Cell Adhesion & Migration 6:6, 569–573; November/December 2012; © 2012 Landes Bioscience

VEGF levels and the angiogenic potential of the microenvironment can affect surgical strategy for colorectal liver metastasis

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Keywords: colorectal liver metastases, microenvironment, angiogenesis, VEGF, pre-metastatic niche, surgical resection

Abbreviations: AAG, anti angiogenic agent; Ang-2/Ang-1, angiopoietins 1 and 2; CA9, carbonic anhydrase 9; CD31, cluster of differentiation 31; EPCs, endothelial progenitors cells; HIF-1α, hypoxia-inducible factor-1; HPCs, hematopoietic progenitor cells; VEGF, vascular endothelial growth factor; VEGFR-1, vascular endothelial growth factor receptor 1; VEGFR-2, vascular endothelial growth factor receptor 2

The hypotheses emerging from basic research on colorectal liver metastases must be tested in clinical situations for the adaptation of current treatment strategies. Pre-metastatic niches have been shown to exist in human colorectal synchronous metastases, with the liver parenchyma adjacent to the synchronous liver metastases providing a favorable, angiogenic environment for metastatic tumor growth. The role of the VEGF signaling pathway in liver regeneration and tumor growth remains unclear, but the use of antiangiogenic agents in combination with surgical treatment is almost certainly beneficial.

Colorectal cancer is the second leading cause of cancer-related deaths, often due to uncontrolled metastatic disease.[1] The liver is the most common site of metastasis for colorectal cancer. Almost half the patients present liver metastases at diagnosis (synchronous metastasis) or develop liver metastases (metachronous) during the course of the disease. No randomized trial has been performed to assess the benefits of the surgical resection of liver metastases, but 25% to 30% of patients survive for at least five years after the complete resection of metastases, whereas very few unresected patients survived three years in historical series.[2]

The major elements of liver metastasis treatment are listed in **Table 1**. These elements are of importance because they may have major consequences. In particular, patients may die during the postoperative period, if the remnant liver is nonfunctional; death may be late and related to a disease recurrence if the metastases are not completely resected. New strategies have been developed and could be combined:

(1) Surgical methods of liver metastasis ablation, such as cryotherapy, radiofrequency treatment and laser hyperthermia ablation, could facilitate the treatment of central and/or multiple metastases;

(2) Preoperative radiological portal embolization to induce the hypertrophy of a particular segment of the liver, to increase the technical possibilities for liver resection;[3]

(3) Preoperative and postoperative chemotherapy, including VEGF-targeting or other antiangiogenic agents.[4,5]

Unfortunately, recurrences are still observed in two thirds of patients after the resection of liver metastases, and various approaches to reducing this risk are being investigated.[4-6] One such approach involves the use of preoperative treatment to select patients for surgery. Patients with multiple, large metastases diagnosed shortly after the resection of a stage III primary colon cancer are known to have a higher risk of recurrence after liver resection than those with small, solitary metastases occurring several years after the resection of a stage II cancer.[7,8] Long-term survival is possible only with surgical treatment. This has led to a trend to be more aggressive, with an increase in indications for the surgical resection of liver metastases. Long-term survival is now observed in patients undergoing the resection of large or multiple liver metastases, who would have been refused surgery in the past.

The optimal moment for chemotherapy, with or without antiangiogenic treatment, remains unclear and there is still debate about whether pre- or postoperative chemotherapy is preferable.[5]

Several recent studies have reported that the addition of a biological agent, such as cetuximab, panitumumab or bevacizumab, to the chemotherapy regimen increases the response to treatment and renders a larger proportion of tumors suitable for resection (**Box 1**).[9] Despite the proposal of new drugs for treatment, new concepts, such as the tumor microenvironment and metastatic niches, have not yet reached surgical practice. We performed a translational study, using VEGF-based concepts and hypotheses about interactions with the tumor microenvironment to reassess treatment in particular clinical situations.

