Clinical trials with angiogenesis inhibitors

[haematologica reports]
2005;1(9):38-39

GIACCONE G
VAN CRUIJSEN H

Department of Medical Oncology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Angiogenesis is essential for tumor growth and metastasis formation. Many agents have been developed to inhibit this process. Two major anti-angiogenic strategies have been so far mostly developed: the vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and several tyrosine kinase inhibitors (TKI) to VEGF receptors.

Bevacizumab is the first specific anti-angiogenic agent registered. This registration was based on the results of the phase III trial which compared first-line chemotherapy plus bevacizumab to chemotherapy alone in patients with metastatic colorectal cancer. Treatment with chemotherapy plus bevacizumab resulted in higher response rates (chemotherapy, 35%, chemotherapy plus bevacizumab, 45%) and longer median survival (chemotherapy, 15.6 months, chemotherapy plus bevacizumab, 20.3 months).[1] Recently results of more phase III studies have become available. Adding bevacizumab to the standard platinum-based chemotherapy for the treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) resulted in an improved response rate (10% versus 27%), progression-free survival (4.5 months versus 6.4 months) and median survival (10.2 months versus 12.5 months) compared to chemotherapy alone.[2] Another phase III study of paclitaxel as first line vs paclitaxel plus bevacizumab also demonstrated a survival benefit from the combination.[3] Another phase III study in second-line chemotherapy of metastatic colorectal cancer also demonstrated a significant increase in survival in the bevacizumab arm.[4] The summary of the results of the three last studies presented at the American Society of Clinical Oncology 2005 are reported in Table.[1] Besides, phase II/III trials have been conducted to assess the safety and efficacy of bevacizumab in metastatic breast carcinoma in later stages when added to chemotherapy and as single agent in metastatic renal cell carcinoma.[5]

At least 17 different VEGFR TKI's with their own selectivity profile are currently in clinical development, among others PTK/ZK, AZD2171, SU111248, and BAY 43-9006. Recently results of the phase III study in patients with metastatic colorectal carcinoma receiving chemotherapy and PTK/ZK, a TKI of all VEGF receptors, or chemotherapy and placebo were presented. These results suggest a positive effect on progression-free survival of chemotherapy with PTK/ZK.[6] Data about survival are awaited, but it would appear that the extent of benefit is probably smaller than the one achieved with bevacizumab. Besides, in pretreated patients with metastatic renal cell carcinoma BAY 43-9006, a Raf kinase and VEGFR inhibitor, prolongs progression-free survival compared with placebo.[7]

To date, no studies have been conducted to compare oral TKIs of VEGFR with monoclonal antibodies although small molecules could be preferable. Oral formulation, promiscuity of the target, no risk of hypersensitivity and a possible preferable toxicity profile are advantages of tyrosine kinase inhibitors over monoclonal antibodies.

Along with the clinical development of anti-angiogenic agents questions raise how to monitor and evaluate anti-cancer activity. Can certain biomarkers predict and monitor response to anti-angiogenic therapy and is tumour evaluation based on tumour diameters still sufficient? Another discussion is about the dosing schedule of anti-angiogenic agents. Given the low single agent activity of anti-angiogenic agents, these agents should be integrated in standard systemic therapies. What is a rational combination and sequence?

The challenge for preclinical and clinical studies includes to address these questions leading to an optimal study-design and eventually to better outcomes for cancer patients.

Table. Bevacizumab phase III. ASCO 2005.

Tumor	#pts	Therapy	RR(%)	PFS(m)	Surv(m)
CRC 2nd M	829	FOLFOX	9.2	5.5	10.7
		FOLFOX-B(10)	21.8*	7.4#	12.5@
		B(10)	3.0	3.5	10.2
Breast 1ST M	715	PXL	14.2	6.1	HR .674
		PXL-B(10)	28.2*	11#	*p*=.01
NSCLC 1ST M	878	PXL-CRB	10	4.5	10.2
non-SQ		PXL-CRB-B(15)	27.2*	6.4*	12.5
				p=.007	

#*p*=.0003; @*p*=.0224; **p*<.0001

References

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