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Commentary

Alternative Chemotherapies: Angiotensin-Converting Enzyme Inhibitors Reduce Myeloid-Derived Suppressor Cells to Benefit Older Patients with Colorectal Cancer

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Abstract

Older individuals are more likely to develop solid cancers, but at the same time are more sensitive to the side effects of chemotherapy. In addition, older adults are more likely to present with chronic diseases (comorbidities) and immunosenescence that may decrease immunosurveillance against cancer. Clinical outcomes for the older patient with cancer are different from the younger patient and require different research and treatment approaches. Thus, alternative therapeutic approaches tailored specifically to the older patients are required. Colorectal cancer (CRC) has a high incidence in older individuals and is the third leading cause of cancer death globally. Anti-hypertensives are used by a large proportion of older patients and some studies have pointed to a positive impact of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) on CRC outcomes. As we have previously shown in a mouse model, lung metastases express ACE and contain many infiltrating myeloid-derived suppressor cells (MDSC); particularly high levels of MDSC are also present in the blood of older patients with CRC and other cancers, and are associated with disease severity. In this Commentary, we hypothesize that one mechanism responsible for the positive impact of ACEi or ARB on the outcome of CRC is the modulation of myeloid cells contributing to their maturation to non-suppressive neutrophils/monocytes and diverting them away from retaining an immature MDSC phenotype.

Keywords: longevity; comorbidities; colorectal cancer; immunosenescence; myeloid-derived suppressor cells; angiotensin-converting enzyme

1. Colorectal Cancer (CRC) in Older Adults

Increasing life expectancy in most countries is linked to improvements in prevention and treatment of non-transmissible diseases and vaccination against transmissible diseases. It has been projected that by 2050, one in six people in the world will be older than 65 years (16%) [1]. Considering that chronological ageing does not exactly parallel biological ageing, individuals older than 65 years can be healthy or present one or more morbidities (comorbidities) [2] and chronic diseases lead to disabilities in a great percentage of the ageing population [3]. Besides the negative impact on activities of daily living of the older adult, there is an economic burden by the loss to the workforce and increased medical expenditure [4,5]. The incidence of most solid cancers is higher in older individuals and thus cancer has been considered an age-related disease [6]. Ageing and cancer are cellular and molecular processes sharing similarities since both are associated with accumulated mutations [7,8]. The average age of CRC appearance is 67 years [9] and in patients with metastases, the one-year survival is 70–75%, 30–35% of patients survive more than 3 years and only 20% survive for 5 years (reviewed in [10]). The risk of death is increased in CRC patients from 50 to 74 years of age and is highest in patients older than 75 [11]. The outcome of older patients with CRC is thought to be different from young individuals mostly because of increased comorbidities and immunosenescence. The latter can be described as resulting in decreased immunity against pathogens and cancer due to changes occurring in the organs of the immune system which impair the generation and function of immune cells. These differences commonly encompass disproportionate increases of myeloid cells which act as immune suppressors (MDSCs). Therefore, immune cell number and function altered during the ageing process can be assessed and employed as biomarkers [12–14]. In addition, most of older adults suffer from one or more morbidities which also impact cancer outcome [15,16]. The use of five or more drugs for such morbidities (polypharmacy) is not unusual in the older population, which is an important point to be considered also in the context of anti-cancer therapy. Erning *et al.* [17] surveyed 2735 patients with CRC at age >70 years, reporting that 1342 were receiving 7 or more drugs, 41% took 1–6, and only 10% were free from the use any drug.

2. CRC and Anti-Hypertensives

Amongst older CRC patients, hypertension and cardiovascular disease are quite common. Data from 2005 to 2008 on 12,648 metastatic CRC patients showed that 52% were $\geq$65 years old and 48.3% were hypertensive. In that study, the most commonly-used drugs were antibiotics and anti-hypertensives (61.7% and 49.7% respectively) [18]. The use of anti-hypertensives such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) has been evaluated in CRC because there is evidence of cancer risk reduction in patients taking these drugs. A meta-analysis of 6 studies with 113,048 patients found that the incidence of CRC was significantly reduced in patients receiving ACEi/ARB relative to non-users, and that they had a better clinical outcome [19]. There may therefore be an argument for administering these drugs to older CRC patients even if they are not hypertensive. Mechanistically, angiotensin has been linked to tumor growth because Active Mediator Angiotensin II (AT2), the active product derived from angiotensin, is associated with cell growth, angiogenesis and activation of the AT1R receptor. Intracellular signaling through the Angiotensin II Type I Receptor (AT1R) is involved in many pathways, including fibroblast growth factor, epidermal growth factor, transforming growth factor-beta, platelet-derived growth factor, nitric oxide synthase, protein kinase C, angiopoietin 2, and metalloprotease (reviewed in [20]).