There is considerable debate about the most appropriate treatment options for patients with colorectal cancer and synchronous

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Submitted: 10/06/12; Revised: 12/10/12; Accepted: 12/13/12
http://dx.doi.org/10.4161/cam.23247

Table 1. Available treatment strategies for colorectal liver metastases

Major element	Purpose	If not possible or uncertain	Possible consequences if not obtained
Complete resection or ablation of metastases	Cure	Preoperative chemotherapy with AAG	Liver recurrence
Prior systemic chemotherapy	Control of premetastic niches	Preoperative chemotherapy	Metastatic progression, even outside the liver
Ensuring a large enough volume of liver parenchyma	Avoiding postoperative failure	Portal vein embolization or two surgical interventions on the liver	Postoperative mortality
Ensuring that the remnant liver is biologically functional	Avoid postoperative failure	Stop preoperative chemotherapy	Postoperative mortality
Preoperative chemotherapy	Controlling and decreasing the size of the tumor	VEGF-targeting agent associated with chemotherapy	Liver recurrence
Postoperative chemotherapy	Decreasing the rate of tumor recurrence	VEGF-targeting agent associated with chemotherapy	Liver recurrence or metastatic progression, even outside the liver

AAG, anti-angiogenic agent.

unresectable metastases.[10] The impact of chemotherapy on the survival of such patients is unknown, with various authors presenting different opinions on this matter, but no conclusive evidence is yet obtained. Almost all the studies performed to date have been retrospective single-center or registry-based studies. It should be emphasized that in the series reported by Karoui et al., anti-VEGF therapy was a significant factor associated with overall survival in multivariate analysis.[10] The study populations were often heterogeneous in terms of chemotherapy regimen, the onset of metastatic disease (i.e., synchronous vs. metachronous) and the characteristics of the metastases. There is therefore a need to investigate more theoretical concepts originating from basic research.

Kaplan et al. showed that bone marrow-derived hematopoietic cells (HPCs) expressing VEGFR-1 colonize pre-metastatic sites in a mouse tumor model, thereby preparing the way for the arrival of the metastatic cells.[11] This new concept, the metastatic niche concept, was heralded as a major breakthrough. However, the animal model used, which is far removed from an orthotopic animal model, is of limited relevance, and no clinical demonstration was provided.

Seven years later, an analysis of human tissues led to the description of pre-metastatic niches in human specimens.[12] The study concerned aimed to investigate whether the presence of primary colorectal cancer was associated with changes in the angiogenic status of the adjacent liver parenchyma in patients with liver metastases. The authors compared three groups of patients, undergoing: (1) simultaneous resection of synchronous liver metastases and primary tumors (SS-group), (2) resection of synchronous liver metastases 3 to 12 mo after resection of the primary tumor [late synchronous (LS-group)] and (3) resection of metachronous metastases more than 14 mo after resection of the primary tumor (M-group). Gene expression and the localization of CD31, HIF-1α, components of the vascular endothelial growth factor (VEGF) and angiopoietin (Ang) systems were studied by quantitative RT-PCR and immunohistochemistry, in colorectal liver metastases and non-tumorous liver parenchyma adjacent to the tumors.

In all three groups, the authors reported the levels of angiogenic factors to be higher in the adjacent liver parenchyma than in the metastases. The VEGFR-2 gene was strongly expressed in the adjacent liver parenchyma in all three groups. This highlights the need to focus research not only on the cancer cells themselves, but also on their microenvironment, including angiogenesis-related aspects in particular. VEGF-A and VEGFR-1 levels in the adjacent parenchyma in the SS-group were approximately 2.5 and 10 times higher, respectively, than those in metachronous adjacent liver parenchyma. The VEGFR-2 gene was systematically more strongly expressed in the adjacent liver parenchyma than in the corresponding metastases, with the highest levels of expression for this gene recorded for the liver parenchyma adjacent to SS metastases. In this particular situation, VEGFR-2 mRNA levels were 14 times higher in the adjacent liver parenchyma than in the metastases. The Ang-2/Ang-1 ratio, indicating the net angiogenic effect of angiopoietins, was highest in the SS group, in both the metastases and the adjacent liver, and this high ratio was accompanied by a high turnover of tumor cells. The authors concluded that, in the presence of the primary tumor, the liver parenchyma adjacent to the synchronous liver metastases provided an angiogenic environment favoring metastatic tumor growth.

