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Review Article

Pathways of Targeted Therapy for Colorectal Cancer

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Abstract

One of the most common and deadly cancers in the world, colorectal cancer (CRC) caused around 881,000 melanoma deaths in 2018. The third most frequent cause overall cancer-related death worldwide is colorectal cancer (CRC). A difficult issue related to chemotherapy is the subsequent adverse effects brought on by the toxicity of conventional medications. Location-specific/targeted distribution of chemotherapeutic medicines precisely to the afflicted site of something like the colon in a foreseeable and reliable way is obviously of concern. For many years, cancer sufferers' initial choices have been surgery and chemotherapy. The prognosis for CRC, particularly for those with metastatic tumours, has never been satisfactory. A recent optional strategy called targeted therapy has been effective in extending patients with CRC's overall survival. Following achievements with the anti-EGFR (epidermal growth factor receptor) agent cetuximab and the anti-angiogenesis agent bevacizumab, new drugs that inhibit several important pathways and immune checkpoints are being developed at an unheard-of rate. The growing number of high-quality clinical trials is being used as a basis for updating guidelines worldwide regarding the recommended targeted medications. An overview of current CRC-targeted drugs and their underlying processes is given in this review, along with a discussion of their drawbacks and potential directions.

Keywords: Colorectal cancer, Chemotherapeutic medicines, Bevacizumab, Cetuximab,

Introduction

The second most deadly and third most common malignant tumor in the world is colorectal cancer (CRC). Nearly 10% of all new cancer cases and fatalities globally occurred in 2018 due to the 1.8 million new CRC cases that were diagnosed and the 881,000 deaths that were reported [1]. By 2035, the number of new cases may reach nearly 2.5 million[2]. The survival time for CRC has been increasing as a result of improvements in main and adjuvant therapies. The optimum CRC treatment typically entails surgical surgery to completely remove the tumor and any metastases[3]. However, despite the development of numerous screening programs to lower CRC incidence, 20% of the remaining cases may develop metachronous metastases, which make curative surgical control challenging and ultimately lead to tumor-related deaths. Nearly 25% of CRCs are diagnosed at a later stage with metastases[4-7]. The goal for patients with refractory lesions or those who are not surgical candidates is optimal cancer shrinking and suppression of further tumor spread and progression. Radiotherapy and chemotherapy are the most effective methods for managing disease in these individuals. It should be noted that in some circumstances, chemotherapy or radiotherapy may be used as neoadjuvant or adjuvant treatments before or after surgery to help the tumor be reduced and stabilized to its full potential [8-11]. Currently available chemotherapy options include myriad regimens with one or more medicines, such as oxaliplatin (OX), irinotecan (IRI), and capecitabine, as well as standard therapy, which is mostly based on fluoropyrimidine (5-FU) (CAP or XELODA or XEL). The combined therapy regimens FOLFOX (5-FU+OX), FOXFIRI (5-FU+IRI), XELOX or CAPOX (CAP+OX), and CAPIRI (CAP+OX) remain the standard first-line treatments, while patients with poor performance or at low risk of deterioration are advised to receive single-agent therapy. This is true even though study results have asserted that first-line single-agent therapy is not subordinate to combined regimens in terms of overall Effectiveness seems to be comparable when selecting additive agents, and only negative impacts may vary across different regimens [11-16]. In the multiple-agent regimen FOLOXIRI (5-FU+OX+IRI), which is rarely used because it has the potential for greater toxicity, emerging evidence does not suggest higher efficacy[17, 18]. Chemotherapy does have several drawbacks, though, including systemic toxicity that already exists, an unsatisfactory response rate, unpredictability in innate and acquired resistance, and a lack of tumor-specific selectivity. The concept of molecular targeted therapy has been around for a while. The idea of a chemical agent that particularly targets a microorganism was first put forth in the early 1900s, expanded to include cancer treatment in 1988 [19], and has since been revived and prospered over the past 20 years[20]. By specifically preventing cell division, migration, and proliferation, targeted medicines can effectively treat malignant cells. Targeted medications may also change the tumor microenvironment, which includes local blood vessels and immune cells, to reduce tumor development and

strengthen immune surveillance and defense. Targeted therapies rely heavily on small molecules like monoclonal antibodies[21-23]. Small molecules are a class of molecules with a molecular weight of less than 900 Da that can enter cells and work primarily inside cells to inactivate certain enzymes, inhibiting the tumor cell proliferation and even inducing apoptosis. The majority of the molecular targets include proteasomes, poly ADP-ribose polymerase, and cyclin-dependent kinases. Some examples include rucaparib for BRCA-positive ovarian cancer, carfilzomib for multiple myeloma, and ribociclib for metastatic breast cancer[20]. Monoclonal antibodies or therapeutic antibodies can detect and bind receptors outside of cells, such as cell surface receptors or membrane-bound sites, to directly control subsequent cell cycle progression and cell death. Additionally, several monoclonal antibodies target immune cells and other cells outside cancer cells, which aids in the manipulation of the immune system to attack cancer.

