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Short Communication

Targeting colorectal cancer with targeted therapies: Pathways

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Colorectal cancer (CRC), one of the world's most prevalent and deadliest tumors, resulted in around 881,000 melanoma fatalities in 2018. Colorectal cancer (CRC) is the third-most common cause of all cancer-related deaths globally. The ensuing side effects brought on by the toxicity of conventional drugs are a challenging problem associated with chemotherapy. It is understandably problematic to deliver chemotherapeutic medications precisely to the affected site of something like the colon in a predictable and dependable manner. Chemotherapy and surgery were the only options available to cancer patients for a long time. The prognosis for CRC has never been good, especially for patients with metastatic cancers. Targeted therapy, a recent optional method, has been successful in extending the overall survival of CRC patients. Following successes with the anti-EGFR (epidermal growth factor receptor) drug cetuximab and the anti-angiogenesis drug bevacizumab, new medications that inhibit a variety of critical pathways and immunological checkpoints are being developed at an unheard-of rate. Guidelines for the recommended targeted drugs are being updated globally based on the growing body of high-quality clinical research. This study provides a summary of the present CRC-targeted medications and their underlying mechanisms, along with a discussion of their shortcomings and potential future possibilities.

Keywords: Chemotherapeutic medicines, Bevacizumab, Cetuximab, Colorectal cancer

Introduction

Colorectal cancer (CRC) is the world's third most prevalent and second-most lethal malignant tumour. Due to the 1.8 million newly diagnosed CRC cases and the 881,000 reported deaths, about 10% of all new cancer cases and fatalities worldwide occurred in 2018. Nearly 2.5 million more cases could be reported by 2035 [1-4]. Due to advancements in main and adjuvant therapy, the survival time for CRC has been rising. The best CRC treatment usually involves surgical removal of the entire tumour and any metastases. Despite the development of several screening programmes to reduce CRC incidence, 20% of the remaining cases may develop metachronous metastases, making curative surgical control difficult and ultimately leading to tumor-related fatalities [4-6]. Approximately 25% of CRCs are diagnosed with metastases at a later stage. The goal for patients with refractory lesions or those who are not surgical candidates is to decrease the tumour as much as possible while preventing future tumour spread and progression. Radiotherapy and chemotherapy are the most effective treatments for these patients. To help the tumour be shrunk and stabilised to its maximum capacity, chemotherapy or radiotherapy may occasionally be employed as neoadjuvant or adjuvant treatments before or after surgery. Currently, a wide range of chemotherapy regimens with one or more drugs, such as oxaliplatin (OX), irinotecan (IRI), and capecitabine, is accessible [7-11]. There are also standard therapies, which are mostly based on

fluoropyrimidine (5-FU) (CAP or XELODA or XEL), as well as other choices. While patients with poor performance or at low risk of deterioration are encouraged to receive single-agent therapy, the combined therapy regimens FOLFOX (5-FU+OX), FOXFIRI (5-FU+IRI), XELOX or CAPOX (CAP+OX), and CAPIRI (CAP+OX) remain the conventional first-line treatments [12, 13]. This is accurate despite study findings suggesting that first-line single-agent therapy is not inferior to combined regimens in terms of overall Effectiveness and looks equivalent when choosing additive agents, and only adverse effects may vary across different regimens. Emerging evidence does not support better efficacy in the multiple-agent regimen FOLOXIRI (5-FU+OX+IRI), which is seldom utilised due to its potential for greater toxicity [14-16]. However, chemotherapy has certain disadvantages, such as the already present systemic toxicity, the inadequate response rate, the unpredictability of innate and acquired resistance, and the lack of tumor-specific selectivity. Molecular targeted therapy is an idea that has been around for a long. Initially proposed in the early 1900s, the concept of a chemical agent that specifically targets a microorganism was later broadened to encompass cancer treatment in 1988 and has since been revitalised and flourished over the past 20 years. Targeted medications can successfully treat malignant cells by selectively blocking cell division, migration, and proliferation. Aside from reducing tumour growth and enhancing immune defence, targeted drugs may also alter the tumour microenvironment, which includes nearby blood arteries and immune cells. Monoclonal antibodies and other small compounds play a significant role in targeted therapy. Small molecules are compounds with a molecular weight of less than 900 Da [17-19]. They can penetrate cells and function primarily inside cells to inactivate specific enzymes, limiting the development of tumour cells and even induce apoptosis. Proteasomes, poly ADP-ribose polymerase, and cyclin-dependent kinases make up most of the molecular targets. Examples are carfilzomib for multiple myeloma, rucaparib for BRCA-positive ovarian cancer, and ribociclib for metastatic breast cancer. In order to directly influence subsequent cell cycle progression and cell death, monoclonal antibodies or therapeutic antibodies can find and bind receptors outside of cells, such as cell surface receptors or membrane-bound sites. Additionally, a number of monoclonal antibodies target cells other than cancer cells and immune cells, aiding in the manipulation of the immune system to combat cancer [20-24].

