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Commentary

Clinical Trials in Colon Cancer: Developments in Molecular Targeting, Immunotherapy and Personalized Treatment Approaches

Heling Oshiro*

Department of Medicine, Waseda University, Tokyo, Japan

DESCRIPTION

Colon cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. The disease typically develops from precancerous polyps in the colon or rectum and progresses through a multistep genetic and molecular pathway. Over the past few decades, clinical trials have played an important role in refining treatment protocols, introducing targeted therapies and improving patient survival rates.

Evolution of chemotherapy in colon cancer trials

Historically, Fluorouracil (5-FU) formed the basis of colon cancer treatment. Early clinical trials demonstrated its effect on tumor shrinkage and survival extension in patients with advanced disease. Subsequent studies focused on combining 5-FU with other agents such as leucovorin, irinotecan and oxaliplatin. These trials led to the development of regimens such as FOLFIRI (5-FU, Leucovorin, Irinotecan) and FOLFOX (5-FU, Leucovorin, Oxaliplatin), which became standard treatment options for advanced and metastatic colon cancer.

Randomized controlled trials comparing these regimens have shown differences in efficacy, toxicity profiles and suitability depending on patient characteristics. Adjuvant therapy trials in early-stage disease, such as the MOSAIC trial, established that the addition of oxaliplatin to 5-FU-based therapy improved disease-free survival in stage III colon cancer, influencing treatment guidelines globally.

Targeted therapy trials

With a deeper understanding of molecular pathways in colon cancer, attention shifted to targeted therapies. The Epidermal Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF) pathways were among the first to be investigated. Agents such as cetuximab and panitumumab (EGFR inhibitors) and bevacizumab (a VEGF inhibitor) were evaluated in several phase II and III trials.

A key observation from these trials was the impact of KRAS gene status on the effectiveness of EGFR inhibitors. Patients with KRAS mutations did not benefit from cetuximab or panitumumab, leading to the introduction of molecular testing before treatment. Trials such as CRYSTAL and PRIME demonstrated the improved outcomes of EGFR inhibitors in combination with chemotherapy for patients with wild-type KRAS.

Similarly, bevacizumab combined with FOLFOX or FOLFIRI showed a survival benefit in metastatic settings, although the magnitude of improvement varied across trials. These studies highlighted the importance of individualized treatment planning based on tumor biology.

Immunotherapy and biomarker-driven trials

The application of immunotherapy in colon cancer has been more limited compared to other cancers, but select groups of patients have shown marked benefit. Trials investigating immune checkpoint inhibitors such as pembrolizumab and nivolumab revealed favorable responses in patients with Microsatellite Instability-High (MSI-H).

The KEYNOTE-177 trial was particularly influential, demonstrating that pembrolizumab improved progression-free survival compared to chemotherapy as a first-line treatment in MSI-H metastatic colon cancer. These findings led to regulatory approval and updated clinical practice guidelines for this subgroup.

Trials continue to explore the use of immunotherapy in Microsatellite-Stable (MSS) tumors, which comprise the majority of cases. Strategies include combination approaches with chemotherapy, radiation, or targeted therapies, with the goal of enhancing immune responsiveness.

Neoadjuvant and surgical trials

In recent years, several trials have investigated the role of neoadjuvant therapy treatment given before surgery in colon cancer. The FOxTROT trial examined preoperative chemotherapy in locally advanced colon cancer and showed it could reduce tumor size and improve surgical outcomes without

Correspondence to: Heling Oshiro, Department of Medicine, Waseda University, Tokyo, Japan, E-mail: oshiroheling@wau.edu.jp

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compromising safety. These results suggest a possible shift in treatment sequencing for select patients.

Surgical trials have also focused on minimally invasive techniques, quality of resection and the timing of surgery following neoadjuvant therapy. Trials comparing open *versus* laparoscopic resection continue to influence surgical guidelines, particularly in terms of recovery time, complication rates and long-term outcomes.

Challenges in colon cancer trials

Despite progress, several challenges remain. Patient recruitment and retention can be difficult, especially in trials requiring genomic profiling or long follow-up periods. Additionally, disparities in access to trials persist across geographic and socioeconomic groups, limiting the generalizability of some findings.

The complexity of molecular classifications and the emergence of multiple subtypes of colon cancer also complicate trial design. Stratifying patients according to biomarkers requires large sample sizes or adaptive trial designs, which can increase cost and duration.

CONCLUSION

Clinical trials have significantly advanced the understanding and treatment of colon cancer. From conventional chemotherapy to molecular-targeted agents and immunotherapies, each generation of trials has added new options and insights. Continued innovation in trial design, biomarker development and interdisciplinary collaboration will be essential to improve outcomes for patients with this complex disease.