The Effective Role of Targeted Therapy in Advanced Colorectal Cancer

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Abstract:

Though chemotherapy is the major strategy to manage patients with advanced-stage colorectal cancer (CRC), the main challenge is the progression of CRC despite using combination of different chemotherapeutic agents. So, to overcome this challenge, a new class Of therapy was developed naming “Targeted-therapy”. This class of drugs aim to target specific overexpressed or aberrant enzyme, receptor, or gene that have critical role in the growth and survival of colorectal cancerous cells. So that, by using combination of traditional strategy (chemotherapy) and targeted-drug, this will lead to improve survival and prevent the progression of advanced CRC.

Key words: colorectal cancer (CRC), metastatic, chemotherapy, targeting drug.

الدور الفعال للعلاج الموجه في سرطان القولون والمستقيم المتقدم

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الخلاصة:

على الرغم من أن العلاج الكيميائي هو الاستراتيجية الرئيسية لعلاج المرضى الذين يعانون من سرطان القولون والمستقيم في مراحل متقدمة، فإن التحدي الرئيسي هو تطور سرطان القولون والمستقيم على الرغم من استخدام مجموعة من عوامل العلاج الكيميائي المختلفة. لذلك للتغلب على هذا التحدي ، تم تطوير فئة جديدة من العلاج تسمى "العلاج الموجه". تهدف هذه الفئة من الأدوية إلى استهداف إنزيم أو مستقبلات أو جين محدد مفرط التعبير أو شاذ له دور حاسم في نمو الخلايا السرطانية في القولون والمستقيم وبقائها. لذلك ، من خلال استخدام مزيج من الإستراتيجية التقليدية (العلاج الكيميائي) والعلاج الموجه، سيؤدي ذلك إلى تحسين البقاء على قيد الحياة ومنع تطور الخلايا السرطانية في القولون والمستقيم.

الكلمات المفتاحية: سرطان القولون و المستقيم, النمو في مكان آخر, العلاج الكيميائي, العلاج الموجه.

Introduction

In Iraq, colorectal cancer (CRC) ranks the second most common type of cancer in men, while in women ranks the fourth most common cancer according to Globocan 2020 (1). Like other types of cancers, CRC pathogenesis involves multiple levels (genetic and epigenetic) leading to aberrant activation of certain pathways leading to proliferation, growth, and surviving of cancerous cells (2). The main strategies that are used to manage CRC are surgical intervention, radio-therapy, chemotherapy, targeted therapy, and immunotherapy(3).

Surgery is an ideal initial option to eradicate the primary CRC and its metastases(4). However, about 20% of patients with CRC are diagnosed at advanced stage with multiple metastases that make surgical option less beneficial as compared with patients with who diagnosed at early stage(5).

In case of CRC that cannot be removed by surgery due to numerous metastases or due to patient factors, chemotherapy or radiotherapy become an ideal option(6). Moreover, chemotherapy is useful as adjuvant (after surgery to eradicate micro-metastases) or neoadjuvant (before surgery to shrink the tumor)(7).

The stage at which the CRC is diagnosed represents the main determinant for choosing the suitable strategy for treatment (8). In case of advanced (metastatic CRC), the physician usually decides combinations of several strategies in order to improve the quality of life and also to prolong the overall survival (9).

Chemotherapeutic agent of choice for CRC is 5-Flurouracil (5-FU), leucovorin is added to 5-FU to enhance its activity, so that combination of 5-FU with leucovorin is considered the main treatment for advanced CRC (10). Other Chemotherapeutic agents (oxaliplatin, irinotecan, capecitabine) are added to 5-FU in order to produce combination regimens aimed to make the survival time more prolonged than 5-FU alone(11). The most common combination regimens for metastatic CRC are FOLFOX (oxaliplatin, 5-FU, leucovorin), FOLFIRI (5-FU, leucovorin, irinotican), and XELOX (oxaliplatin with capecitabine)(12).

Despite this, the main problem with the use of chemotherapy are different grades of systemic toxicities due to low selectivity and also the development of resistance even in case of combination regimens (13). This leads to innovation of drugs that target specific pathways which are overstimulated in cancer cells to enable them to proliferate indefinitely and metastasis to other sites, this class of drugs are called targeted therapy (14). The main classes of targeted therapy (**Figure 1**) that show promising efficacy in advanced metastasized CRC are: angiogenesis-targeting drugs, drugs targeting epidermal growth factor receptor, BRAF-targeting drugs, and HER2-targeting drugs. Other targeted therapies for metastasized CRC are immune check point inhibitors (approved for selected patients) and new drugs that need further clinical studies to be approved for advanced CRC (e.g., MEK inhibitors, HGF (hepatocyte growth factor) inhibitors, and c-MET (mesenchymal–epithelial transition factor) blockers (15,16).

