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Contents

Weekly Volume 30 Number 26 July 14, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Basic Study

CASE REPORT

LETTER TO THE EDITOR

Contents

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LETTER TO THE EDITOR

Photo-activated microtubule targeting drugs: Advancing therapies for colorectal cancer

Naresh Singh, Samantha Sharma

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Abstract

Over the years immunotherapy has demonstrably improved the field of cancer treatment. However, achieving long-term survival for colorectal cancer (CRC) patients remains a significant unmet need. Combination immunotherapies incorporating targeted drugs like MEK or multi-kinase inhibitors have offered some palliative benefit. Nevertheless, substantial gaps remain in the current therapeutic armamentarium for CRC. In recent years, there has been a surge of interest in exploring novel treatment strategies, including the application of light-activated drugs in conjunction with optical devices. This approach holds promise for achieving localized and targeted delivery of cytotoxic agents, such as microtubule-targeting drugs, directly to cancerous cells within the colon.

Key Words: Colorectal cancer; Therapy; Microtubule; Photo pharmacology; Immunotherapies

Core Tip: While progress has been made in colorectal cancer (CRC) treatment, significant challenges remain, as highlighted by the persistently low five-year survival rate. Integrating chemotherapy with other targeted therapies has shown promise, particularly in immune cold microsatellite stable or mutation-related CRCs. The emergence of personalized medicine, leveraging photo-switchable microtubule (MT)-targeted drugs, represents a novel approach in CRC management. While traditional MT-targeted drugs like taxanes have shown limited efficacy in CRC, optically controlled MT-drugs hold potential for improving treatment outcomes in CRC patients.

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TO THE EDITOR

Could light be the key to better colorectal cancer (CRC) treatment? The recent review by Kita *et al*[1], titled "Recent clinical trials and optical control as a potential strategy to develop microtubule-targeting drugs in colorectal cancer management" is particularly timely and clinically relevant article offering the potential of optical control for more effective CRC treatment. The review is aimed towards improving treatment of CRC patients with a focus on therapeutic potential of microtubule (MT)-inhibitor drugs. The review provides new insights in using combination therapy of optical devices and photo-activable drug allowing to locally target advanced stage of CRC cells.

Over the years, significant advancements have been made in the field of CRC therapeutics, resulting in improved survival rates attributed to progress in both primary and adjuvant treatment methods[2]. Notably, the integration of chemotherapy as either a neoadjuvant or adjuvant intervention has emerged as a strategic approach to mitigating tumor burden, reducing its size, and stabilizing its growth[3]. Chemotherapy retains its central role in current treatment protocols of CRC tumors[4]. However, its effectiveness is hindered by a narrow therapeutic window, notable adverse effects, and the frequent development of acquired resistance. Additionally, various chemotherapy agents, radiotherapies, and other physical interventions also induce cellular and tissue destruction, releasing immunogenic signals that paradoxically activate the immune system[5]. This phenomenon highlights the complex interplay between treatment modalities and the tumor microenvironment. However, currently few combinations of chemotherapy regimens have been used in the treatment of CRC patients. This includes the use of bevacizumab and fruquintinib representing a humanized anti-vascular endothelial growth factor-A antibody and vascular endothelial growth factor receptor tyrosine kinase inhibitor, respectively[6,7]. These interventions lead to a significant decrease in disease progression. Although these interventions also cause an increase in treatment related adverse effects.

Immune checkpoint inhibitors (ICIs) have demonstrated encouraging clinical results in treating CRC by blocking proteins that regulate immune responses[8]. ICIs exhibit superior efficacy in microsatellite instability-high/mismatch repair-deficient tumors due to their ability to enhance tumor neoantigen presentation, leading to potent immune recognition and elimination of cancer cells. These therapies demonstrate efficacy; however, inherent tumor heterogeneity, as exemplified by microsatellite stable/mismatch repair-proficient CRC, limits patient response, necessitating tailored treatment strategies[9]. MT-targeted drugs, a chemotherapy drug disrupt the cytoskeletal network vital for cell division, impeding tumor proliferation[10]. While demonstrating efficacy, their effectiveness varies among patients, prompting ongoing research to refine treatment protocols. This challenge is compounded by the intrinsic or acquired resistance of CRC tumors to a broad spectrum of chemotherapeutics, potentially due to high P-glycoprotein expression[11]. While numerous MT-targeted have shown success in cancers like breast, ovarian, and lung, current CRC clinical trials primarily focus on paclitaxel and its derivatives[12]. Nevertheless, these MT-targeting drugs did not provide much improved overall survival in CRC patients.

In CRC treatment, traditional natural compound-based drugs have demonstrated effectiveness, with recent advancements utilizing biosynthetic bioengineering techniques to refine these agents. For instance, combretastatin A-4 (CA-4) and its analogs have undergone extensive synthesis and evaluation[13]. Among these, isoCA-4 has shown promise due to its stability and similar efficacy to CA-4[14]. However, the trans-isomer of CA-4, which is less efficient in inhibiting CRC cell growth and prone to isomerization during storage and metabolism, poses a challenge due to its heightened toxicity [15]. Nonetheless, if local conformational modulation can be achieved, CA-4 or its analogs hold potential as potent anti-cancer chemotherapy agents. CA-4 acts by destabilizing MTs and exhibiting anti-angiogenic effects, like the mechanism of action of paclitaxel and navicixizumab.

Photoactivation emerges as a promising strategy for localized activation of CA-4, enabling targeted control over drug release within tumors. The first photoactivated CA-4, dithiaporphyrin-aminoacylate-CA-4, introduced in 2013, efficiently liberates CA-4 upon irradiation with a 690 nm laser (over 80% release within 10 minutes)[16]. However, this approach comes with a trade-off, as it exhibits a 6-fold increase in the half-maximal inhibitory concentration, potentially indicating reduced potency. In 2015, photo switchable photostatins (PSTs) were developed, replacing the C=C double bond with an N=N double bond, leading to more efficient photoactivation[17]. The most promising variant demonstrates a 101-fold activation upon photo-isomerization. While PSTs do undergo spontaneous cis-to-trans isomerization, rapid conversion back to the active cis-form can be achieved using short light pulses. Additionally, PSTs demonstrated stability with over 5000 switches over two days, offering a potentially promising, photoactivatable CA-4. Alongside CA-4, other MT-targeted drugs were developed as photo switchable derivatives, namely paclitaxel and docetaxel[18]. However, these faced challenges such as toxicity and low solubility, respectively. Novel photo-switchable compounds have emerged from established MT-targeting medications. Nevertheless, their potency shift dynamic range currently does not match that observed in combretastatin analogs, which may range from 60 to 100 folds. Advancements in optical fiber technologies have facilitated the directed delivery of two-photon excitation beams into tissues, extending the application of two-photon excitation to colon cells[19]. This progress led to the development of the first clinical two-photon endoscope in the same year. However, to date, there have been no reports on attempts to photo-activate CA-4 analogs *in vivo*. Further exploration of CA-4-based photo pharmacology is anticipated.

In conclusion, the merger of light and medicine ignites a revolutionary approach to CRC therapy. Emerging optical control strategies for MT-targeting drugs unlock a new paradigm in CRC management, offering unprecedented potential to overcome limitations associated with conventional options. This exciting avenue complements the promise of ICIs, each strategy pushing the boundaries of personalized CRC treatment. While challenges remain, advancements in optical fiber technologies have expanded the application of two-photon excitation and further exploration of photo-pharmacology, particularly with CA-4 analogs, holds promise for advancing CRC treatment.

FOOTNOTES

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