Literature review: New drug treatment protocols for colorectal cancer.

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Abstract

This paper looks at various drug treatment protocols for colorectal cancer. From the findings of Thanikachalam and khan's the improvement of cancer screening techniques has brought about a reduction in the occurrence and mortality from colorectal cancer. 5-FU which showed promise in the treatment had limitations with regard to its bioavailability and toxicological damage it had to the gastrointestinal tract among other limitations. TAS-102 had prospects to overcome the shortcomings of 5-FU. Prior to the approval of TAS-102, TAS-OX was the option for treatment. Clinical studies were carried out to see the effect of a combined treatment of TAS-102 and TAS-OX. On the other hand, Nanotechnology based 5-FU delivery system was developed to avoid side effects.

Keywords: Colorectal cancer, Clinical studies, Nanotechnology, Bioavailability, 5-FU, TAS-102, TAS-OX, Drug delivery.

Introduction

According to the findings from the research of Thanikachalam and Khan's (2019), efficient cancer screening techniques have resulted in a positive drop in the incidence and death rate of colorectal cancer. However, the imperativeness of a prospective drug is stressed in the current scenario. As opined by Kishore and Bhadra (2021), the 5-Fluorouracil (5-FOU) is currently at the top tier regarding its effectiveness as a chemotherapy drug for Colorectal Cancer [1].

However, on subjecting the patients to the drug, a sense of repulsiveness was observed among most of them. The prospect of the 5-Fluorouracil was also emphasized in the research of Kazi et al., (2019) and Entezar-Almahdi et al., (2020). These researches have acknowledged the efficacy of the 5-Fluororacil drug due to its newly observed resonance. Within the last decade, demand for this antimetabolite chemotherapeutic drug has skyrocketed. 5-FU has been widely utilized as a first-line antineoplastic drug in the treatment of colon and rectum, head and neck, breast, abdominal, and pancreatic cancers [2].

Because of its water solubility, 5-FU is commonly used intravenously. However, administrators have observed limitations in the drug's clinical implementation, initially in its appearance. The attention was redirected towards its bioavailability, which, consequently, has reflected a cure rate of less than 15% for advanced CRC [3].

Furthermore, it was also observed that the application of the 5-FU drug results in severe toxicological damage to the gastrointestinal system (GI) and blood factors. Additional repercussions include detrimental effects of the neurological, dermatological, and cardiological nature. Following these implications, the need to develop promising DDSs for the administration of 5-FU to ensure better therapeutic effect with lessened side effects have been stressed [4].

The inimical implications of the 5-FU drug have underlined the need for an effective drug design to treat CRC. The study conducted by Cecchini et al., (2021) focused on the very notion by exploring the prospects of the TAS-102 due to its plausibility in overcoming the short half-life and poor efficacy of the 5-FU drug [5].

TAS-102 is a novel antimetabolite, which has been recently approved for the treatment of refractory metastatic Colorectal Cancer. Before the approval of TAS-102, the contemporary field was limited to the application of oxaliplatin (TAS-OX) for the treatment of metastatic CRC. However, under the guidance of the aforementioned researchers, it was determined if the integration of TAS-102 and TAS-OX would be effective at boosting the treatment efficacy of metastatic CRC [6].

The nature of the study was investigator-initiated, open-label, sing-arm phase 1b study. Patients with metastatic CRC who had previously been treated with 5-fluorouracil, irinotecan, or oxaliplatin were enrolled in the research. TAS-102 was given at three dosage levels of 25, 30, and 35 mg/m2 twice daily from day 1 to day 5 in 14-day cycles with 85 mg/m2 oxaliplatin on day 1 [7].

Upon completion, the study observed that while the amalgamated administration of TAS-12 and TOS-OX did not reveal any clinically meaningful ORR, the experiment was well-tolerated among the patients with no protruding side-effects [8].

While a combined administration of TAS-102 and TAS-OX did not affect the patients adversely the overall benefits have been dwarfed due to the surmountable potential of the 5-FU

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drug. Although the 5-FU is considered among the superior chemotherapeutic agents for the treatment of CRC, the disadvantages hinder its prospect for future applications [9].

Rapid spike in metabolism, short half-life (10 - 20 minutes), limited bioavailability, high cell cytotoxicity, and insufficient selectivity for malignant cells are all factors that restrict the drug's effectiveness [Table 1]. Based on this assumption, researchers have focused the development of innovative 5-FU delivery methods, which are expected to reduce the harmful effect of anticancer drugs on healthy tissues [10].

The Nanotechnology-based 5-FU system was developed as the first protocol towards a delivery system void of side effects. An organized view of Nanotechnology-based 5-FU delivery systems can be observed in Figure 1.

Evident from the table below, the discovery of the Solid Lipid Nanoparticles or SLN-Based Delivery Systems reflected several benefits due to its colloidal nature. These benefits included competence towards controlling the patterns of drug consumption, boosted drug sturdiness, and enhanceddrug loading capacity. Following these discoveries, the 5-FU medication was included into the shells of the SLNs for the treatment of Erlich's malignancy (tumor). The implementation resulted in an elevated release behavior of Vitro. The utilization of Sodium Carboxymethyl Cellulose (NaCMC) gel matrix for the diffusion and dissipation of SLNs increased its Efficacy. The discovery concluded SLNs as an enhancer of 5-FU through local administration [11].

