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REVIEW

Optimal combination of antiangiogenic therapy for hepatocellular carcinoma

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Abstract

The success of sorafenib in prolonging survival of patients with hepatocellular carcinoma (HCC) makes therapeutic inhibition of angiogenesis a component of treatment for HCC. To enhance therapeutic efficacy, overcome drug resistance and reduce toxicity, combination of antiangiogenic agents with chemotherapy, radiotherapy or other targeted agents were evaluated. Nevertheless, the use of antiangiogenic therapy remains suboptimal regarding dosage, schedule and duration of therapy. The issue is further complicated by combination antiangiogenesis to other cytotoxic or biologic agents. There is no way to determine which patients are most likely respond to a given form of antiangiogenic therapy. Activation of alternative pathways associated with disease progression in patients undergoing antiangiogenic therapy has also been recognized. There is increasing importance in identifying, validating and standardizing potential response biomarkers for antiangiogenesis therapy for HCC patients. In this review, biomarkers for antiangiogenesis therapy including systemic, circulating, tissue and imaging ones are summarized. The strength and deficit of circulating and imaging biomarkers were further demonstrated by a series of studies in HCC patients receiving radiotherapy with or without thalidomide.

Key words: Antiangiogenesis; Hepatocellular carcinoma; Biomarker; Cytokines; Dynamic contrast enhanced magnetic resonance imaging

Core tip: Antiangiogenic therapy has become an important component of treatment in hepatocellular carcinoma (HCC) patients. However, traditional anatomic imaging of tumor shrinkage is not appropriate to evaluate the efficacy of antiangiogenesis achieved by normalizing tumor vasculature and systemic suppression of angiogenic and inflammatory cytokines. To identify and validate potential response biomarkers, standardized systemic, circulating, tissue and imaging assays should be incorporated in to preclinical and clinical studies regarding the combination of antiangiogenic agents to cytotoxic or biologic agents. The optimal dosage, schedule and duration of antiangiogenic during com-

bination therapy for HCC patients should be titrated according to these response biomarkers.

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INTRODUCTION

Patients with advanced hepatocellular carcinoma (HCC) have a poor prognosis. Systemic therapy with cytotoxic agents provides marginal benefit[1,2]. HCC, a highly vascularized tumor, requires angiogenesis to grow, invade and metastasize[3]. The success of pharmacological inhibition of angiogenesis in HCC provided by sorafenib[4,5], makes it the first and only systemic agent to notably improve survival in HCC patients.

Although the inhibition of angiogenesis in HCC is an established modality of cancer treatment, concerns regarding toxicity and drug resistance still constitute barriers to be overcome. Recent randomized studies comparing multikinase inhibitors - sunitinib[6], brivanib[7], and linifanib[8] - and the combination of sorafenib plus erlotinib[9] with sorafenib alone does not reveal better survival rates or tolerability. In this review, issues brought up by combining antiangiogenic agents with chemotherapy, or other targeted therapy will be summarized. A series of our study, incorporating thalidomide, an antiangiogenic agent, during radiotherapy for HCC patients will be introduced.

STRATEGIES TO IMPROVE ANTIANGIOGENESIS THERAPY IN HCC

To improve the clinical outcomes of antiangiogenic therapy in HCC, the combination of antiangiogenic agents with cytotoxic chemotherapy or with other molecularly targeted therapies may act synergistically to generate additive effects. A better understanding of the mechanisms regarding the action of sorafenib on HCC plus the investigation for predictive biomarkers may allow us to select patients suitable for anti-angiogenesis therapy.

Combinations of anti-Vascular endothelial growth factor (VEGF) agents with chemotherapy in HCC are under evaluation. Treatment with bevacizumab/capecitabine/oxaliplatin or with bevacizumab/gemcitabine/oxaliplatin in HCC patients resulted in median survivals of less than 10 mo[10,11]. Based on the encouraging data from sorafenib plus doxorubicin in HCC[12], a phase Ⅲ randomized study (CALGB80802) comparing sorafenib plus doxorubicin with sorafenib alone is underway in patients with advanced HCC. Studies combining sorafenib with gemcitabine/oxaliplatin, modified FOLFOX, or capecitabine/oxaliplatin are ongoing.

