Cancer Letters 400 (2017) 311–318

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Resistance to metronomic chemotherapy and ways to overcome it

Maria Riesco-Martinez [a], Karla Parra [b], Ronak Saluja [c], Giulio Francia [b], Urban Emmenegger [c, d, e, *]

[a] Division of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain
[b] Border Biomedical Research Center, University of Texas at El Paso, El Paso, TX, USA
[c] Biological Sciences Platform, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
[d] Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[e] Institute of Medical Science, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form
20 February 2017
Accepted 22 February 2017

Keywords:
Therapeutic resistance
Chemoresistance
Metronomic chemotherapy
Antivascular tumor therapy

ABSTRACT

Therapeutic resistance is amongst the major determinants of cancer mortality. Contrary to initial expectations, antivascular therapies are equally prone to inherent or acquired resistance as other cancer treatment modalities. However, studies into resistance to vascular endothelial growth factor pathway inhibitors revealed distinct mechanisms of resistance compared to conventional cytotoxic therapy. While some of these novel mechanisms of resistance also appear to be functional regarding metronomic chemotherapy, herein we summarize available evidence for mechanisms of resistance specifically described in the context of metronomic chemotherapy. Numerous preclinically identified molecular targets and pathways represent promising avenues to overcome resistance and enhance the benefits achieved with metronomic chemotherapy eventually. However, there are considerable challenges to clinically translate the preclinical findings.

Introduction

Twenty years after the late Judah Folkman had described the conceptual framework of antivascular tumor therapy, in the 1990's vascular endothelial growth factor (VEGF) pathway inhibitors (VEGFi), notably the monoclonal anti-VEGF antibody bevacizumab, entered clinical development with very high expectations [1,2]. In fact, antivascular tumor therapy was heralded as a promising way to overcome inherent or acquired therapeutic resistance, a key characteristic of malignant growth, and as a treatment modality potentially 'resistant to resistance' [3,4]. It was thought that diploid, genetically stable tumor endothelial cells were less prone to acquire mutational resistance than genetically unstable tumor cells.

Although VEGFi have become important components of standard treatment regimens for advanced stages of numerous tumor types over the last 15 years, a number of shortcomings of antivascular tumor therapy came to the fore: (i) most tumors are inherently resistant to VEGFi and other anti-vascular therapies used alone; (ii) even when used in combinations that increase the initial response rate, responsive tumors typically develop acquired resistance within a few months; and (iii) as opposed to life-prolonging applications of antivascular tumor therapies in advanced disease stages, the adjuvant use of these agents did not increase cure rates [5].

Resistance to antivascular tumor therapies is thought to be largely distinct from resistance to conventional cytotoxic treatment [6]. Based on mainly preclinical studies a number of mechanisms of resistance to VEGFi have been proposed, including evasive resistance due to angiogenic growth factor redundancy or HIF1α mediated overexpression of angiogenic factors, vascular remodeling resulting in more mature and VEGFi resistant tumor blood vessels, preferential expansion of VEGFi resistant vessel subtypes, the selection of hypoxia-resistant tumor cell subpopulations with reduced vascular dependence, the integration of trans-differentiated tumor cells with endothelial cell properties into the tumor vasculature in a process named vasculogenic mimicry, vessel co-option by tumor cells capable of exploiting the abundant presence of pre-existing host vessels in organs such as liver and lungs, tumor infiltration by bone marrow derived leukocytes with proangiogenic properties, and stromal cell activation (Fig. 1) [5,7–9].

* Corresponding author. Odette Cancer Centre, Sunnybrook Health Sciences Centre, T2-054, 2075 Bayview Avenue, Toronto, Ontario, Canada. Fax: +1 416 480 6002.
E-mail address: urban.emmenegger@sunnybrook.ca (U. Emmenegger).

http://dx.doi.org/10.1016/j.canlet.2017.02.027
0304-3835/

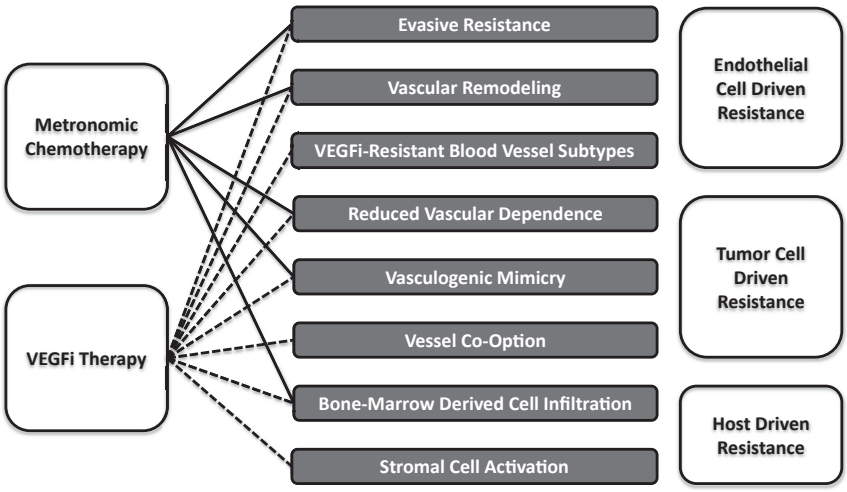

Fig. 1. Mechanisms of resistance to metronomic chemotherapy or vascular endothelial growth factor pathway inhibitors (VEGFi) – concepts. Numerous mechanisms of resistance to VEGFi have been described, involving endothelial cell, tumor cell, and host-driven mechanisms. Many of these mechanisms were also found to be functional when it comes to resistance to metronomic chemotherapy.