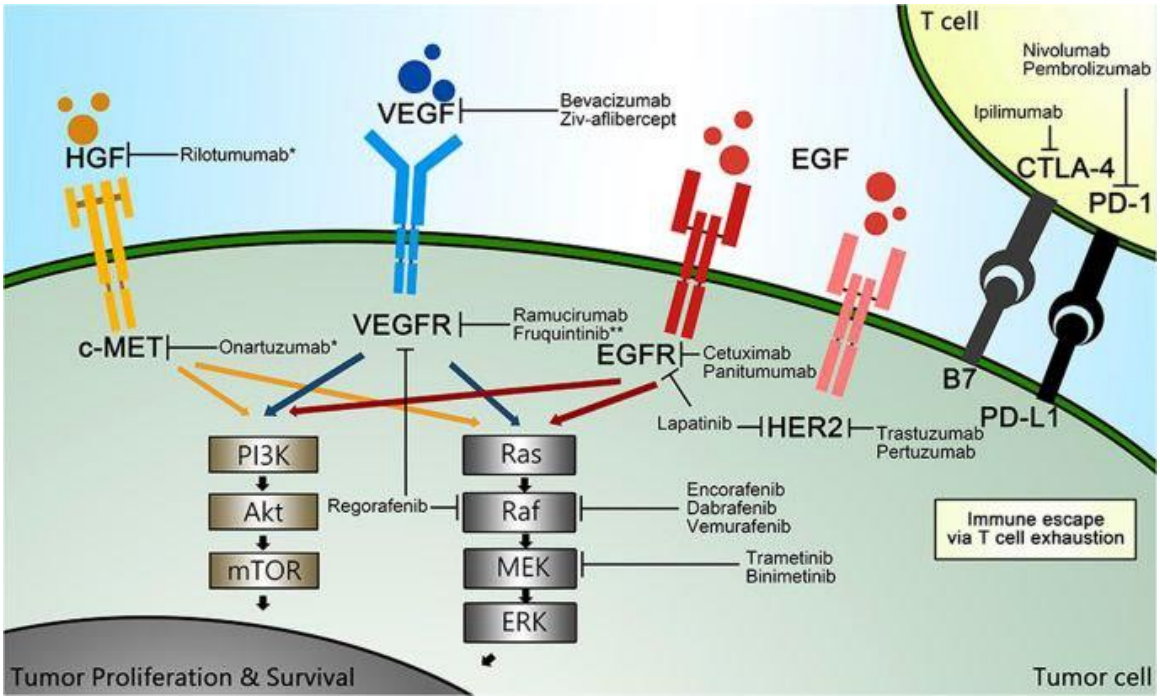

Figure1: Overview of National Comprehensive Cancer Network (NCCN)-recommended targeted agents. HGF: hepatocyte growth factor; c-MET: mesenchymal–epithelial transition factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; EGFR: epidermal growth factor receptor; EGF: epidermal growth factor; HER2: human epidermal growth factor 2; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; PD-1: programmed death-1; PD-L1: programmed death ligand 1; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B, also known as PKB; mTOR: mammalian target of rapamycin; MEK: mitogen-activated protein kinase; ERK: extracellular signal regulated kinase.

Angiogenesis- Targeting drugs:

Angiogenesis is among the strategies by which cancer cells can survive and migrate to sites away from their primary location. This process includes formation of new network of blood vessels to obtain the essential nutrients, oxygen, and allow the invasiveness of cancer cells (17). Angiogenesis is controlled by several growth factors, VEGF(vascular endothelial growth factor) is the major one and become attractive target in treatment of advance CRC (18).

Bevacizumab is a mAb manufactured as humanized immunoglobulin G (IgG) which is act against VEGF-A so leading to significant depletion in vascular network that is formed by angiogenesis (19). In 2004, FDA approved bevacizumab for metastatic CRC in combination with the first-line treatment FOLFIRI (5-FU, leucovorin, irinotican) as this anti-angiogenetic drug lead to improve overall survival (OS) and progression-free survival (PFS) (20). Later, FDA approved bevacizumab to be used in combination with second-line FOLFOX (oxaliplatin, 5-FU, leucovorin) as bevacizumab proved its effectiveness in prolongation of OS and PFS in patients with metastatic CRC who progressed on first-line FOLFIRI (21).

Ziv-aflibercept is another anti-angiogenesis drug that is manufactured as soluble receptor recombinant fusion protein to block VEGF-A, VEGF-B and P1GF (placental growth factor) with higher affinity than bevacizumab toward VEGF-A (22).

Although both bevacizumab and Ziv-aflibercept have the same indication (for

metastatic CRC in combination with irinotecan or FOLFIRI) but bevacizumab are preferred and most commonly prescribed than Ziv-aflibercept since the latter has higher cost and more toxicities(23).

Drugs targeting epidermal growth factor receptor (EGFR):

EGFR consist of parts: extracellular ligand-binding domain and intracellular tyrosine kinase domain (24). Activation of this receptor by growth factor, lead to activation of downstream pathways which resulting in cellular surviving, migration, proliferation, and angiogenesis. As a result, cancer cells depend largely on this receptor for their growth and metastasis. So EGFR is an valuable target to approve drug act against it (25) .

Cetuximab is the first FDA approved anti-EGFR drug, it is chimeric IgG1 mAb that has the ability to bind to the extracellular ligand-binding domain preventing growth factors from binding to EGFR, so leading to inhibition of surviving pathways which depend on the activation of EGFR (26). Cetuximab was approved in KRAS Wild type metastatic CRC in combination with FOLFIRI (irinotecan, 5-FU, leucovorin) as first-line treatment (27).