Pathways of current CRC-targeted therapy

Desirable targets for targeted therapy can be found in a number of pathways that control the onset, progression, and migration of CRC, including Wnt/-catenin, Notch, Hedgehog, and TGF- (transforming growth factor-)/SMAD, in addition to those that can activate signaling cascades, like phosphatidylinositol 3-kinase (PI3K)/AKT or RAS/rapidly accelerated fibros [24,25]. A substantial number of targeted drugs are still in preclinical models or phase I trials due to the complexity of down-stream signalling pathway and the challenges associated with completely inhibiting particular biological interactions. As a result, not all CRC-related pathways can indeed be satisfactorily tried to interfere with, and the available data only cover a small number of pathways in which experimentally identified targeted agents can be demonstrated to be effective in clinical studies.

The VEGF/VEFGR pathway

Angiogenesis, a physiological process through which new blood vessels develop or remodel from pre-existing ones, is essential for the development, growth, and spread of tumors. A number of proangiogenic and antiangiogenic substances, including VEGF, fibroblast growth factors (FGFs), TGF-, TGF-, platelet-derived endothelial cell growth factor (PDGF) and angiopoietins produced by cancer or stromal cells, are involved in the complicated regulation of angiogenesis [26-28]. Until the discovery of VEGF-A (also known as VEGF) and the creation of its monoclonal antibody inhibitor, the link between neo-vessels and carcinogenesis remained hypothetical. This was followed by conclusive evidence of the tumor-promoting role of angiogenesis[29]. For a tumor to form, grow, and spread, angiogenesis, a physiological process wherein new blood capillaries form or reorganize from already-existing ones, is required. VEGF, fibroblast growth factors (FGFs), TGF-, platelet-derived endothelial cell growth factor (PDGF), and angiopoietins produced by cancer or stromal cells are only a few of the proangiogenic and antiangiogenic chemicals that are involved in the intricate regulation of angiogenesis[26-28]. Neo-vessels and carcinogenesis were thought to be unrelated till the identification of VEGF-A (popularly called as VEGF) and the development of its monoclonal antibody inhibitor. Thereafter, unambiguous proof of angiogenesis' participation in tumor promotion was presented.

Immune checkpoint inhibitor therapy

In addition to methods directly blocking pathways that contribute to tumor growth and spread, accumulating data suggest that targeting other pathways to enhance immune recognition and the response against cancer cells might be effective. Malignancies harboring various genetic and epigenetic alterations may be identified and obliviated by the host immune system via the expression of abnormal antigens. The detection process comprises several steps, including T cells binding to major histo-compatibility complex (MHC) molecules held by antigen-presenting cells (APCs), followed by the next step involving secondary signals mediated via co stimulatory or inhibitory receptors that play a vital role in the activation and tolerance of T cells [30,31]. The mounting research shows that targeting alternative pathways to improve immunorecognition and the response against cancer cells may be useful in contrast to techniques that directly disrupt pathways that support tumor development and spread. Through the production of aberrant antigens, the host immune system is able to recognize and eradicate cancers that possess a variety of genetic and epigenetic abnormalities. The detection method involves a number of steps, starting with T cells binding to major histocompatibility complex (MHC) molecules held by antigen-presenting cells (APCs), then moving on to secondary transmissions mediated by co - stimulatory or inhibiting receptors, which are crucial for the stimulation and sensitivity of T cells [30,31]. A dual system is crucial in disastrous disorders to allow for flexible attack of aberrant cells as well as physiological functions to prevent an overwhelming immune response[32].

The EGFR-related pathway

EGFR (epidermal growth factor receptor) is one of 4 members of the ErbB/HER family: ErbB1 (EGFR/HER1), ErbB2 (Neu/HER2), ErbB3 (HER3), and ErbB4 (HER4) [33, 34]. which also includes erythroblastosis oncogene B and human epidermal growth factor receptor. The ErbB receptors are highly distinctive among the variety of receptor tyrosine kinases and were initially thought to be associated with cancer approximately 30 years ago. These transmembrane glycoproteins can only be activated after homo- or heterodimerization with HER2, HER3, or HER4 by specific binding, mostly by EGF or TGF-, due to the decreased kinase activity of HER3/ErbB3 and the lack of a direct ligand for HER2/ ErbB2. In order to control cell growth, survival, and migration, a number of downstream intracellular signaling pathways, such as the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), RAS/RAF/MEK/ERK, PI3K/AKT, and JAK/STAT3 pathways, are triggered once they have been activated [35-37].

