Advancements in Colorectal Cancer Therapies

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Surgery, often combined with chemotherapy and radiation, remains the cornerstone of Colorectal cancer (CRC) treatment. Advances in genomics and related fields now enable personalized approaches, which are crucial, given the significant heterogeneity between individuals.

Colorectal cancer ranks as the third most common cancer globally and the second leading cause of cancer-related deaths. In 2020, CRC claimed approximately 930,000 lives, representing 10% of all cancer fatalities worldwide. Consequently, extensive research efforts are dedicated to developing novel and enhanced CRC treatments with the potential to improve survival rates and reduce overall morbidity and mortality.

1. Recent advances in targeted therapy for colorectal cancer (CRC)

Targeted therapy is a form of cancer treatment that focuses on specific biological molecules to halt the growth and spread of tumor cells. By identifying the key pathways involved in colorectal cancer (CRC) development and metastasis, drugs can be designed to selectively destroy these cancerous cells. Targeted therapies utilize small molecule drugs, which readily penetrate cells, and monoclonal antibodies. Since 2004, numerous targeted therapy drugs for CRC have been developed and approved by the FDA.

Targeting BRAF:
BRAF, a serine/threonine kinase, is a key component of the RAF/MEK/ERK signaling pathway, which is crucial for cell growth and division (proliferation). This pathway acts like a cascade of molecular events, where each protein activates the next one in line, ultimately leading to changes in gene expression and cell behavior. Specifically, BRAF is a protein kinase, meaning it adds phosphate groups to other proteins (serine and threonine in this case), thereby modifying their activity. In the RAF/MEK/ERK pathway, BRAF activates MEK, which in turn activates ERK, and ERK then goes on to regulate various cellular processes, including cell proliferation.

A specific mutation in the BRAF gene, called V600E, is found in a significant portion of colorectal cancers (CRCs). It's estimated that 8% to 12% of CRC tumors have this particular mutation. The V600E mutation causes the BRAF protein to be constitutively active, meaning it's turned "on" all the time, even when it shouldn't be. This leads to continuous activation of the RAF/MEK/ERK pathway, resulting in uncontrolled cell growth and contributing to the development and progression of cancer.

Encorafenib and Binimetinib:
Encorafenib, a BRAF inhibitor, offers extended activity compared to earlier BRAF inhibitors, while binimetinib targets MEK. The Phase III BEACON trial evaluated triplet therapy (encorafenib, binimetinib, and cetuximab), doublet therapy (encorafenib and cetuximab), and a control group (chemotherapy and cetuximab) in patients with BRAF-V600E mutated metastatic colorectal cancer (mCRC) whose disease had progressed after one or two prior treatment regimens. The trial demonstrated superior median overall survival for both the triplet and doublet therapies compared to the control arm. Consequently, the combination of cetuximab and encorafenib, approved by the FDA in 2020, is now recommended by ASCO for patients with BRAF-V600E mCRC that has progressed despite at least one prior line of therapy.

2. Recent advancement in Immunotherapy for CRC:

Cancer immunotherapy harnesses the body's own immune system to fight cancer cells, offering the advantage of targeting malignancies without the toxic side effects often associated with traditional therapies. Immunotherapy, both as a standalone treatment and in combination with conventional approaches, has become a successful standard of care for several cancer types. To counter the mechanisms by which tumor cells evade immune surveillance, various immunotherapeutic strategies have been developed and are now clinically utilized. These include immune checkpoint inhibition, adoptive cell transfer (ACT), cytokine therapy, and dendritic cell vaccines.

Adoptive Cell Transfer (ACT):
Adoptive cell transfer (ACT), a form of immunotherapy targeting specific molecular pathways, is a passive approach that leverages a patient's own lymphocytes, stimulated outside the body (ex vivo), to fight tumors. ACT can be broadly categorized into two types based on their mechanism: (1) using tumor-infiltrating lymphocytes (TILs), and (2) employing T-cell receptor gene therapy, such as chimeric antigen receptor (CAR) T cells. While six CAR-T cell therapies have gained FDA approval as of 2023, all are for hematological malignancies (B-cell leukemia and lymphoma, and myeloma), and none are currently approved for colorectal cancer (CRC).

However, research in ACT for CRC shows promise. Studies using cytokine-induced killer (CIK) cells combined with dendritic cells (DCs) in CRC patients have demonstrated improved overall survival and progression-free survival (PFS). Furthermore, postoperative CIK cell therapy combined with chemotherapy has shown potential in preventing recurrence and extending survival in advanced CRC.

Carcinoembryonic antigen (CEA), a common antigen in CRC, has also been a target for ACT. Clinical trials using CEA-targeting CAR-T cells have reported a 70% disease control rate with no significant adverse events. However, more recent research has highlighted the importance of selecting the appropriate single-chain variable fragment for effective CAR-T cell therapy in CEA-expressing tumors.

Despite these advances, several challenges remain before ACT can be considered a first-line treatment for CRC. Key limitations include poor infiltration of transferred T cells into the tumor microenvironment and the risk of systemic cytokine release. Although clinical trials assessing ACT safety have generally shown a low incidence of severe adverse events, further optimization is still underway.

Further clinical trials are essential to refine treatment strategies, establish best practices, and ultimately determine the optimal individualized therapy, considering the diverse range of available options.