Holistic Integrative Oncology

COMMENTARY

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Antiangiogenic therapy: how far is it to upgrade?

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Abstract

Early vascular-targeted drugs represented by VEGF single-pathway inhibitors pioneered the idea of regulating the tumor growth microenvironment and enhanced the chemotherapy effect in a variety of tumors. However, their shortcomings of "only winning PFS but not OS" have gradually revealed and warned that drug-resistant growth of tumors is unavoidable after long-term use. The activation of intracellular bypass signaling after inhibiting a single target may be an important reason. In order to eliminate this problem, attempts have been made to expand the combination of drug types and increase the intensity of drug treatment. The possibility of replacing single-target antiangiogenic therapeutic drugs with multiple targets has also be explored. A new generation of "dual-dimension, multi-pathway" drugs that simultaneously inhibit multiple targets both in tumors and microvascular endothelial cells can be used either as single drugs in multiple tumor types, or in combination with chemotherapy, EGFR-TKI, or even immunological drugs. It demonstrates good efficacy and great potential and hope for upgrading vascular targeted therapy. It also enlightens us that future treatment and new drug development strategies cannot rely solely on the most precise target inhibition, but should have a "dual-dimension, multi-pathway" integration concept that looks at the overall situation from one corner.

Keywords Antiangiogenesis, Microenvironment, VEGF, Bevascizumab, Aolotinib, PD-L1

1 The urgency of replacement

Antiangiogenic therapy, i.e, vascular targeted therapy was once hailed as the "Breakthough of the year" for tumors (https://www.sciencemarg.org.2003), but the early drug defects cannot be ignored. This paper only makes a short comment on the necessity and possibility of "upgrading" for the sake of our fellow travelers.

1.1 The embryonic form of "holistic cancer treatment" has gradually taken shape

Since the use of nitrogen mustard, "tumoricidal" chemotherapy has become mainstream. However, the intense drug use did not remove the tumor but caused tumor's growing after therapy. It is suggested that tumor is not "isolated and helpless", and treatment should not be "fighted alone". In 1971, Folkman proposed that cancers are dependent on blood vessels and that preventing their formation can "starve tumors to death", thus elevating the "transformation of soil" to the same significant status as the "destruction of tumors". In 1997, with the advent of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, the idea of a "regulatory environment" entered clinical practice.

1.2 The emergence of the concept of "rational tumor control"

Different from chemotherapy, which kills active cells and causes the proliferation of remained dormant cells, vascular targeted drugs inhibit blood supply by neovasculature, weaken tumor cell metabolism, and prevent them from entering the S-phase of proliferation from the G1

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phase; so these "indolent" cells occupy space and impede the proliferation of stem-like cells in G0 phase, constituting the balance of "controlling tumor with inert tumor", ensuring tumor stability (SD) and long-term survival of patients [1]. Bevacizumab combination therapy improved the survival of the patients with advanced colorectal cancer by 30% and the patients with lung cancer by 19% (Hurwitz, et al. NEJM 2004; Sandler, et al. NEJM 2006) and was soon be used for various cancers.

1.3 Does tumor rebound seem to form a vicious cycle?

With vigorous development, confusion is gradually emerging: in follow-up practice, always bevacizumab reached prolongation on PFS rather than OS (Reek, et al. JCO 2009, lung cancer; Miller, et al. NEJM 2007, breast cancer, etc.). This suggests "drug-resistance rebound" after long-term use. Some studies have found that VEGF inhibitors even induce tumor cell invasion and metastasis (Wick W, et al. N Engl J Med, 2017; Xu Y, et al. JECCR 2012;). Amidst criticism, in 2010, the FDA withdrew its approval for the indication of triple-negative breast cancer. Obviously, if the problem of drug resistance is not solved, it will be difficult to continue the efforts of vascular targeted therapy.

1.4 Single-target drug's highlighting limitations

The failure forced us to return to the laboratory to find the cause. The study found that after the successful inhibition of the VEGF pathway, single-target drugs could induce the conduction of multiple signaling bypasses, such as bFGF, PDGF, and TGF, and "activate" the tumor cells (Rogosin. S, et al. Clinical Lung Cancer 2012; Gabriele. S, Nat Rev Cancer 2008; Liu ZJ, et al. Frontiers in Oncology 2022), produce a series of malignant biological behaviors, such as high-jack of vessel in adjacent tissue and mimicry (Xu Y, et al. JECCR 2012), and can even induce the activation of signaling bypass in vascular endothelial cells that has always been considered "stable" in gene, promoting their proliferation and tube formation to form a network blood supply (Zhang XL, et al. CBM 2020), repairing tumor damage and offsetting the effect of therapy. At this time, the control of the tumor growth environment has become a disturbance on the contrary.