Glioma, melanoma, medulloblastoma, gastrointestinal malignancies such esophageal, colorectal, and gastric cancers, as well as cancers of the lung, breast, bladder, prostate, pancreas, and ovary have indeed been found to express EGFR and HER abnormally[33]. A poor prognosis may also be indicated by the overexpression of EGFR, which has been seen in 15-30% of breast tumors, 60% of NSCLCs (non-small-cell lung cancer), and 2-77% of CRCs[38, 40]. 20-30% of breast and ovarian cancers[37, 41], 3.8-36.6% of gastric cancers[38]and 1.3-47.7% of CRCs exhibit HER2 over expression[33, 40]. HER3 was not allowed to be a pharmacological target due to the difficulty in locating its ligand, despite the fact that it expressed at a higher level in malignancies of the breast, ovary, and bladder, as well as 83% of gastrointestinal tumors, than in normal tissues. Given that both cancer-promoting and cancer-suppressing effects have been observed, HER4 is still a contentious topic[45, 46]. As a result, significant efforts are being made to create widely used, targeted medicines for HER1 and HER2, despite the threat of drug resistance brought on by HER1 and HER2 mutations.

The HGF/C-MET Pathway

Hepatocyte growth factor (HGF) as well as the MET proto-oncogene-encoded receptor tyrosine kinase, also called as mesenchymal-epithelial transition factor (c-MET or MET), are essential for the growth, survival, metastasis, and development of drug resistance in tumors[47-51]. In the 1980s, a human osteosarcoma cell line containing TPR-MET fusion genes (translocated promoter region locus on chromosome 1 and MET sequence on chromosome 7) was utilized to identify this signaling pathway for the very first time. At the time, HGF was also known as scatter factor since it had briefly sequestered from rat platelets and existed in charge of epithelial dissemination in organ regeneration and recovery. The only known ligand for MET at this time is[52-55]. HGF, which is mostly released by mesenchymal tissues. Its tissue and serum expression levels are associated with a poor prognosis in patients with several malignant tumors, including breast, esophageal, gastric, and most significantly CRC malignancies[56]. At the time of diagnosis, blood HGF levels are higher in patients who have advanced CRC and they drop after the cancer has been removed[57, 58].

Other pathways

It seems that the creation of novel targeted drugs based on pathways other than those already well-known to science proceeds relatively slowly. Drugs targeting IGF-1R, Wnt, Notch, Hedgehog, human death receptor 5, and TGF- were the subject of a few clinical trials, but as yet, no promising findings have been seen. In phase II trials, for instance, the -secretase inhibitor RO4929097 used in Notch blockade therapy and the Hedgehog pathway inhibitor vismode gib had negligible effects[59, 60]. Review was also done on the meager success of anti-TGF- and anti-Wnt treatment against CRC[61, 62]. When it comes to Wnt inhibition, medicines like COX-2 inhibitors have been proven to be useful in CRC prevention; however, alternative agents that could improve chemotherapeutic sensitivity while also directing CRC-control-targeted medications with high affinity to single targets are currently being developed. The fact that therapy is ineffective and many other challenges, such as finding outcome monitor markers, screening patients who would respond well, and effectively blocking specific targets, have emerged, but this has not stopped research on novel drugs[63].

Future directions and conclusions

Because of improving sequence technology, human genomic, transcriptional, proteomic, and epigenetic details have never been as accessible as they were in the last few years. Changes in cell differentiation, proliferation, and survival caused by genetic profile changes contribute to the onset and progression of cancer. Based on the identification of these heterogeneities, treatments targeting specific enzymes, growth factor receptors, and signal transducers enable customized cancer therapy, allowing many oncogenic cellular systems to also be effectively interrupted to, holding the pledge of accurate cancer elimination and improved patient care. After decades of investigation and production, significant steps have been taken to update CRC-targeted medications for improved patient compliance, fewer adverse effects, and more personalized therapy regimens. While targeted therapy has been linked to longer survival, it comes with a number of drawbacks like When current chemotherapy is substantially affordable than more tailored regimens, especially for patients who may require numerous targeted drugs, the cost-benefit balance is unclear and Targeted therapy may result in unexpected side effects. In general, we are inspired not simply by the reality that patients with CRC are living longer lives with a plethora of targeted treatments, one or more of which may eventually be beneficial, but we also anticipate the development of even more services to the patients that promote even longer survival, have fewer adverse reactions, and have the prospects for complete recovery.

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