In another study conducted by Lang et al., (2020), a series of Chitosan-graft-poly (ε-caprolactone) micelles (CS-g-PCL) was investigated as a 5-FU delivery system's efficiency. According to the results of the experiment, the length of the copolymer's hydrophobic chain had a substantial effect on the micelle properties. Upon observation of the copolymers, the results exhibited a controlled release behavior. An additional observation was the interaction levels between the copolymers and 5-FU, which played a crucial role in adjusting the release rate. The verdict drawn from the research was that the 5-FU-loaded micelles had significantly higher biocompatibility as well as equally lower cytotoxicity when compared to a free 5-FU due to the slow release pattern of the former. However, despite these dynamics, the efficiency of the 5-FU-loaded micelles in eliminating cancerous cells was considerably higher when compared to that of a free 5-FU (Zhang et al., 2019) [12].

The recent changes in the drug development protocol have also resulted in the discovery of additional approaches that were developed adjacent to the CS-g-PCL. The creation of a 5-FU prodrug covalently attached to low molecular weight chitosan (LMWC) with a photo-responsive linker was one of the breakthroughs. The structure was an amalgamation of 5-FU, 4-bromomethyl-3nitrobenzoic acid, which is considered

Table 1: *Types of 5-FU Nano-Delivery Systems (Source: self-made).*

Main Format	Structure	Particle Size
Solid Lipid Nanoparticle	Stearic acid, lecithin, poloxamer 188	137±5.5 nm to 800±53.6 nm
Chitosan	CS-g-PCL LMWC-4-bromomethyl-3-nitrobenzoic acid CS-PAsp CG5-FU-NPs and FCGS-FU-NPs	61.4-108.6 nm 365 nm 85-300 nm 31-33 nm
Magnetic Nanocarrier	Fe_3O_4-encapsulating carbon nanospheres (TMMIPs) Samarium ferrite ($SmFeO_3$) nanoparticles coated with poly(methylmethacrylate) CEINs-PEI-βCD-FA	150 nm -50 nm < 100 nm
Carbon Nanotube Silica NP	Multi-walled CNTs Epidermal growth factor-hollow mesoporous silica nanoparticles	- 120 nm and pore size = 2.5 nm
Molecularly Imprinted Polymer	MIP-CS-g-PMMA TMMIPs	130 nm I50 nm
Polymeric NP and MP	Poly(3-hydroxybutyrate-co-3 hydroxyhexanoate) (PHBHHx) PLA and PLA-PEG FA-PLGA	160 nm and 3 µm 294 nm and 283 nm 224±18 nm
Protein NP	Bovine serum albumin (BSA)	210 nm
Dendrimer	PEG-PAMAM PDEA-mPEG-PAMAM (PPD)	270-307 nm 43.0 nm at pH 4.0, 41.6 nm at pH 6.5 and 11.6 nm at pH 7.4
Liposome	Transferrin-conjugated liposome Folate-PEG-DSPE	- 174 nm

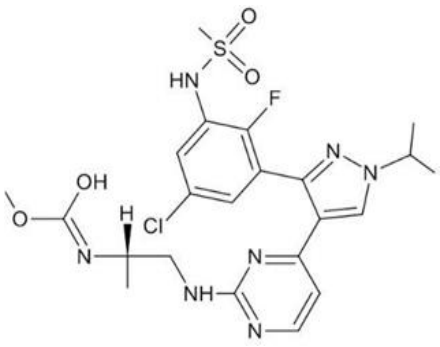

Figure 1: *Schematic representation of Encorafenib (Braftovi).*

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a cleavable linker. As part of the developmental approach, UV light at 365 nanometres was utilized so that the designed linker can be cleaved. The results led to the conclusion that the connected polymer had higher solubility and enhanced cell penetration capability (with a mean size of 100 nanometres) when compared to the LMWC. The former was also observed to produce hydrogel as well as DMSO-based gel (Narayan et al., 2021) [13].

As illustrated by the case scenario of the 5-FU medicine, the occurrence of treatment resistance acts as one of the deadlocks for the high death rates of CRC patients. The effective treatment of colorectal cancer has yearned for a clearer understanding in the context of innate and acquired therapeutic resistance. The protocols applied in the development of drugs for CRC treatment have been recently influenced due to the implications of the Tumor Micro Environment (TME). As a result of its development, a thorough review of clinical trials to look at immune-cell infiltration as a prognostic and predictive sign is required [14].

The works of Yaghoubi et al., (2019) drawn upon the recent indications to explore the use of immunotherapy. The use of immunotherapy for the treatment of CRC has been considered a paradigm-shifting discovery, marking it as a promising avenue for further research. In recent years, it has been observed that the administration of immunotherapy has reflected optimistic results along with the use of immune checkpoint inhibitors in CRC in subgroups of patients [15].