Another approach has been to combine antiangiogenic therapy with inhibitors of other angiogenesis or molecular targets. Tivantinib, a c-MET inhibitor, was compared with placebo in a randomized phase Ⅱ study in advanced HCC. Improved time to progression with tivantinib, especially for patients with tumors of high MET expression was noted[13]. Cabozantinib, a receptor tyrosine kinase inhibitor of c-MET/VEGF receptor 2 (VEGFR2), is undergoing phase Ⅲ evaluation in HCC patients failed or could not tolerate sorafenib[14]. The mTOR inhibitor everolimus was compared with best supportive care alone in a randomized phase Ⅲ trial (EVOLVE-1) in the second-line treatment of HCC patients. No significant survival benefit was noted using everolimus in HCC patients relapsed from sorefinib[15]. Everolimus was also combined with sorafenib in a phase Ⅰ trial of HCC, and 43% of the patients developed grade 3/4 thrombocytopenia[16].

Other inhibitors of genetic or epigenetic targets of HCC including basic fibroblast growth factor (bFGF) inhibitors, heat-shock protein inhibitors, histone deacetylase inhibitors, MEK inhibitors, insulin growth factor (IGF)/IGF receptor inhibitors, Wnt signal inhibitors, immunotherapy with or without the combination of antiangiogenesis are under clinical investigation in advanced HCC[17].

With all the efforts in improving clinical outcomes of antiangiogenesis, the optimal dosing schedule of antiangiogenic agents alone or in combination for HCC patients is largely unclear. Along with the development of new therapies, a parallel effort must be made to identify biomarkers of response, and toxicity in order to provide HCC patients with safe and effective therapies.

RESPONSE BIOMARKER

Anatomic imaging biomarkers that quantify liver tumor response to cytotoxic therapy are based on temporal change in the size of the tumors. Objective response by size-based decrease in tumor, may translate to an early clinical endpoint, in substitution for overall survival[18]. Anti-VEGF therapy has primarily cytostatic effects, may prune and normalize the tumor vasculature, and can have substantial systemic effects such as modulation of circulating proangiogenic and proinflammatory cytokines and cells[19-24]. These effects may not shrink but rather stabilize the tumor size and prolong survival[25,26]. Unlike conventional chemotherapy, an effective dose of an antiangiogenic agent can be less than the maximum tolerated dose, whereas certain toxicities may be dose-related[27]. The development of antiangiogenic therapy or other biologic therapy requires new methods for measuring response to therapy.

Blood pressure as a biomarker

Hypertension has been observed in patients with cancer treated with anti-VEGF antibodies or tyrosine kinase inhibitors (TKIs) and is clinically manageable in most cases with medication. There is evidence that patients

Table 1 Circulating biomarker of hepatocellular carcinoma patients receiving antiangiogenic therapy

Treatment	Patient enrolled	Patient *n*	Predictive value	Prognostic value	Ref.
Sorafenib, bevacizumab or thalidomide/oral 5FU	Elevated AFP	72	AFP responder (AFP decline > 20% in 4 wk) correlate with response	Early AFP responder: associate with PFS, OS	Shao *et al*[103]
Sorafenib	Advanced	30		High baseline IL-8 correlates with PD; high Ang2, G-CSF, HGF, leptin correlate with shorter PFS	Miyahara *et al*[104]
Sorafenib	Advanced	491	High baseline sc-KIT, low HGF correlate with sorefinib response	Baseline Ang2, VEGF, AFP correlate with survival	Llovet *et al*[36]
Sorafenib	Post-operative	29	High phosphor MET correlate with sorafenib resistance		Xiang *et al*[105]
Sunitinib	Advanced	34		High baseline AFP, IL-8, IL-6, SDF1, TNF correlate with PFS and OS; decreased IL-6, sc-KIT at day 14 correlate with improved PFS and OS	Zhu *et al*[24]
Sunitinib	Advanced	37	High baseline VEGFC correlates with response	High base VEGFC correlates with TTP; change in VEGFA, sVEGFR2 correlate with OS	Harmon *et al*[106]
Sunitinib	Advanced	23	Decrease sVEGFR2 or TNF correlate, with decrease in K^{trans} K_{ep}; Decrease K^{trans}, K_{ep} at week 2 correlate with response		Sahani *et al*[107]
Bevacizumab	Advanced	43	Increase CEC on day 15 , low IL-8 correlate with disease control	High baseline IL-8, IL-6 correlate with short PFS, OS	Boige *et al*[108]
Bevacizumab	Advanced	59	High Ang2, EGFR, endothelin 1, no acneiform rash correlate with poor outcome		Kaseb *et al*[109]
Thalidomide	Advanced	47	No predictive value of VEGF, bFGF, PlGF		Hsu *et al*[110]
Thalidomide/tegafur/uracil	Advanced	43		High IL-6, IL-8 correlate with short survival	Shao *et al*[111]
Thalidomide/radiotherapy	Advanced	24	No predictive value of VEGF, bFGF, IL-6, SDF1, TNF	Baseline IL-6, SDF1 at week 2 correlate with PFS. SDF1 at 1 mo post radiotherapy correlates with OS	Ch'ang *et al*[89]
TSU68	Advanced	35	High sVCAM1 correlates with response		Kanai *et al*[112]