Pathways of current CRC-targeted therapy

Wnt/-catenin, Notch, Hedgehog, and TGF- (transforming growth factor-)/SMAD are among the pathways that regulate the onset, progression, and migration of CRC. Other pathways that can activate signalling cascades include phosphatidylinositol 3-kinase (PI3K)/AKT and RAS/rapidly accelerated fibrosis [25-27]. Due to the intricacy of the downstream signalling cascade and the difficulties in entirely suppressing specific biological interactions, many targeted medicines are still in preclinical models or phase I studies. As a result, not all CRC-related pathways can be successfully interfered with, and the data only cover a few pathways where experimentally identified targeted drugs can be shown to be effective in the clinical research [28-30].

The VEGF/VEFGR pathway

Tumour development, growth, and dissemination all depend on angiogenesis, a physiological process by which new blood vessels form or remodel from pre-existing ones. The complex regulation of angiogenesis involves a variety of proangiogenic and antiangiogenic compounds, including VEGF, fibroblast growth factors (FGFs), TGF-α, TGF-β, platelet-derived endothelial cell growth factor (PDGF), and angiopoietins produced by cancer or stromal cells [31-33]. Prior to identifying VEGF-A (also known as VEGF) and developing an inhibitory monoclonal antibody, the relationship between neo-vessels and cancer was purely conjectural. The role of angiogenesis in generating tumours was then proven conclusively. Angiogenesis, a physiological process in which new blood capillaries develop or existing ones are reorganised, is necessary for a tumour to develop, grow, and spread. VEGF, fibroblast growth factors (FGFs), TGF-α, platelet-derived endothelial cell growth factor (PDGF), and angiopoietins produced by cancer or stromal cells are only a few of the proangiogenic and antiangiogenic substances that are involved in the complex regulation of angiogenesis [34-36]. Before the discovery of VEGF-A (also known as VEGF) and the

creation of an inhibitory monoclonal antibody, it was believed that neo-vessels and cancer were unconnected. After then, unequivocal evidence of angiogenesis' involvement in tumour promotion was given [36-38].

Immune checkpoint inhibitor therapy

Accumulating evidence indicates that targeting alternative pathways to improve immune identification and the response against cancer cells may be effective in addition to techniques that directly disrupt pathways that contribute to tumour growth and spread [39-41]. The host immune system can detect and eliminate cancers that have different genetic and epigenetic changes by expressing aberrant antigens. The major histocompatibility complex (MHC) molecules are held by antigen-presenting cells (APCs) in the first step of the detection process, which is followed by secondary signals mediated by co-stimulatory or inhibitory receptors that are crucial for the activation and tolerance of T cells [42-44]. In contrast to methods that directly interrupt pathways that allow tumour development and spread, the growing body of evidence suggests that targeting alternate pathways to enhance immunorecognition and the response against cancer cells may be beneficial. The host immune system can identify and eliminate tumours with a range of genetic and epigenetic abnormalities by producing aberrant antigens [45-47]. T cells must first bind to major histocompatibility complex (MHC) molecules held by antigen-presenting cells (APCs) before moving on to secondary transmissions mediated by co-stimulatory or inhibiting receptors, which are essential for the stimulation and sensitivity of T cells. A dual system is essential in debilitating illnesses to enable flexible attack of abnormal cells as well as physiological activities to prevent an excessive immune response [48-50].

