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Prolonged Survival in Metastatic Gastrointestinal Cancer and the Significance of the Modulation of the Activity of Cells of the Tumor Microenvironment

Koch BA* **and Uflacker L**

St. Vincenz Hospital, Internal Medicine, Datteln, Germany

***Corresponding author:** Bernhard A Koch, St. Vincenz Hospital, Internal Medicine, Datteln, Germany; E-mail: B.Koch@vincenz-datteln.de

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Abstract

Several reports have described cases with a prolonged survival time of patients with various advanced gastrointestinal tumours after long-term treatment with antiangiogenic agents. We summarise arguments to appreciate the value of the blockade of cells of the tumour microenvironment indicating their role as additional drivers in the tumour progress.

Keywords: *Tumor microenvironment; Antiangiogenic therapy; Protumoral inflammation; Thymidine phosphorylase; Tumor associated macrophages*

Introduction

The course of malignant diseases results from the interaction of multiple factors. Some of these are the characteristics of the tumor itself, others are the composition of the tumor microenvironment (TME), and the therapeutical procedures applied. Immunohistological studies have demonstrated the presence of inflammation associated cells in the TME. The significance of the cells within the TME is in the focus of interest [1]. There is a complex interaction between a tumor itself and the surrounding cells. Some cell populations support the tumor growth, summarised under the term protumoral inflammation (PTI), some attack the tumor and delay tumor growth. So aspects of the inflammation may mediate beneficial and other may have deleterious effects [2]. When the significance of a therapeutical regimen against a malignant process has to be judged one has to consider the primary and secondary factors influencing each other. To achieve a better understanding of the complex network behind one should turn the attention to the procedures resulting in the effect of a prolonged survival, and one should look if there are common targets involved. Since the PTI is one factor which supports tumor progression, the blockade of factors involved in a PTI will lead to a deceleration of tumor growth, and may result in a prolonged survival time [3].

Cells in the TME of gastrointestinal tumors and prognosis

The TME is linked to the presence of inflammation associated cells such as tumor associated macrophages (TAMs), endothelial cells, and myeloid cells such as neutrophiles, stromal fibroblasts, and dendritic cells.

Macrophages are an important however heterogeneous cell population in the stromal compartment of gastrointestinal tumors [4]. One may distinguish between pro-inflammatory M1-like macrophages and anti-inflammatory M2-like macrophages. In colorectal cancer a high tumor stromal density of M2-like macrophages was associated with a worse cancer specific survival whereas tumor stromal density of M1-like macrophages was not. A high M1:M2 density ratio in tumor stroma was associated with better cancer specific survival [5]. In gastric cancer a meta-analysis showed that the numbers of infiltrating M2 macrophages and total TAMs might be negative prognostic factors, while M1 macrophage infiltration may be associated with a favorable survival rate [6]. In pancreatic cancer higher levels of tumor infiltrating pan-macrophages and M2 macrophages were related

to shorter survival, the ratio of M1 macrophages to pan-ta-macrophages with longer survival [7]. A metanalysis of the value of the TAMs in hepatocellular carcinoma (HCC) showed that a high expression level of CD206 positive intratumor M2 macrophages was associated with poor prognosis [8].

Table 1: *Survival time of patients with advanced or metastatic gastrointestinal cancer following antiangiogenic single agent therapy in phase II or phase III studies (A) following prolonged treatment in single cases (B).*

(A)					
Cancer	treatment	No of patients	mPFS#	mOS#	reference
EGJ	cap *	30	11	17	[32]
	BSC*	30	7	11	
HCC	metronomic cap**	58	3,1	12	[33]
	BSC**	53		9	
pancreatic	cap***	43		17	[34]
CRC	TAS-102*	534		7,1	[35]
	placebo*	266		5,3	
gastric	TAS-102*	337		5,7	[36]
	placebo*	170		3,6	

(B)			PFS#	OS#	
CRC	cap maintenance****	1	>87		[37]
gastric	S-1 maintenance ****	1	>96		[38]
CRC	S-1 maintenance*/****	1	>54		[39]
gastric	TAS-102 */****	1		38	[40]

* following (multiple) anticancer pretreatment
** following sorafenib discontinuation or intolerance
*** following cap and radiation
**** following surgery (R1)
# months
mPFS: median progression free survival
mOS: median overall survival
BSC: best supportive care
EGJ: esophagogastric junction adenocarcinoma
HCC: hepatocellular carcinoma
CRC: colorectal cancer
CAP = capecitabine
S-1 = Tegafur + Gimeracil + Oteracil
TAS-102 = trifluridine + tipiracil