AFP: α-fetal protein; PFS: Progression free survival; OS: Overall survival; IL: Interleukin; PD: Progressive disease; Ang2: Angiopoetin 2; G-CSF: Granulocyto colony stimulating factor; HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor; SDF: Stem cell derived factor; TNF: Tumor necrosis factor; TTP: Time to progression; sVEGFR: Soluble VEGF receptor; K^{trans}: Transfer constant; K_{ep}: Redistribution rate constant; CEC: Circulating endothelial cells; EGFR: Epidermal growth factor receptor; bFGF: Basic fibroblast growth factor; PlGF: Placental growth factor; sVCAM1: Soluble vascular cell adhesion molecule 1.

with hypertension have better survival outcomes[28,29]. A significantly improved progression-free survival (PFS) for patients with grade 2/3 hypertension after receiving bevacizumab is noted compared to those who did not develop hypertension on bevacizumab treatment (P = 0.04). These findings suggest the possibility of titrating the dose of anti-VEGF therapy by hypertension for efficacy optimization.

VEGF as a biomarker

The most extensively studied biomarker in antiangiogeni therapy has been VEGF (Table 1). Free VEGFA is rapidly cleared from the circulation, and a wide variation in plasma VEGF concentrations has been reported due to different assay sensitivities[30]. After immune-depletion of VEGF bound to bevacizumab, Loupakis *et al*[31] reported that the concentrations of free and active VEGF decreased significantly from day 0 to day 14 after bevacizumab treatment.

Associations between outcomes of antiangiogenic therapy with VEGF levels in the circulation have been reported in clinical trials of breast cancer and HCC[32,33]. However, in other cancers neither the intra-tumoral nor the circulating VEGF was associated with the outcome of bevacizumab treatment[34,35]. Baseline VEGF and angiopoietin-2 concentrations were found to be independent prognostic markers in the sorafenib HCC assessment randomized protocol trial. However, these biomarkers were not predictive of response to sorafenib[36].

Many studies have shown a lack of correlation between VEGF levels at baseline and the outcome of antiangiogenic therapy[35,37]. Intriguingly, the circulating levels of VEGF seemed to be significantly elevated after most antiangiogenic therapies targeting this pathway[38]. Similar phenomenon was noted after therapy with anti-VEGFR TKIs[39-44]. Preclinical data indicate that this increase in VEGF may be induced by a host-response to hypoxia in tumors.

On the other hand, the VEGF genotype has emerged as a predictive biomarker from the phase Ⅲ study of bevacizumab in metastatic breast cancer (ECOG 2100). VEGF-2578AA genotype was associated with a superior overall survival in the combination arm[45].

Placental growth factor and soluble VEGFRs as biomarkers

Circulating plasma levels of placental growth factor (PlGF) increase consistently in response to anti-VEGF treatment. Thus, plasma PlGF is now being considered as a potential biomarker of anti-VEGF therapy[41,43,46]. Of interest, the increase in PlGF may be due to systemic effects, as tumor-derived PlGF may actually be decreased after bevacizumab treatment[46]. Ziv-aflibercept, a recombinant fusion protein that blocks multiple factors in the angiogenesis network by binding VEGFA, VEGFB and PlGF. Results of the EFC10262-VELOUR study revealed a significant improvement in the primary endpoint of overall survival (OS) with ziv-aflibercept and FOLFIRI compared to FOLFIRI alone[47], despite approximately one-third of the patients having received prior bevacizumab treatment. These findings underscore the potential role of other VEGF family members in tumor angiogenesis.