Panitumumab is a IgG2 type human mAb, act as EGFR inhibitor, it is approved for Wild-type (NRAS and KRAS) metastatic CRC in combination with FOLFOX (oxaliplatin, 5-FU, leucovorin) as first line treatment (28). Since panitumumab is fully human mAb, so the risk of hypersensitivity reaction is much less than cetuximab (29). Both cetuximab and panitumumab showed proven efficacy as monotherapy for chemo-refractory metastatic CRC (30).

RAS pathway is among the critical pathways for vital cellular processes e.g. multiplication, differentiation, survival,.. etc (31). About half of the patients with metastatic CRC have mutation in RAS proteins (mostly KRAS and NRAS)(32). There are FDA- approved tests special for determination whether the patient (with metastatic CRC) harbor mutated-RAS or not prior to treatment with EGFR inhibitor because mutated KRAS and mutated-NRAS CRC have resistance to cetuximab and panitumumab therapy (33). Several clinical trials showed that the site of colon cancer (whether left-sided or right-sided) can effect on the response to EGFR-targeting drug, those with left-sided wild-type CRC showed better response as compared with right-sided CRC (34).

BRAF-targeting drugs:

BRAF is a gene that upon its expression will give protein called BRAF protein, this protein is essential for cell division and growth. It is found that (8-12)% of metastatic CRC patients harbor BRAF mutations which resulting in poor prognosis especially with BRAF mutation subtype V600E (35).

Vemurafenib is an orally-active, BRAF-V600E inhibitor, approved in 2011 by FDA as monotherapy to treat patients with late-stage melanoma harboring BRAF-V600E mutation (36). Vemurafenib is ineffective as monotherapy in patients with metastatic CRC (harboring BRAF-V600E mutation) as shown in preclinical studies (37). The phase 2 SWOG S1406 clinical trial proved that vemurafenib improved PFS and better control of disease when it is used in combination with cetuximab and irinotecan as compared with (cetuximab and irinotecan) in patients with BRAF-V600E mutated metastatic CRC (38).

HER2-targeting drugs:

HER2 is a member of EGFRs family that its overexpression play important role in the pathogenesis of cancer e.g. certain types of breast cancer (39). Also, it is found that overexpressed-HER2 in (2-11)% of metastatic CRC might play significant role in resistance to anti-EGFR drugs especially in left-side colon cancer and rectal cancer (40).

Trastuzumab is HER2 -inhibitor mAb approved for HER2-positive gastric and breast cancers (41). Trastuzumab and other

HER2 inhibitors (lapatinib, pertuzumab) are investigated in two phase 2 clinical trials to manage patients with HER2-positive metastatic CRC (wild-type KRAS) who became refractory to other therapies, the results showed that trastuzumab improved the overall response rate in these patients. So, there are ongoing clinical trials to explore the promising role anti-HER2 drugs in metastatic CRC (42,43).

Immune checkpoint inhibitors:

One of the essential strategies for cancer cells to survive is to escape from immune system surveillance, so this class of drugs aimed to enforce the role of immune system in detection and killing the abnormal precancerous and cancerous cell (44). Immune checkpoint has important role in regulation the immune system regarding to self-tolerance and this function is done by binding of PD-1 (program cell death protein1) on activated-T cell and PD-L1 (program death-ligand1) on the other cells (45). Cancer cells can be hidden from immune system by upregulation of PD-1/PD-L1. So, by blocking PD-1/PD-L1 using PD-1/PD-L1 blocker drugs (Immune checkpoint inhibitors), the immune response toward the cancer cells will be increased (46).

Although immune checkpoint inhibitors have made great success in treatment of advanced tumors like melanoma, their benefit in metastatic CRC have been restricted to (3-7) % of patients with defective mismatch repair (dMMR)/ Microsatellite instability-high (MSI-H) (47). Pembrolizumab and nivolumab are both monoclonal antibodies type IgG4 which bind and inhibit PD-1(48). They are FDA-approved drugs for progressive with advanced stage melanoma and non-small cell lung cancer (49). Then they are approved for metastatic CRC with dMMR/MSI-H that become advanced despite treatment with 5-FU, oxaliplatin, and irinotecan (50).

Because the mechanism of action of these drugs depend on PD-1 inhibition, so their toxicities are due to increase T-cells activity against normal tissue leading to inflammatory autoimmune adverse effects like skin rash, colitis, or endocrine disorders e.g. diabetes and thyroid dysfunctions (51).

Conclusion:

At the end of this review, we can deduce that metastatic CRC cells contain aberrant (overactive) proliferating and surviving pathways that attract the researchers to develop drugs targeting these abnormal pathways in order to manage patients who become refractory to the traditional tools of care (especially chemotherapy). Also, specific molecular- targeting approach in cancer care will decrease the damage against normal rapid-multiplicating cells (e.g., bone marrow), this will add advantage to targeting-therapy in comparison with chemotherapies that do not distinguish between cancer cells and normal-proliferating cells.

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