Similar results were obtained in cholangiocarcinoma where a high level of CD163+ M2 macrophages was related with worse survival [9]. Another important cell population within the TME are the endothelial cells as representatives of the angiogenesis. The level of angiogenesis may be reflected by the micro vessel density (MVD). In colorectal cancer a meta-analysis showed that MVD could be interpreted as a prognostic factor. A high MVD significantly predicted poor relapse free survival and overall survival (OS) [10]. In gastic cancer a high MVD was significantly associated with lymph node metastasis and poor survival [11]. A correlation between high MVD and poor survival could also be detected in pancreatic cancer [12]. In hepatocellular carcinoma (HCC) MVD was correlated to metastasis and worse prognosis [13]. In hilar cholangiocarcinoma a higher incidence of MVD was related to lymph node metastasis and to local recurrence, and also to worse disease free survival and OS [14].

Currently admitted drugs for the modulation of the activity of cells in the TME of gastrointestinal tumors

Various drugs may modify the activity of the inflammatory cells thereby emphasising their significance for the course of the malignant process. Antiangiogenic therapy (AAT) may be performed by targeting growth factors necessary for the propagation of endothelial cells, or growth factor receptors, or intracellular structures of cells in the TME which modify their function.

Targeting may be achieved by several methods:

By monoclonal antibodies against the vascular endothelial growth. Factor (VEGF) such as bevacizumab, - by a fusion protein such as aflibercept acting as inhibitor of VEGF, - by antibodies against VEGF-R such as ramucirumab, - by tyrosin kinase inhibitors such as sorafenib targeting VEGFR2 on endothelial cells, - or by the exposition to 5-FU or its prodrugs capecitabine or tegafur [15-20]. Capecitabine is one prodrug of 5-FU. The conversion to 5-FU is dependent on the presence of the enzyme thymidine phosphorylase (TP). Once 5-FU is generated the exposed cells will go into apoptosis as shown with colorectal tumor cells and with peripheral blood leukocytes [21]. Tegafur also is a prodrug of 5-FU and is a component of the drug Teysuno R (=S-1). S-1 has proven its value in the treatment of gastric cancer [22]. Tipiracil is an inhibitor of TP, increases the effect of trifluridine on exposed cells, and is a component of the drug Lonsurf R (=TAS-102) [23].

Role of thymidine phosphorylase

An important target in the TME is the enzyme TP, whose role has been extensively reviewed [24]. TP has got alternative designations: platelet-derived endothelial-cell growth factor (PDECGF) and gliostatin. Its activity has been demonstrated in various diseases situations, both in oncology and in inflammatory diseases such as rheumatoid arthritis. The localisation in normal human tissues has been described many years ago [25]. It has has been ascribed to endothelial cells, to cells of the macrophage-lineage, and to fibroblasts, which play a role in stromatogenesis [26]. The analysis of the occurrence of TP in human solid tumors has revealed its presence in various cancer situations. TP has been reported to mediate angiogenic activity and has been demonstrated in the TME of colorectal carcinoma, of gastric carcinoma, of pancreatic carcinoma, and of gallbladder adenocarcinoma [27-30]. TP may be induced by low dose radiation and interacts with cytokines released during chronic infections as reviewed earlier. This may explain a connection between chronic infections and cancer. Angiogenesis related to peritumorally induced TP by low dose radiation may be treated by a neoadjuvant concept combining radiation and antiangiogenic therapy (AAT) as demonstrated in rectal cancer [31].

Survival times of a prolonged single agent AAT with orally available drugs targeting cells in the TME of patients with metastatic gastrointestinal tumors

The effects of the administration of AAT with prodrugs of 5-FU or with tipiracil are listed in table 1. Demonstrated are the results of a treatment of patients with various gastrointestinal malignancies such as colorectal cancer, gastric cancer, pancreatic cancer, and hepatocellular cancer. Capecitabine is converted to 5-FU and the treatment with prodrugs of 5-FU results in the apoptosis of the exposed cells. Tegafur also is a prodrug of 5-FU and is a component of the drug Tesuno R. Tipiracil enhances the efficacy of trifluridine and both are components of the drug Lonsurf R.

Displayed are the results of a treatment in phase II and phase III studies (section A) and the results of the treatment of single cases indicating survival following maximal treatment time (section B) [32-40]. The results of the studies in section A showed that the single agent AAT was significantly superior to the controls. The survival time of single patients in section B was clearly superior in comparison to the median OS of the affiliated entities as known from the SEER data bases. The results demonstrate the potency of an AAT targeting cells in the TME.

Conclusions

The tumor characteristics, the modalities of the therapy, and the characteristics of the infiltration pattern of the TME are related to the survival time. All these factors interact with each other and have to be judged in the context with each other. The efficacy of the antiangiogenic treatment underlines the importance of endothelial cells and macrophages as protumoral acting cells in certain stages of the tumor growth.

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