients with a history of HTN, thromboembolism, bleeding, or preexisting proteinuria, as these conditions may be exacerbated by Ziv.

In elderly patients (above or 65 years), there was slightly increased (5%) incidence of diarrhea, dizziness,

asthenia, weight decrease and dehydration as compared to younger patients. Overall survival was same in all these patients. There is no dose adjustment recommended for elderly. Its safety profile in children is unknown. Animal studies in rabbits have shown that Ziv causes fetal abnormalities. Although there is no data on the effects of Ziv on human fetal development (Table 4), its use during pregnancy is not recommended based on experimental data in animals.

Currently there are no specific dose recommendations for patients receiving Ziv who have preexisting renal or hepatic dysfunction. Consideration of withholding Ziv should also be done in patients with low platelet counts or who are at an increased risk of bleeding. The manufacturer recommends permanent discontinuation of Ziv in patients with serious bleeding, gastrointestinal perforation or wound dehiscence requiring medical intervention. Patients who develop moderate to severe proteinuria while on treatment with Ziv should have treatment held until resolution or proteinuria.

Ziv was shown to be of benefit in metastatic colorectal cancer, while increasing patient response rates and prolonging survival. Additional information is needed to identify other diseases and stages most likely to benefit from anti-angiogenic agents and the optimal sequences

and therapeutic combinations also should be studied.

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