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Ways to Achieve an Increase of the Efficacy of Anticancer Therapies via A Double Antiangiogenic Therapy and How to Avoid Pitfalls

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Abstract

The improvement of the efficacy of an antiangiogenic therapy in cancer therapy is a valuable goal. There exist different methods how to achieve and what should be avoided.

Keywords: Antiangiogenic therapy; Thymidine phosphorylase; Endothelial blockade

Introduction

Antiangiogenic therapy (AAT) is directed against one of the hallmarks of cancer [1]. The blockade of AAT offers one possibility to retarden tumor growth. The inhibition of neoangiogenesis may achieved by several ways. The blockade of activity of vascular endothelial growth factors or its receptors may be achieved by antibodies against vascular endothelial growth factor (VEGF) or by tyrosin kinase inhibitors (TKI) directed against vascular endothelial growth factor receptors (VEGFR) such as regorafenib, fruquintinib, lenvatinib, sunitinib, or apatinib. Endothelial cells may be led into apoptosis by the use of endothelial located enzymes such as thymidine phosphorylase (TP) [2] resulting in apoptosis of the harbouring cells by 5-FU or its prodrugs such as capecitabine or S1 [3]. Alternatively, an inhibition of endothelial TP may be performed by tipiracil which is a component of TAS102 (trifluridine-tipiracil).

Methods

We looked for methods how to strengthen the efficacy of the concept of a double AAT.

Results

There have been attempts to increase the AAT by the combination of AAT activities by the parallel treatment via the anti VEGF antibody bevacizumab and with the drug capecitabine compared to capecitabine alone as performed in the in the AVEX trial [4] and by the parallel therapy with bevacizumab and TAS102 compared to TAS 102 alone in the SUNLIGHT Trial [5]. The double AAT of patients with metastatic colorectal cancer (crc) resulted in an increased efficacy. However, the double AAT with Ramucirumab, an antibody against VEGFR2, and with TAS102 containing tipiracil as an inhibitor of TP in patients with metastatic colorectal cancer (crc) resulted in no increased efficacy [6]. Also, a double AAT with an antibody against VEGFR2, cisplatin and fluoropyrimidine compared to cisplatin fluoropyrimidine in patients with metastatic gastric or junctional adenocarcinoma resulted in no increased efficacy (RAINFALL trial) [7]. The combination of S1 which is a prodrug of 5-FU plus oxaliplatin with or without ramucirumab followed by paclitaxel plus ramucirumab in patients with advanced gastric cancer did not prolong overall survival among East Asian patients (RAINSTORM Trial) [8]. In patients with metastatic colorectal cancer a first line therapy with TAS 102 plus bevacizumab was not superior to capecitabine plus bevacizumab (SOLSTICE Trial) [9] arguing that in the combination therapy TAS 102 was not more efficient than capecitabine. In patients with advanced metastatic breast cancer a combination with VEGF receptor antibodies with capecitabine compared to capecitabine alone showed no superiority [10].

Discussion

We searched for a possible reason for these results.

The combination therapy of patients with crc with an antibody against VEGF and an endothelial blockade via TAS102 or capecitabine is directed against different targets. An anti-VEGF antibody targets VEGF-A [11], whereas TAS102 or 5-FU or its prodrugs inhibit endothelial cells. The action of an anti VEGFR2 antibody also inhibits endothelial growth like TAS102. However, in the combination therapy it is provided that the anti-VEGFR2 antibody still has the possibility to target an antigen located on the cell surface. It has to be acknowledged that VEGFR2 significantly is located intracellular in an endosomal storage [12]. The VEGFR2 receptor translocation to an extracellular position is possible [13] however is depending on a still living cell. In vivo, a peripherally applied antibody will have problems to modify translocation activities of already apoptotic endothelial cells. This partly may explain the low results of a combination therapy of substances simultaneously directed against extra- and intracellular targets.

A combination therapy with substances directed against targets located on the cell surface and a TP inhibitor offers a good way to achieve an increase in efficacy, However, the translocation of an intracellular located target to the cell surface is dependent on a still living cell. If endothelial cells are already apoptotic the result of the activity of the component directed against an intracellular endothelial target is likely to be not very efficient.

Conclusion

The efficacy of an AAT combination has to be acknowledged. The combination of bevacizumab with an antineoplastic therapy promises good results. However, when applying combination therapies the location of the desired targets within the cells and the capabilities of the applied substances should be considered.

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