2 The endeavor to overcome the shortcomings

The frustration made us realize that the blockage of a single pathway will open multiple conduction channels, and the hypoxic environment created by the inhibition of the blood supply network will also activate tumor cells (Wang YY, et al. Cell & Bioscience 2015) and promote the "revitalization of vasculature" and "high-jack" into adjacent tissue (Gabriele. S et , al. Nat Rev Cancer 2008). Therefore, synergitic strategies have emerged as the times require.

2.1 The "A plus" strategy means to use jointly with drugs that target different pathways and cell proliferation cycle so strive to completely cover all pathways and proliferation phases both of the blood vessel endothelial and tumor cells

For example, the Beyond study (Zhou CC, et al. JCO 2015), which used vascular targeted drugs in combination with chemotherapy, and the CTONG1509 study (Wu YL, et al. Cancer Cell 2021), which used vascular targeted drugs in combination with EGFR-TKI, can both delay tumor progression.

2.2 The "holistic combination" strategy means to integrate vascular targeted drugs with physical, surgical and other means to synergize; it is especially suitable for patients with tumors in large size or special location where drugs are not easy to enter and permeate

For example, combined radiotherapy (especially for tumors with high VEGFR2 expression) [2] and combined microwave ablation have been used for the treatment of non-small cell lung cancer (NSCLC) (Meng M, et al. JTO 2017).

2.3 "Multitarget" strategy, that is, the attempt of multitarget pathway drugs, such as chemotherapy plus vandetinib or sorafenib for the treatment of NSCLC; however, OS was not significantly prolonged, and the effect is not satisfactory

The above efforts are remedial measures after the realization that only targeting a single target and ignoring the deficiencies of bypass pathways, and have indeed improved the efficacy. However, due to the large number of drug combinations and the complexity of synergic means, the most efficacy of each element and "seamless connection" in time and space cannot always be achieved. The "disconnection of treatment", may even affect the efficacy; for example, in the use of the "vascular normalization" effect of vascular targeted drugs in synergistic chemotherapy, the promotion is difficult due to the uncertain and short time of the "normalization" window (Astrid AM Van der Veldt, et al. Cancer Cell 2012). The application of a variety of methods has also led to adverse reactions and increased treatment costs. In addition, most early multitarget drugs targeted only similar pathways in a single dimension. For example, although some drugs can inhibit multiple pathways, they still focus on molecules such as VEGFRs and PDGFR-β in vascular endothelial cells and do not target other signaling pathways in tumor cells, allowing them to remodeling

the vascular network so that the previous efficacy completely lost. Therefore, these measures are not enough to significantly improve the efficiency, and it is difficult to shoulder the responsibility of "upgrading" upon the early multitarget drugs.

3 Exploration of "upgraded efficacy"

3.1 Expansion of the A plus strategy

To reconfirm the potential feasibility of vascular targeted combination with chemotherapy, their application range of tumor types is expanded. However, the results of "losing OS" [3] or the win–win of PFS and OS only in specific populations [4] have been repeated.

3.2 The intensification of the A plus strategy

That is to increase the intensity of the drugs combined with it, such as the four-drug regimen based therapy, which can indeed achieve better efficacy and improve the quality of life [5]. However, the final analysis of the canonical Impower150 trial still showed that the addition of bevacizumab failed to prolong the OS of all patients (13.5 Mark A. Socinski, et al. JTO 2021), suggesting that it is necessary to identify the "synergy advantage population". There has been much exploration on the issues of therapeutic efficacy prediction [6, 7].

3.3 Renewal of the A-plus strategy

Although the performance of the early VEGF inhibitors was not satisfactory, people are still trying to combine them with different drugs, e.g., ramucirumab combined with immune checkpoint inhibitors (ICIs) in the treatment of NSCLC, the bevacizumab maintenance therapy in the BEYOND study, and the ARIES study for the treatment of advanced non-squamous NSCLC, all won longer OS and were included in the Chinese expert consensus on anti-angiogenic drug therapy (Chinese Society of Clinical Oncology Vascular Expert Committee on Targeted Therapy. China Medical Journal 2020, 2022). In the observation of bevacizumab ± trifuridine/tipiracil in the treatment of metastatic colorectal cancer, the combined therapy group won the OS by 10.8 months beyond the chemotherapy group (7.5 months), (HR 0.61, 95% CI 0.49-0.77, $P<0.001$) [8]. In a small-sized study in colorectal cancer patients, this regimen resulted in a longer PFS than chemotherapy combined with immune checkpoint inhibitors (ICIs) (6.3 months vs. 3.0 months, $P=0.041$) and OS (12.0 months vs. 6.0 months. $P=0.013$) [9], but in the subsequent observation of a large number of cases, it was still lost to chemotherapy combined with immunotherapy (OS: 34.3 vs. 37.9 months, $P=0.03$) [10]. In the PAOLA-1/ENGOT-ov25 trial of bevacizumab combined with the PARP inhibitor, Olaparib, for treating ovarian cancer, the OS of the combination was longer than that of bevacizumab alone among the patients with homologous recombination deficiency (HRD)[11]. However, the study design lacked the olaparib monotherapy control group, which casts doubt on the conclusion of "synergy" between the two. It seems that VEGF inhibitors can win OS in some tumor types and populations, but to popularize their use, the most suitable partner regimens are still needed.