The discovery and development of new drug design trends have been one of the major focus points in the studies Krajewska et al., (2019). The research has implied that discovering approaches to improve the responsiveness to checkpoint inhibitors would be a significant achievement to ensure a leap towards a risk-free CRC treatment. The hope for a positive outcome through the administration of immunotherapy for CRC treatment was further dissuaded by the research of Le Saux et al., (2020). The research led to the discovery that unresponsiveness among the CRC patients subjected to immunotherapy continues to be an obstacle to the development of a prospering CRC treatment approach [16].

The recent emergences in the field of drug designing and development for the treatment of CRC have also influenced research on Platinum-based (Pt) anticancer drugs. However, the research conducted by Mahmud et al., (2021) has shed insights regarding the implications of drug implementation. According to the research, despite the extensive application of Platinum-based drugs in the treatment of CRC, the prospect for their sustainability has been declined due to their inherent toxicity and low drug resistance of the patients subjected to the drug. Such findings have piqued interest in discovering alternative drug-designing protocols that are metal-based [17].

Lee et al., (2020), through their research, led to the observation that Ruthenium-based chemotherapeutics exhibit optimistic anticancer activity on the virtue of their unique chemical properties. Multiple cell signaling pathways have been discovered to modulate the anticancer effects of Ru-based drugs in CRC cells. These routes are involved in cell proliferation, bisection, augmentation, and relocation, either directly or indirectly. In commercially accessible CRC cell line models, several Ru-based anti-cancer medications have also been found to be more effective than Pt-based anti-cancer therapies. (Nielson 2020) [18].

The quest of new drugs discovery has been eternal since the identification of human ailments and diseases. The success rates and speed of invention have greatly improved as a result of the combination of science, technology, and R&D. It can be hopefully claimed that problems of cancer within the colons or the rectum area would cease to exist in the near future. FDA approved drugs and their chemical structures (made with chem sketch). This FDA-approved drug is used for the treatment of adult metastatic CRC patients with a BRAF V600E mutation (Al-Salam 2021) [Figure1].

This FDA-approved drug (monoclonal antibody) is administered in combination with radiation therapy for the local or initial treatment of specific neck & head cancer types known as squamous cell carcinoma (Gomar et al., 2021) [Figure 2].

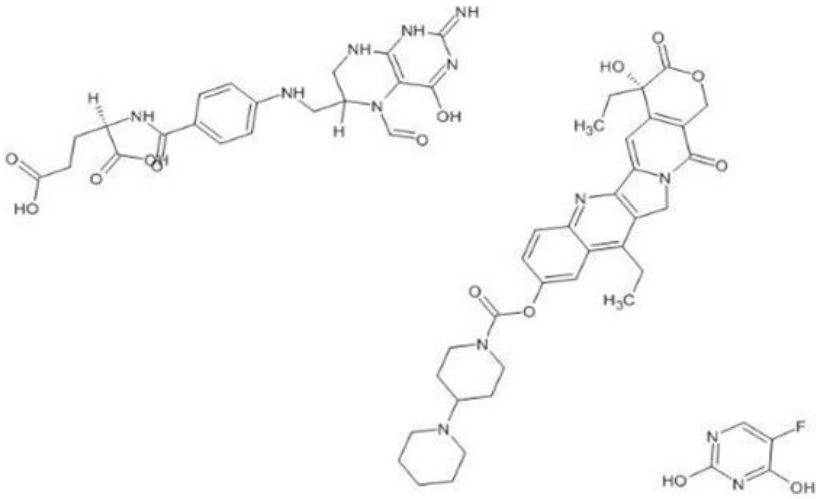

Figure 2: *Schematic representation of Cetuximab (Erbitux).*

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Conclusion

Apart from the promising effects of the 5-FU drug line and the Pt-based products, some of the recent chemotherapeutic approaches for the treatment of Colorectal Cancer have reflected better results. The high mortality rates of CRC patients have been minutely addressed with the introduction of some of the new FDA-approved drugs. The significance of ICIs in the sector of immunotherapy within patients is constantly surging. Their efficacy while dealing with heavily mutated tumors like melanoma has been influencing researchers to delve into its compatibility with metastatic CRC treatment. The use of ICIs as an alternative to classic systemic therapies is highly coveted for future development. This is due to the approach of ICIs to boost the immunity standard of the patients against tumor cells without severe corollary is further supported by the spectacularly durable RRs among the subjected. Studies are being focused on the domain of dMMR-MSI-H mCRC to develop compliant treatment approaches. The approval of anti-PD-1 agents, such as Pembrolizumab and Nivolumab has shed light on the treatment of the CRC subset (Kreidieh et al., 2020).

For future endeavors, the key to success would lie in the development of a suitable novel treatment approach for the remaining subsets of the CRC manifestations. The current research points towards the failure of immunotherapy regarding single-agent checkpoint inhibitors. Anticipating the patterns of the pMMR tumors towards immunotherapy would be effective at altering the environment of the tumors, rendering both the pMMR-MSI-L and the dMMR-MSI-H effective towards concurrent immunotherapy techniques (Huyghe et al., 2020).

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