Circulating levels of soluble VEGFR2 and VEGFR3 proteins are decreased by TKIs that directly target these receptors, but not by bevacizumab. Studies showed that patients with higher plasma levels of sVEGFR1 had a poor outcome after treatment with bevacizumab, sunitinib, vandetanib, and cediranib[24,48-51]. Polymorphisms in the *FLT1* gene that are associated with higher VEGFR1 expression have been associated with poor outcome of bevacizumab containing regimens in phase Ⅲ studies[52]. The mechanisms by which these changes occur, their biological significance, and their utility as predictive biomarkers are not understood.

Other proteins as biomarkers

Collagen Ⅳ is one of the main constituents of tumor vascular basement membranes. Proteolytic degradation of the basement membrane during vascular normalization by antiangiogenic agents can release soluble collagen Ⅳ in blood circulation. In recurrent gliobastoma patients, increase in plasma collagen Ⅳ levels after anti-VEGF therapy was associated with an increase in PFS[53]. In patients with metastatic colorectal cancer, responses to vatalanib plus chemotherapy correlated positively with tissue mRNA levels of VEGFR1, lactate dehydrogenase (LDH) A and glucose transporter (Glut) 1 and inversely with hypoxia inducible factor 1-α[54]. In addition, patients with high baseline serum LDH levels had longer PFS and OS after treatment with vatalanib and chemoradiation[55]. Baseline soluble intracellular adhesion molecule (ICAM)-1 was shown to be an independent prognostic factor of OS in patients treated with bevacizumab and chemotherapy or chemotherapy alone in metastatic non-small cell lung cancer (NSCLC)[37].

Certain inflammatory cytokines might have potent proangiogenic effects. In patients with advanced NSCLC who were treated with vandetanib plus chemotherapy, vandetanib alone or chemotherapy alone, increase plasma VEGF levels for vandetanib monotherapy and increase in plasma interleukin (IL)-8 for combination therapy were associated with increased risk of disease progression[56]. A phase Ⅱ study suggested that IL-8 A-251T polymorphism may be a molecular predictor of response to bevacizumab based chemotherapy in ovarian cancer[57]. In phase Ⅱ studies, the extent of increase in inflammatory cytokines such as IL-10 in the plasma during treatment was associated with an inferior outcome in patients with rectal and ovarian cancer after bevacizumab and chemoradiation treatment, and an inferior outcome in patients with advanced HCC after sunitinib therapy[11,23,46]. Association between increased plasma stem cell derived factor (SDF)1α after treatment and poor outcome in anti-VEGF studies in recurrent glioblastoma, sarcoma and breast cancer were reported[19,58,59]. Increased plasma SDF1α and plasma IL-6 have been associated with poor outcomes in locally advanced rectal cancer and HCC patients treated with bevacizumab, chemoradiation and sunitinib[24,60]. In line with these findings, preclinical studies have shown that sunitinib can induce elevation of circulating inflammatory cytokines in mice, which might result in more aggressive recurrent or metastatic tumors[61,62].

Other circulating factors reported to be associated with clinical outcomes after antiangiogenesis includes plasma angiopoetin-2, bFGF, platelet derived growth factor-BB, soluble Tie2, sICAM-1, and matrix metalloproteinases[24,49,56,63-66] (Table 1).

Tissue biomarkers

Tissue based biomarkers are difficult to establish because of the invasive and costly nature of these procedures and the variations in immunohistochemical procedures and interpretations. Intratumoral levels of VEGF have not been shown to predict survival outcome of anti-VEGF therapy[35,67], although correlations with response rates have been reported[68]. On the other hand, increased SDF1 and CXCR4 were noted in rectal cancer patients after anti-VEGF treatment[58,69]. High carbonic anhydrase IX expression was associated with better tumor shrinkage for metastatic renal cell carcinoma patients treated with sorafenib[70]. Genetic studies of colorectal cancer did not associate *p53*, *KRAS* or *BRAF* mutations with bevacizumab treatment outcome[71]. Single nucleotide polymorphisms (SNPs) in VEGF, VEGFR2 and VEGFR1 were associated with survival after treatment with bevacizumab based regimens[45,52,72]. In line with the important role of inflammatory cytokines in angiogenesis, a consistent finding appeared to be the association between SNPs in *CXCR2* and *IL-8* genes and the outcome after anti-VEGF therapies[57,73,74]. More extensive investigation and validation are warranted to determine a biomarker for antiangiogenesis therapy.