3.4 "Concentration" of the A plus strategy

All kinds of "target control effects" are condensed into a new drug to achieve the most efficient synergy in time and space. Anlotinib covers multiple targets in the "dual domains" from the environmental vascular endothelium to tumor cells, such as VEGFR, PDGFR, FGFR, c-kit, and Met kinase (Sun Y, et al. JHO 2016; Lin B, et al. al. Gene 2018; Taurin. S, et al. Int J Gynecol Cancer 2018; Lei TY, et al. Pharmacol Res 2023), therefore achieved the cooperation of the "complementary length" in the inhibition on signaling pathway. After improving PFS and OS in drug-resistant and recurrent advanced NSCLC (Han BH, JAMA Oncology 2018), it has also been successful in soft tissue sarcomas, thyroid cancer, cervical cancer and other tumors (Wang ZM, et al. Clin Cancer Res 2022; Huang NS, et al. Thyroid 2021; Xu Q, et al. JCO 2022). Its coverage of "dual domains and multiple signaling pathways" makes it effective as a single agent [12], making the strategy of "free chemotherapy" come true; moreover, its use in combination with other drugs has won the "Double-S" honor in multiple drug-resistant tumors unprecedentedly: PFS 8.02 months and OS 11.04 months in combination with standard chemotherapy for extensive-stage small cell lung cancer (SCLC); PFS 15.1 months and OS 30.0 months in combination with icotinib for NSCLC (ALTER-L004 trial) [13, 14]。Since it has long been recognized that inhibiting VEGF improves the immune microenvironment (Voron T, et al. J Exp Med 2015), this strategy is also regarded as the best partner for immunotherapy; however, some studies have found that single-target inhibitors can promote tumor blood vessels endothelial cells express PD-L1, blocking active immune cells from entering the tumor (MARTINA S, et al. Science Translational Medicine 2017; Liu SC, et al. Cell Death and Disease 2020) and reducing the efficacy. Anlotinib can weaken this "barrier" by inhibiting multiple pathways and downregulating PD-L1 expression. (Liu SC, et al. Cell Death and Disease 2020), demonstrated its enormous potential to synergize immune therapy [15] and was successful in treating various tumors [16]; due to the downregulation of PD-L1 in tumor vascular endothelial cells, it can also inhibit the immunosuppressive regulatory T cells (Treg cells) and has the effect of preventing the hyperprogression (HP) induced by immunotherapy

[17]. In addition, combined immunotherapy combined with low dose of anlotinib can be a win–win for both PFS and OS [18], therefore and it also reduces treatment risk and cost.

4 Bottleneck that has yet to be broken through

(1) The drug resistance dilemma remains to be solved. The new multitarget drugs are not effective all the time, indicating that the activation of new transduction pathways still occurs during treatment. It has become an urgent need to seek reliable and practical efficacy-predictive markers and to establish a dynamic efficacy prediction system suitable for vascular targeting [19, 20]. In addition, the research and development of more efficient new products that can target multiple signaling pathways (one fit all) by the inhibition of key upstream "hubs" (competent one fit all) is also a hot topic of attention. Future drug replacements should not only cover the tumor but also the environment and can be used as a monotherapy or as the best synergist. Other bottlenecks are (2) the screening of advantageous populations for treatment and (3) the reduction of drug toxicity, which will not be described in detail here.

5 Enlightenment and prospects

Since the launch of bevacizumab, vascular targeted therapy has experienced constant growth and ups and downs for 26 years. From focusing on tumors to taking into account the environment, we have made a leap in understanding from partial to global, and the concept of tumor control from "single target" to "holistic" has begun to take shape; setbacks have forced us to return to the cells and trace the cause of drug resistance from the macroscopic whole, which elucidated the crux of single target therapy-induced bypass activation and the activation of tumors in hypoxic environment, shifted focus from a single pathway to the whole and proposed a treatment strategy covering "dual-domain, multi-pathway". From this, we realized that the improvement of efficacy depends on increasingly accurate target inhibition, but to achieve the most efficient accurate targeted therapy, it is necessary to have the integration concept of looking at the overall situation from one corner. It is believed that under its guidance, the upgrading of vascular targeted therapy will become true.

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