Prophylaxis with these drugs may also be beneficial. Thus, in patients without cancer at colonoscopy, the use of ACEi or ARB (for at least 180 days) was evaluated and correlated with tumor development between 3 and 36 months after the negative diagnosis. After 3 years of follow-up, patients using ACEi/ARB (n = 30,856, 61–78 years of age) exhibited a significantly lower incidence of CRC than non-users [21]. Also, a retrospective study with 13,982 patients ($\geq$65 years of age) diagnosed with CRC found that the use of ACEi, beta blockers and thiazide diuretics was associated with reduced mortality. A correlation between adherence to therapy with anti-hypertensives and decreased specific mortality due to CRC was also seen. It was therefore suggested that these drugs could be used as supplements to the anti-tumor therapy for the treatment of CRC in stages I–III [22]. In another example, Morris *et al.* [23] evaluated patients with rectal cancer treated with neoadjuvant radiotherapy or chemo-radiotherapy followed by surgical resection and found that there was a significant positive correlation between taking ACEi/ARB anti-hypertensives and increased regression and lower tumor grade. It was concluded that ACEi/ARB may modulate the tumor response to neoadjuvant therapy in CRC patients [23]. Engineer *et al.* [24] also reported that patients (60–65 years) with stage III CRC, taking ACEi/ARB drugs or beta blockers and treated with chemotherapy or radiotherapy had less tumor progression, less hospitalization, and reduced mortality relative to non-users. However, in contrast, in a smaller study (n = 112, mean age 62 years), Zeman *et al.* [25] reported that patients with adenocarcinoma and cancer-positive regional lymph nodes had worse survival after neoadjuvant therapy and rectal resection. The reason for this discrepancy may be the different nature of the small number of patients in that study, or perhaps more likely the focus only on regional lymph nodes.

3. CRC and Myeloid-Derived Suppressor Cells (MDSCs)

Thus, the overwhelming consensus from large epidemiological surveys is that use of ACEi/ARB is protective against CRC. The mechanism therefore is not clear, but may involve an effect of the drugs on MDSCs. Our group (VB and NMF) has investigated these cells in experimental models of lung cancer and in clinical cases of CRC [26–30]. In the urethane-induced lung cancer model, we found an increased percentage of infiltrating MDSC, high expression of ACE mRNA and protein in addition to intense expression of ACE protein in tumor nodules in the lungs [29]. In clinical cases of CRC we observed that MDSCs from peripheral blood of older patients were present in higher numbers in step with disease severity (in metastatic disease, 5.35×10^5 MDSCs/mL blood-vs-1.48×10^5 in non-metastatic CRC and 0.7×10^5 in healthy controls [30]. The age of the controls was associated with these MDSC numbers: in healthy donors >80 years of age, significantly more MDSCs might suggest a more suppressive microenvironment that could contribute to cancer development in the older adult [12]. Recently, we reported that healthy older adults aged 64–67 years exhibited ACE expression by peripheral immune cells of all phenotypes of CD4+ and CD8+ T cells (i.e., naive, central memory, effector memory, effector memory re-expressing RA) as well as B cells (naive, non-switched memory, switched memory, double negative) cells. Myeloid cells also expressed ACE but in lower percentages [31]. We are at the moment investigating whether the percentages of MDSCs from ageing healthy individuals and from ageing CRC patients expressing ACE are similar or greater in the latter. We are also comparing CRC patients that are using or not using ACEi to explore differences in outcome and identify any immunological associations, particularly regarding the MDSCs. The hypothesis to be tested is that ACEi bind ACE expressed by MDSC and modulate their activity.

4. Therapies Targeting MDSCs

It has been suggested that targeting MDSCs will be beneficial in anti-tumor therapy to relieve their inhibition of anti-cancer effector activity of T and B cells and reduce their facilitation of the development of T regulatory cells [32,33]. However, drugs that inhibit MDSC, such as Gemcitabine or 5-fluorouracil [34,35] may cause bone marrow suppression [36] and other side effects, and may be especially problematic in older patients. Thus, new agents with

less toxicity and greater specificity are required. The major mechanisms by which MDSCs inhibit T cells include arginase 1 (ARG1) production and induced nitric oxide synthase (iNOS). These moieties interfere with the metabolism of L-arginine (essential for T cells) and inactivate the T cell receptor (TCR), respectively [37–39]. Therefore, ARG1 and iNOS are potential targets for reprogramming MDSCs from a suppressive to a pro-inflammatory phenotype. Support for this notion comes from data on CBP/EP300-BRD inhibition of ARG1 and iNOS in a model of colon carcinoma, leading to a delay in tumor growth [40].

As discussed above, the use of ACEi is likely associated with a better outcome in CRC [21–25] but the mechanisms responsible are not fully understood and it is not yet clear whether the benefit to the patient observed in ACEi users is linked to MDSCs. ACE expression in myeloid cells is reported as a fundamental requirement for normal myelopoiesis, but ACE could also be responsible for myeloid cell modulation during the process of differentiation. In experimental models, Shen *et al*. [41] found that enforced expression of ACE by monocytic cells led to a decreased percentage of MDSCs within the myeloid lineage. They also observed that transgenic mice overexpressing ACE in myeloid cells displayed decreased numbers of MDSCs in blood and spleen in a tumor model [41]. In a model of mammary carcinogenesis, irradiation and ACEi (captopril) administration delayed tumor growth, reduced the expression of VEGF by tumor cells, and discretely modulated granulocytic MDSCs [42].

Taken together, the findings discussed in this Commentary are consistent with the hypothesis that one of the possible mechanisms associated with a positive impact of ACEi or ARB on the outcome of CRC patients would be via the modulation of myeloid cells contributing to the maturation of neutrophils/monocytes and preventing the acquisition of the immature phenotype associated with the suppressive function of MDSCs.

Author Contributions

VB—contributions to conception and design, drafting the manuscript, approved the final version to be published. NMF—contributions to conception and design, critical revision, approved the final version to be published. GP—contributions to conception and design, critical revision, approved the final version to be published.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. GP is serving as the Editor-in-Chief of this journal. We declare that GP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MM.

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