The EGFR-related pathway

The EGFR gene encodes one of the four proteins that make up the ErbB/HER family: ErbB1 (EGFR/HER1), ErbB2 (Neu/HER2), ErbB3 (HER3), and ErbB4 (HER4) together with human epidermal growth factor receptor and erythroblastosis oncogene B [51-53]. The ErbB receptors stood out among the various receptor tyrosine kinases and were first suspected to be connected to cancer about 30 years ago. Because HER3/ErbB3's kinase activity is decreased and HER2/ErbB2 lacks a direct ligand, these transmembrane glycoproteins can only be activated following homo- or heterodimerisation with HER2, HER3, or HER4 by specific binding, primarily by EGF or TGF-α [16, 54-56]. After being activated, a number of downstream intracellular signalling pathways, including the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), RAS/RAF/MEK/ERK, PI3K/AKT, and JAK/STAT3 pathways, are initiated to regulate cell growth, survival, and migration. There is evidence that glioma, melanoma, medulloblastoma, gastrointestinal cancers such as oesophageal, colorectal, and gastric cancers, as well as tumours of the lung, breast, bladder, prostate, pancreas, and ovary, express EGFR and HER inappropriately [57-59]. The overexpression of EGFR, which has been seen in 15–30% of breast tumours, 60–% of NSCLCs (non-small-cell lung cancer), and 2–77% of CRCs, may also be an indicator of a bad prognosis. 20–30% of breast and ovarian cancers, 3.8–36.6% of gastric cancers, and 1.3–47.7% of CRCs show overexpression of the HER2 gene. Despite the fact that HER3 expression was higher in gastrointestinal tumours (83%) than normal tissues (breast, ovarian, and bladder cancers), as well as 83% of all tumours, it was not permitted to be a pharmaceutical target due to the difficulties in identifying its ligand. HER4 is still a contested subject, given that both cancer-promoting and cancer-suppressing actions have been reported [60-62]. As a result, despite the possibility of medication resistance posed by HER1 and HER2 mutations, major efforts are being made to develop widely used, targeted treatments for HER1 and HER2 [63, 64].

The HGF/C-MET Pathway

For the growth, survival, metastasis, and emergence of treatment resistance in tumours, hepatocyte growth factor (HGF) and the MET protooncogene-encoded receptor tyrosine kinase,

also known as mesenchymal-epithelial transition factor (c-MET or MET), are crucial [65, 66]. The TPR-MET gene fusion (translocated promoter region locus on chromosome 1 and MET sequence on chromosome 7) was initially discovered in a human osteosarcoma cell line in the 1980s. HGF was also known as scatter factor at the time because it had momentarily separated from rat platelets and was in charge of epithelial spread during organ regeneration and recovery. The only currently recognised MET ligand is HGF, which is mostly secreted by mesenchymal tissues. Patients with a variety of malignant tumours, including breast, oesophagal, gastric, and, most critically, CRC cancers, have a poor prognosis when their tissue and serum expression levels are high. Blood levels of HGF are higher in patients with advanced CRC at the time of diagnosis and fall after the disease has been removed [67-71].

Other pathways

It appears that the development of innovative targeted medications based on routes other than those that science is already well-aware of moves along at a very modest pace. Several clinical trials, including drugs targeting the IGF-1R, Wnt, Notch, Hedgehog, human death receptor 5, and TGF-α, were conducted, but no encouraging results have been reported to date. For instance, the Hedgehog pathway inhibitor vismode gib and α -secretase inhibitor RO4929097 used in Notch blockade therapy had little impact in phase II trials. A review of the modest efficacy of anti-TGF- α and anti-Wnt therapy against CRC was also conducted [72-76]. 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 [19, 77-82].

Conclusion

Human genomic, transcriptional, proteomic, and epigenetic information has never been easier to acquire than it has been in the past few years because to advances in sequence technology. Cancer begins and develops as a result of genetic profile changes that alter cell differentiation, proliferation, and survival. Based on the discovery of these heterogeneities, therapies that target particular enzymes, growth factor receptors, and signal transducers allow for customised cancer therapy. This also makes it possible to effectively disrupt a number of oncogenic cellular systems, holding the promise of precise cancer elimination and enhanced patient care. Significant steps have been taken to update CRC-targeted drugs for better patient compliance, fewer side effects, and more individualised therapy regimens after decades of research and production. Although targeted therapy has been associated with extended survival, it has a variety of disadvantages, including Targeted therapy may have unanticipated adverse effects when current chemotherapy is far less expensive than more individualised regimens, especially for individuals who may need a number of targeted medications. In general, we are encouraged by the fact that patients with CRC live longer thanks to various targeted treatments, some of which may ultimately prove helpful. However, we are also looking forward to the creation of additional services for the patients that will encourage even longer survival, have fewer side effects, and have the potential for a full recovery.

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