Circulating cells

In response to sunitinib, the number of circulating endothelial cells (CECs) and monocytes can be decreased in patients with HCC and gastrointestinal stromal tumors (GISTs)[22,24]. However, In GISTs

Table 2 Imaging biomarkers of hepatocellular carcinoma patients receiving antiangiogenic therapy

Treatment	Imaging study	Patient *n*	Predictive value	Prognostic value	Ref.
Sorefinib or sunitinib	Perfusion CT, DCEUS	19	⩽ 40% decrease in AUC at 1 mo correlates with PD		Frampas *et al*[113]
Sorafenib	CEUS	21	Reduction in enhancement correlates with response		Moschouris *et al*[114]
Sorafenib	Perfusion CT	10	Increase in MTT correlates with AFP response		Sacco *et al*[115]
Sunitinib	DCEMRI	24	Decreased K^{trans} or K_{ep} correlate PR/SD		Zhu *et al*[24]
Sunitinib	DWI, MRP	23	Decreased K^{trans} or K_{ep} at week 2 correlate with response	High baseline K^{trans} and decrease in EVF correlate with longer PFS	Sahani *et al*[107]
Bevacizumab	Perfusion CT	25	Low baseline MTT correlates with PD; increased MTT correlates with PR/SD		Zhu[2]
Bevacizumab	DCEUS	42	Decrease between day 0-3 of AUC, AUC during wash-in, AUC during wash-out, time to peak intensity correlate with tumor response	Time to peak intensity correlates with PFS; AUC and ACU during wash-out correlate with OS	Lassau *et al*[116]
Bevacizumab/ gemcitabine and oxaliplatin	Perfusion CT, dual-phase contrast enhanced CT	23	High baseline MTT correlates with PR/SD; high baseline K^{trans} correlates with responder	High baseline MTT correlates with better PFS	Jiang *et al*[117]
Bevacizumab	Perfusion CT	22		Reduction in percentage change of FD and low baseline FD correlate with longer OS	Hayano *et al*[118]
Thalidomide	Power Doppler US	47	High baseline vascular index in responder		Hsu *et al*[110]
Thalidomide	Perfusion CT	18	High baseline blood flow and blood volume correlates with progression		Petralia *et al*[119]
Thalidomide/ radiotherapy	DCEMRI	22	High baseline and week 2 Slope in responder	Perfusion parameters over liver parenchyma correlate with PFS and OS	Liang *et al*[87]
Pazopanib	DCEMRI	26	Reductions in IAUGC and K^{trans} not correlate with pharmacokinetic parameters		Yau *et al*[120]

CT: Computed tomography; DCEUS: Dynamic contrast enhanced ulatrasonography; AUC: Area under curve; PD: Progressive disease; CEUS: Contrast enhanced ultrasonography; MTT: Mean transit time; AFP: α-fetal protein; DCEMRI: Dynamic contrast enhanced magnetic resonance imaging; K^{trans}: Transfer constant; K_{ep}: Redistribution rate constant; PR: Partial response; SD: Stable disease; DWI: Diffusion weighted imaging; MRP: Magnetic resonance imaging derived perfusion parameter; EVF: Extracellular volume fraction; PFS: Progression free survival; FD: Fractal dimension; OS: Overall survival; Slope: Initial first-pass enhancement slope; IAUGC: Initial area under the tissue gadolinium concentration-time curve.

patients, clinical benefit was significantly associated with increases in CECs (P = 0.007) as compared with those with progressive disease[22]. TKIs such as cediranib or bevacizumab combined with chemotherapy did not change the amount of circulating progenitor cells. One of the caveats of using CECs as a biomarker is the means of assessment, which needs to be more rigorously established and standardized.