These results have important implications because one of the treatment options for cases of colon cancer with synchronous liver metastases is prolonged chemotherapy without primary cancer resection. Conversely, several retrospective studies have analyzed survival in patients with unresectable colorectal liver metastases, comparing groups of patients in which the primary section was or was not resected. These studies were not randomized and were performed almost at a single center, and most reported few data concerning the use of systemic therapy. In addition, patients with extensive disease were more likely to be offered chemotherapy rather than surgery, and this introduced an additional bias. Despite these limitations, median overall survival was found to be higher in patients undergoing resection than in those not undergoing resection, in most studies. A recent meta-analysis of eight retrospective, comparative studies including 1,062 patients

showed an improvement in the survival of patients managed by palliative resection of the primary tumor.[13] However, results from an ongoing high quality randomized controlled trial will help to answer this question, because others meta-analysis did not reported improvement of survival with surgical resection.

If the primary cancer creates a pre-metastatic niche, as suggested for ovarian cancer,[14] then primary tumor treatments that do not include resection are unlikely to be effective. The primary tumor should thus be resected, or specific combinations of drugs should be administered together with chemotherapy, to control the formation of pre-metastatic niches.

However, in patients undergoing partial hepatectomy, there is an instantaneous release of endothelial progenitor cells (EPCs) after laparotomy and liver mobilization. Recent studies have shown that bone marrow-derived EPCs play an important role in regulating the metastatic angiogenic switch.[11,15] In a model of lung cancer based on subcutaneous injection and a model of spontaneous breast cancer in transgenic mice, Gao et al. showed that the transition from micro (< 1 mm) to macro metastases in the lung was accompanied by the formation of a vascular network.[15] The EPCs infiltrated the periphery of avascular micro-metastases and were then incorporated into the lumina of macrovascular metastasis vessels. The transcription factor Id1 is known to be involved in tumor angiogenesis, and Id1 knockout mice display impaired tumor growth due to damage to angiogenesis-related bone marrow progenitors.[16,17] Id1 appears to be crucial for the mobilization of EPCs and their recruitment to micro-metastases. Gao et al. showed that EPCs were the only bone marrow-derived cells expressing Id1, and that the inhibition of Id1 expression with shRNA had no effect on initial metastatic colonization of the lung, instead inhibiting de novo angiogenesis and progression to macro-metastasis due to a lack of EPC recruitment. This study highlights the functional importance of EPCs in the metastatic angiogenic switch, because this cell type accounts for only 12% of the total number of endothelial cells in tumor vessels. Kaplan et al. confirmed that EPCs (VEGFR2-positive) arrived with tumor cells, in the pre-metastatic niche formed by the HPCs (VEGFR1-positive). Anti-VEGFR2 treatment did not prevent the formation of HPC clusters, but limited metastatic progression.[11]

Surgery also increases plasma VEGF concentrations.[18] Circulating angiogenic factors in colorectal cancer patients with liver metastases may promote tumor growth and contribute to liver regeneration after partial hepatectomy. New treatments should therefore aim to decrease the risk of liver metastasis, by reducing the population of EPCs and VEGF levels, through immunomodulatory or antiangiogenic treatment.[19]

In conclusion, the VEGF pathway and the pre-metastatic niche may influence oncological results for primary tumors with synchronous metastases, because liver surgery may increase the levels of VEGF and EPCs, thereby promoting cancer growth.

