

Reviewer's report

Title: Hypothesis: Primary antiangiogenic method proposed to treat early stage breast cancer

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Reviewer: Thomas Bachelot

Reviewer's report:

This paper describe a nice hypothesis but our feeling is that it is actually not sufficiently supported by available data to be rapidly tested in a clinical trial. This idea isn't new and has been around as soon as the first results with angiostatin and endostatin were published in 1996. As a consequence, important preclinical works have already been published. Unfortunately, the references the authors use to support there hypothesis are mostly derived from their own theoretical work.

Major Compulsory Revisions:

The authors must give us a broader view and interpretation of both preclinical and clinical data. I list below few conflicting data that should be taken into account

1) The first part of the hypothesis is that the so called "dormant metastases" in breast cancer patients are angiogenesis based. To our knowledge, this have never been demonstrated in human breast cancer. The only known "dormant metastases" ever observed in breast cancer patients were found in the bone marrow and often described as single cells, which would likely fit within the "single cell dormancy" hypothesis. Furthermore, preclinical data are not straightforward and depends greatly on the animal model used in the study. Preclinical data supporting the "angiogenesis hypothesis" of dormant metastases are mostly derived from the famous Lewis Lung Carcinoma model, which do not represent the entire spectrum of metastasis biology. Besides, Staquet and col. have shown that this model is poorly relevant when it comes to predict drug action in human subject (Staquet et col.. Cancer Treat Rep 67:753, 1983).

2) The second part of the hypothesis is that by giving continuous SC endostatin, it is possible to prevent the angiogenic switch of "dormant metastases" and, as a results, prevent disease relapse. The idea to induce tumor dormancy with continuous high level release of endostatin has been extensively tested with mixed results.

Unfortunately, the original results from Boem et al. (Nature, 1997, 390, 404), showing that endostatin has the property to induce the definitive regression of experimental tumors to a microscopic dormant state, never have been reproduced. At best, the reports published afterward have only shown a reduction in tumor growth. Our team have shown that mice transplanted with

hematopoietic stem cells transduced with a retrovirus encoding a soluble form of endostatin have circulating levels of endostatin 7 time higher than control. Despite this result, there is no inhibition of in-vivo angiogenesis nor antitumor activity (Pawliuk et al, Mol Ther, 2002, 5, 345). Other authors have published similar results (Kuo et al. Proc Natl Acad Sci U S A. 2001; 98:4605)

Retsky et al. states in their paper that Down's syndrome is an example of cancer prevention by high levels of circulating endostatin, which should be safe as not associated with delay in wound healing. One could argue that this last statement is in favour of a lack of anti-angiogenesis effect of endostatin. The relation between high serum endostatin levels in those patients and their "resistance" to cancer is hypothetical. Many other hypothesis could be derived from the amount of genetic deregulation associated with trisomy 21. (As collagen XVIII is a major component of the basal membrane of tumor-associated blood vessels, it could well be its uncontrolled expression that is, in fact, responsible for a relative defect in tumor angiogenesis in Down's syndrome patients). Moreover, as suggested by the author as a future work to be done, Sund et al. (PNAS 2005, 102, 2934) have already described an animal model of transgenic mice mimicking Down's syndrome condition with a 1.6 fold increase in circulating endostatin. In this model, tumor growth is slowed, but is not "prevented".

With regard to clinical data, the trials published to date are not in favour of endostatin. Due to the high expectation surrounding endostatin, the Phase I and Phase II clinical trials have been highly publicised and were done following the highest standard with regard to clinical trial methodology and translational research (Herbst RS Curr Oncol Rep. 2001 3:131; Mundhenke C; Clin.Cancer Res. 2001, 7:3366; Herbst RS J.Clin.Oncol. 2002, 20: 3792 and 3804); Those trials failed to show any significant anti-tumor activity and, most importantly, failed to show any biological activity of endostatin, neither in wound healing nor in tumor angiogenesis. This is in sharp contrast with the results of early clinical trials of bevacizumab or sunitinib. As for Endostar, no clinical data have been published in peer review journal so far. As a consequence, we do not think that it is reasonable to propose any hypothetical use of that drug at the moment.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have a small part on a patent on gene therapy using natural inhibitor of angiogenesis