Imaging biomarkers

Noninvasive imaging has been widely applied for monitoring antiangiogenesis therapy in cancer drug discovery (Table 2). The techniques used in molecular imaging include positive emission tomography, single-photon emission computed tomography, molecular magnetic resonance imaging (MRI), optical fluorescence, optical bioluminescence, and targeted contrast -enhanced ultrasound. For example, temporal change in dynamic MRI and computed tomography (CT)-based tissue vascular measures such as blood flow, blood volume, or permeability have been shown to occur after treatment with bevacizumab or anti-VEGFR TKIs in clinical studies[75]. In HCC patients successfully treated with bevacizumab, CT perfusion imaging demonstrated substantial reductions in hepatic tumor blood flow, blood volume and permeability, findings that may predict treatment response[76]. In MRI perfusion studies, HCC nodules treated with sorafenib showed a higher decrease in K^{trans}, which represents the volume transfer constant between blood plasma and the extravascular extracellular space. This finding reflects a decrease in tumor permeability and correlates with longer PFS and OS[77]. The extent of drop in K^{trans} at day 14 after sunitinib in advanced HCC was significantly associated with PFS[24]. The wide spread incorporation of perfusion as a biomarker has been hampered by inconsistencies in quantification results from different software and acquisition methods, as well as the time intensive analysis of data[78,79] (Table 2).

The validation of clinical imaging of angiogenesis will be a slow and costly process. Different types of clinical trials that include histologic analysis will be needed.

CHALLENGES IN IDENTIFYING AND VALIDATING BIOMARKERS

Despite numerous investigations of antiangiogenic biomarkers, no validated biomarkers currently exist for predicting response or identifying appropriate patients for antiangiogenic therapy. Several challenges need to be overcome. Since the mechanisms regarding the actions of the currently approved antiangiogenic agents are not fully understood, there are no adequate criteria of pharmacologic response[80,81]. The development of toxicity or resistance due to the activation of VEGF-independent pathways should also be explored. Besides, the biopsy or blood sample before treatment may not reflect the biology before subsequent treatment. There is also regional heterogeneity with one part of a tumor not necessarily having the same vascularity as another part. A spatially resolved "dynamic biomarkers" are warranted. Furthermore, the measurement of candidate biomarkers should be optimized and standardized before independent validation.

INCORPORATING THALIDOMIDE INTO RADIOTHERAPY FOR HCC: DYNAMIC CONTRAST ENHANCED MRI STUDIES FOR HCC DURING RADIOTHERAPY

With the advancement of modern radiation and respiratory-gating technique, radical radiation to a portion of liver can achieve a high local control rate in patients with advanced HCC[82-84]. However, slow tumor shrinkage and rapid recurrence compromise treatment outcomes. The development of surrogate markers to monitor the response of HCC to radiation is important[85]. The maximal response to radiotherapy is often achieved 6 mo after completion treatment. This slow response makes it difficult to modify an ineffective regimen for HCC in a timely fashion, especially in patients with a low level of serum α-fetal protein. Furthermore, intrahepatic recurrence outside the field of radiation is a common cause of treatment failure[82,83]. Scattered radiation related tissue inflammation and damage may have a deleterious effect on tumor control because of the release of cytokines or angiogenic factors[86].

We evaluated the signal parameters of dynamic contrast enhanced MRI (DCEMRI) over liver parenchuma as well as liver tumor in HCC patients before, during and after radiotherapy. Initial enhancement slope and peak enhancement ratio, representing microcirculation and permeability to contrast material were measured over an operator-defined region of interest. From nineteen patients with advanced HCC, we found that increased signal parameters of the tumor at week 2 during radiation were associated with an improved local response. In the parenchyma, increased signal parameters at week 2 were associated with recurrence or progression[85]. The observation was validated in another forty-three patients. Signal parameters of baseline as well as week 2 during radiotherapy were higher in patients with responsive tumor[87]. Multivariate analysis, however, showed signal parameters over liver parenchyma, but not over tumor, independently predicted PFS and OS[87]. In line with the observation, univariate analysis showed Child-Pugh classification B and poor liver function predicted shorter PFS. These observations emphasized that liver function reserve, but not tumor response, of these heavily pretreated HCC patients impacts the survival after radiotherapy[88].