Based on this theoretical analysis, we can conclude that:

(1) Primary colon cancers should be resected rapidly, to minimize the activation of a pre-metastatic niche;

Box 1. Major effect expected for VEGF targeting agent
- Normal liver regeneration and wound healing modification
- Direct tumor control
- Indirect tumor control regarding microenvironment
- Decrease resistance for associated chemotherapy
- Predict clinical evolution as a prognostic marker
- Predict of response as a predictive marker

(2) Surgery should be followed by systemic chemotherapy associated with a combination of anti-angiogenic drugs to control the progression of liver metastasis;

(3) Any liver metastases should be resected;

(4) Immunomodulatory and anti-angiogenic treatments should be administered to minimize the risk of recurrence.

Each step in this clinical strategy will require testing and evaluation, rendering the design of any phase III clinical trial highly complex. Furthermore, particular situations may affect the likelihood of metastasis, modifying treatment requirements. For example, portal embolization may promote angiogenesis. In specific anatomic cases, portal vein embolization is performed to increase the volume of the non-embolized liver.[3] However, this stimulation of liver growth may also favor metastasis in the remnant liver. For this reason, chemotherapy is continued during the interval between embolization and surgery. In patients treated with bevacizumab before embolization, the question is whether or not to continue the anti-angiogenic treatment, as VEGF is thought to favor liver growth. One French study concluded that liver regeneration is affected by bevacizumab,[20] and suggested that treatment with this drug should be stopped during the interval between embolization and surgery. However, an American study came to the opposite conclusion, finding no effect on liver regeneration, and suggested the continuation of bevacizumab treatment.[21] These conflicting results indicate that the VEGR pathway is not the only pathway that should be targeted and that synchronous metastases are probably specific.

Some studies have reported a relationship between preoperative or postoperative VEGF levels and the risk of recurrence,[22] whereas others have found no such relationship.[23,24] In pathology, analyses of the interface between colorectal liver metastases and non-tumor liver parenchyma have generated conflicting results. Vermeulen et al. observed three different growth patterns (replacement, pushing and desmoplastic).[25] In replacement growth, tumor cells replace the hepatocytes in the hepatic plate, preserving the reticulin network of the liver parenchyma. In pushing growth, the hepatic plates are pushed aside and run parallel to the circumference of the metastases. In desmoplastic growth, the metastases are separated from the surrounding liver parenchyma by a rim of desmoplastic stroma. These authors subsequently confirmed the existence of these three growth patterns, in a larger study of 196 patients. Pushing growth is associated with an angiogenic pattern, with high rates of tumor and endothelial cell proliferation and a poor prognosis. This type of de novo angiogenesis is driven at least partially by hypoxia, with high levels of CA9 expression at the edge of the tumor.[26] Another study, with a smaller number of patients, found no difference in

microvascular density or survival between capsulated and non-capsulated colorectal liver metastases.[27]

However, no clinical test (levels of VEGF or other angiogenic factors, microparticles, microvascular density, etc.) is currently accepted as valid for use in routine practice. Most published univariate analyses have identified VEGF as a prognostic factor related to recurrence after primary tumor resection, but multivariate analyses of prognostic factors have revealed that it is actually lymph node metastasis from the primary tumor, R1 liver resection and general status that are significantly associated with worse prognosis, rather than VEGF.[28]

No biological test is yet available for determining the most appropriate treatment strategy, but the involvement of VEGF in pre-metastatic niches and the balance between tumor growth and liver regeneration could be used in clinical practice, to improve the outcome of surgery. Provided that this concept can be validated, treatment with anti-VEGF agents could be proposed and integrated into surgical strategies. Angiogenic factors are required for wound healing[29] and liver regeneration after the surgical resection of liver metastases. VEGF expression is therefore a physiological requirement to minimize postoperative complications. However, circulating angiogenic factors promote tumor growth and, probably, tumor recurrence, and high VEGF levels are therefore undesirable. The most important translational research target in the next years will be determining the exact balance between positive and negative effects on the patient and maintaining the correct balance at various points in the disease. Translational research will need to focus on plasma profiles of combinations of angiogenic factors, determinations of single factors, such as VEGF, and other associated biological findings, such as microparticle levels.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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