Research activities focusing on targeting the tumor vasculature revealed that many conventional chemotherapeutics and targeted agents exert collateral damage to tumor vessels [10]. In the case of standard, maximum tolerated dose (MTD) chemotherapy (i.e. the cyclical administration of high doses of chemotherapeutics with interspersed treatment-free breaks), the anti-vascular effects seen are similar in nature but also as short-lived as the vascular destruction inflicted by vascular disruptive agents [11,12]. On the other hand, the frequent and sustained use of low doses of conventional chemotherapeutics (i.e. low-dose metronomic chemotherapy; hereafter metronomic chemotherapy, MC) mimics the long-term antiangiogenic activities of VEGFi.

Two seminal preclinical publications described key characteristics of the MC concept, which have been refined over time and largely validated in numerous clinical trials [12–14]. First, MC may overcome resistance to MTD chemotherapy. In other words, the mechanisms of resistance to metronomic versus MTD chemotherapy are at least partially distinct [15]. Second, inducing endothelial cell apoptosis is a main mechanism of action of MC, but MC may also affect other endothelial cell processes such as proliferation, migration, tube formation and sprouting [12,16–18]. Third, the majority of tumors are inherently resistant to MC alone, and even initially responding tumors eventually acquire resistance to MC, similar to what is seen with VEGFi [14]. Fourth, high levels of pro-angiogenic factors may contribute to resistance to MC, but such resistance may be overcome by combination with VEGFi amongst other strategies [13,19].

While initial publications on MC focused on the antiangiogenic activities of MC, there is emerging evidence that MC may also impair vasculogenesis [20,21], target tumor stem cells and their vascular niche [22,23], promote anti-tumor immunity [24,25], delay acquired chemoresistance compared to MTD chemotherapy [25,26], and may induce tumor dormancy [27]. This broad range of MC activities renders studies on mechanisms of resistance to MC challenging. Such studies also need to account for differential effects of distinct chemotherapeutics when used in metronomic manner [28]. Finally, MC is typically applied in combination with other treatment modalities that may affect the resistance phenotype and genotype seen [29].

Herein, we review current knowledge on mechanisms of resistance to MC, and discuss challenges with respect to how the mainly preclinical findings might be translated clinically in the future. Considering the complex anti-tumor activities of MC, an integral understanding of resistance to MC not only involves endothelial cell-intrinsic mechanisms, but also tumor cell and host traits, as outlined in Fig. 1.

Mechanisms of resistance to metronomic chemotherapy

Endothelial cell-driven resistance

Pro/anti-angiogenic balance

When compared *in vitro* to tumor cells, endothelial cells are ultra-sensitive to the pro-apoptotic and anti-proliferative effects of low-dose, sustained chemotherapy administration [16]. This differential sensitivity is mediated in part by MC-induced expression of the endogenous angiogenesis inhibitor thrombospondin 1 by endothelial, tumor and/or stromal cells [30,31]. As such, the preclinical use of the thrombospondin 1 peptide ABT-510 has been shown to amplify the anti-tumor effects of MC [32]. In contrast, proangiogenic factors such as VEGF and basic fibroblast growth factor impair the pro-apoptotic activities of chemotherapeutics towards endothelial cells [19]; and MC was successfully combined with VEGFi in numerous preclinical studies, either upfront or to counteract acquired resistance [13,33].

Vascular remodeling

In a Wilms' tumor model, Huang et al. identified remodeled blood vessels with increased diameter and mural cell proliferation as a mediator of resistance to metronomic topotecan chemotherapy [34]. The remodeling process was associated with platelet-derived growth factor B and ephrin B2 expression.

AKT pathway and stress-activated chemoprotective signaling

The AKT pathway, including the anti-apoptotic factor survivin downstream thereof, has been shown to mediate the chemoprotective effects of VEGF and basic fibroblast growth factor seen *in vitro* in human umbilical vein endothelial cells and human dermal microvascular endothelial cells [19]. Mavroeidis et al. further implicated the AKT pathway in resistance to MC [35]. Briefly, MC may induce severe tumor hypoxia, which in turn is thought to contribute to acquired therapeutic resistance by upregulating the expression of progangiogenic factors amongst others [18]. As such, severe hypoxia reduced the antiproliferative and pro-