Leukemia (2007) 21, 1605

www.nature.com/leu

EDITORIAL

Imaging and angiogenesis in hematological malignancies

Leukemia (2007) **21,** 1605; doi:10.1038/sj.leu.2404790

Angiogenesis, consisting of the formation of new capillaries from pre-existing ones, is involved in several human diseases, such as chronic inflammation and cancer. Tumor angiogenesis plays a critical role in tumor growth and metastasis and there is a strong correlation between angiogenesis and prognosis in solid tumors and hematological malignancies. Therefore, suppression of tumor angiogenesis is expected to show potent effects through different approaches, such as monoclonal antibodies, tyrosine-kinase inhibitors, transcription inhibitors and small-molecule inhibitors.

Antiangiogenesis therapy needs a careful follow-up, and the evaluation of microvascular density (MVD) may reflect the antivascular activity of these therapies, but it is inadequate for overall evaluation of the status of tumor neovasculature. The functional status of blood vessels, including blood flow and vasculature permeability is not determined through MVD, so modern medical imaging techniques can play an important role in the evaluation of antiangiogenic treatment efficacy.

Common imaging techniques, such as dynamic contrast-enhanced perfusion magnetic resonance imaging (MRI), perfusion computed tomography (CT) and others, give only an indirect estimation of angiogenesis. For example, the change in CT image intensity due to contrast agent has a linear relation with blood flow. However, the limitations of CT in the detection of angiogenesis is that perfusion CT cannot detect immature new-forming vessels; besides the sensitivity of CT is limited, and relatively high doses of radiation limits the use of CT for repeated scanning.

New molecular imaging techniques can give an overall estimation of angiogenesis and antiangiogenic therapy effects. These new approaches include nuclear imaging techniques such as single positron emission tomography and positron emission tomography, which have been fused with CT to obviate their shortcomings in anatomical information,[1] particularly MR, that uses paramagnetic nanoparticles to track angiogenesis by targeting $\alpha v\beta 3$ integrin[2] and other specific angiogenesis markers, sonography with novel contrast agents such as gas-filled microbubbles, direct against specific target endothelial cell receptors[3] and optical techniques.[1]

Multiple myeloma is a plasma cell-proliferative disorder, in which there is evidence that angiogenesis is correlated with disease progression. After chemotherapy, MVD in bone marrow of patients responders is lower compared with non-responders, and progression-free survival is significantly longer in patients with decreased MVD. The antiangiogenic therapy represents an important approach for the treatment of this disease, so there is a necessity to detect angiogenesis during the followup of the patients. By using dynamic contrast-enhanced MR imaging, which correlates with capillary blood flow and permeability, and the relative volume of extravascular extracellular space, a correlation between contrast enhancement decrease and a reduced MVD in patients responders and in complete remission[4] has been demonstrated in multiple myeloma.

Acute myeloid leukemia is associated with an increased bone marrow angiogenesis, which correlates with clinical outcome of the patients, and antiangiogenic therapy has been used as a new approach in this disease. In this disease, bone marrow infiltration causes a diffuse and homogeneous decrease in signal intensity on T1-weighted images and MR studies allow to assess bone marrow in response to treatment and the relationship between prognosis and bone marrow MR patterns. A report of functional MR imaging of tumor angiogenesis in acute myeloid leukemia demonstrated that patients with high bone marrow tissue perfusion estimated as peak of contrast enhancement, or high blood flow estimated as initial maximum enhancement slope, which is most influenced by MVD, had decreased disease free-survival and overall survival compared to patients with low perfusion and low blood flow. Therefore, functional MR imaging may help to monitor treatment response to antiangiogenic therapy in patients with acute myeloid leukemia.[5]

In hematological malignancies, the use of antiangiogenesis drugs is now in the clinical practice, but there is no standardized imaging methodology for monitoring therapy. At present, it may be useful to use the dynamic contrast-enhanced MRI, while in the future new molecular imaging modalities, such as MRI with paramagnetic nanoparticles targeted against the $\alpha v\beta 3$ integrin or other angiogenic markers, will give the possibility to detect in more precise and repeatable way the efficacy of antiangiogenic drugs.

Acknowledgements

This study was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC, Regional Funds), Milan, the Ministry for Education, the Universities and Research (FIRB 2001, PRIN 2005 and Project CARSO n. 72/2), Rome and Fondazione Italiana per la Lotta al Neuroblastoma, Genoa, Italy.

V Longo[1], A Vacca[2] and D Ribatti[1]
[1]*Department of Human Anatomy and Histology, University of Bari Medical School, Bari, Italy and*
[2]*Department of Internal Medicine and Clinical Oncology, University of Bari Medical School, Bari, Italy*
E-mail: ribatti@anatomia.uniba.it

References

1 Dobrucki LW, Sinusas AJ. Imaging angiogenesis. *Curr Opin Biotech* 2007; **18**: 1–7.
2 Mulder WJ, van der Schaft DW, Hautvast PA, Strijkers GJ, Koning GA, Storm G *et al.* Early *in vivo* assessment of angiostatic therapy efficacy by molecular MRI. *FASEB J* 2007; **21**: 378–383.
3 Klibanov AL. Ligand-carrying gas-filled microbubbles: ultrasound agents for targeted molecular imaging. *Bioconjug Chem* 2005; **16**: 9–17.
4 Baur A, Bartl R, Pellengahr M, Baltin V, Reiser M. Neovascularization of bone marrow in patients with diffuse multiple myeloma: a correlative study of magnetic resonance imaging and histopathologic findings. *Cancer* 2004; **101**: 2599–2604.
5 Shih TT, Tien HF, Liu CY, Su WP, Chan WK, Yang PC. Functional MR imaging of tumor angiogenesis predicts outcome of patients with acute myeloid leukaemia. *Leukemia* 2006; **20**: 357–362.