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EDITORIAL

Angiogenesis in unknown primary tumors

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Angiogenesis is the process through which new capillaries are formed from pre-existing vessels, and it takes place during the embryonic development and in adult life, under physiological conditions in the female reproductive system and in pathological conditions, as in the chronic inflammation and in tumor growth [1].

Tumor angiogenesis has been extensively investigated in solid and hematological tumors, as well as in pre-malignant conditions, and there are a lot of data regarding the link between tumor angiogenesis, metastasis, and overall survival [2–4].

Unknown primary tumors (UPT) account for 0.5–7% of all malignancies [5]. The term UPT characterizes a metastatic disease, most commonly involving liver, lung, and/or bone, for which diagnostic work-up fails to identify a site of origin. Histologic subtypes of UPT include adenocarcinoma with various degrees of differentiation, squamous cell carcinoma, poorly differentiated carcinoma, and neuroendocrine cancer [5]. Early dissemination and aggressiveness represents a fundamental characteristic of these tumors. Overall, outcome of patients remains poor, with a medial survival ranging from 6 to 12 months [5].

Literature data concerning angiogenesis in UPT are scarce. Hillen et al. [6] have compared microvessel density in liver metastases of UPT with microvessel density in known primaries and in liver metastases of colon and breast tumors. They found no indication for a specific biological role of angiogenesis in the metastatic phenotype of the UPT. In fact, metastases of UPT showed a high degree of vascularization and this pattern was also found in metastatic tumors of primary breast and colon cancer and as in other solid tumors, higher microvascular density was associated with worse prognosis. The same authors in another work demonstrated that immunohistochemical detection of vascular endothelial growth factor-A (VEGF-A) and of the endothelial marker CD34 did not have a prognostic significance in patients with UPT [7].

Karavasilis et al. [8] assessed immunohistochemically the tissue expression of CD34, VEGF, and thrombospondin-1 (TSP-1) in a retrospective study on 81 patients with UPT and correlated these data with clinicopathological parameters. They demonstrated that the expression of VEGF and TSP-1 was not associated with any clinical or pathological parameter and that tumor microvascular density was higher in tumors classified as unfavorable compared to more favorable and was positively associated with VEGF and negatively with TSP-1. The same authors have demonstrated by immunohistochemistry that matrix metalloproteinase-2 (MMP-2) and MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) are widely expressed in patients with UPT, suggesting an essential role of proteolysis in these tumors, also as factors that promote and control angiogenesis [9].

Accordingly to above-described evidence, antiangiogenesis has been proposed as a therapeutic strategy in the treatment of patients with UPT. Hainsworth et al. [10] have evaluated the efficacy and toxicity of combination inhibition of VEGF and epidermal growth factor receptor (EGFR) with bevacizumab and erlotinib in patients with

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UPT. This combination has substantial activity in the treatment of patients with UPT. In fact, the median survival was superior to survival previously reported with second-line chemotherapy and was similar to the results of many first-line chemotherapy trials in this setting. However, since this phase II trial was non-comparative, no definitive conclusions can be stated regarding the efficacy of this combination compared to others.

More recently, Hainsworth et al. [11] have evaluated the efficacy and toxicity of the combination of paclitaxel, carboplatin, bevacizumab, and erlotinib in the first-line treatment of patients with UPT. Results showed that 53% of patients had major responses to treatment. After a median follow-up of 19 months, the median progression-free survival time was 8 months, with 38% of patients' progression free at 1 year and treatment was generally well tolerated.

Overall, these data suggest that angiogenesis is an important event involved in the pathogenesis, maintenance, and progression of UPT, even if it is important to note that since most carcinomas of UPT are adenocarcinomas, it is not surprising that the observations concerning angiogenesis in these tumors are similar to those that have been much more throughly evaluated in a variety of other types of adenocarcinomas.

Moreover, antiangiogenesis may be considered as a potential therapeutic strategy in the adjuvant treatment of this little known pathological condition. Nevertheless, more experimental and clinical studies are necessary to further clarify and support this statement.

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