INCORPORATING THALIDOMIDE INTO RADIOTHERAPY FOR HCC: CYTOKINES AND IMAGE STUDIES

With the a priori DECMRI study in HCC patients receiving radiotherapy, we evaluated the combination effect of thalidomide to radiotherapy within the same population of patients with identical image acquisition and analysis protocols[87,89]. Thalidomide, an angiogenesis inhibitor, was noted to radio-sensitize tumors by reducing interstitial fluid pressure, increase perfusion and tumor reoxygenation[90]. The anti-inflammatory effect of thalidomide could contribute to the radio-sensitization and disease control of HCC[24,91]. Low dose thalidomide resulted in a response rate of less than 10% and a disease stabilizing rate of 50% in HCC patients[92,93]. Twenty-four patients were enrolled and received concomitant thalidomide and radiation. Thalidomide was prescribed at a dose of 100 mg twice daily starting three days before radiotherapy to achieve a steady serum level[94]. The clinical outcomes, cytokine and DCEMRI studies were compared with patients receiving radiotherapy alone. Thalidomide suppressed the serum bFGF significantly and to a lesser extent, the IL-6 and tumor necrosis factor α levels. Multivariate analysis revealed that baseline IL-6 and week 2 SDF1α level independently predicted the PFS. A decreased SDF1α at one month after radiotherapy complete was a significant prognostic factor of longer OS of HCC patients receiving radiotherapy. Patient with responsive or stabilized disease had significant longer OS (288 ± 51 d *vs* 203 ± 52 d, P = 0.02). However, none of the cytokines evaluated correlated significantly with tumor response after radiation. Despite acceptable toxicity and significant suppression of serum bFGF, thalidomide at current dosage and schedule did not correlate with tumor response and survival of HCC patients receiving radiotherapy[89].

On the other hand, DECMRI studies of the 22 HCC patients receiving thalidomide and radiotherapy showed consistently that signal parameters at baseline and at week 2 during radiotherapy correlated with tumor response. However, the addition of thalidomide at current dosage and schedule did not change the signal

parameters significantly compared to the 22 patients receiving radiotherapy only[87]. The inconsistency between serum biomarker and DCEMRI parameter was reported in a study using ribonucleotide reductase M2 inhibitor with radiation in pancreatic cancer patients[95]. In our study, the significant suppression of bFGF by low dose thalidomide may be tumor-independent changes, nonetheless, reflect systemic exposure to thalidomide. They could serve as drug activity markers to determine optimal biological dose ranges, but not as predictive or prognostic biomarkers[20,22]. Our studies indicate that daily dose of 200 mg thalidomide may induce a systemic suppression of angiogenic and inflammatory cytokines. However, the cytokine effect did not translate into vascular change within liver tumor or liver parenchyma. The optimal dosage and schedule of thalidomide during radiotherapy for HCC patients should be further explored.

The superior sensitivity and the lack of radiation put DCEMRI at the forefront of clinical translation as imaging biomarker. However, the analysis of abdominal and thoracic DCEMRI is often impaired by artifacts and misregistration caused by physiologic motion. More recent reports suggested methods available to alleviate post-processing difficulties in DCEMRI for image analysis[96]. DCEMRI parameters seemed to help to predict tumor angiogenesis measured by microvascular density and VEGF expression levels and discriminate malignant from normal tissue[97-99]. A sufficient decrease in tumor vascular parameters was used to assign an appropriate dose for an additional phase Ⅱ trial of an antiangiogenic therapy (AG-013736). The author showed that the day 2 vascular response measured using DECMRI seemed to be a useful indicator of drug pharmacology[100]. However, paradoxical negative correlation between K^{trans} and CD31 expression was reported as well[101,102]. Continuing investigations are needed to accurately depict whether DCEMRI truly has a role in imaging tumor angiogenesis and evaluating response to antiangiogenesis therapy.

CONCLUSION

Recent preclinical and clinical data suggest the advantage of combining antiangiogenic agents with chemotherapy, radiotherapy or other biologic agents in numerous pathologies. However, in order to optimize the effectiveness of the combination, it is essential to study the mechanisms by which antiangiogenesis or strategies over molecular targets are obtained. Standardized systemic, tissue, circulating and imaging biomarkers should be incorporated into well run preclinical and clinical studies, in order to choose the optimal sequence and administration time of these drugs.

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