Original Article

Cytotoxic and Immunologic Effects of Measles Oncolytic Virus on Colon Cancer Cells

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ABSTRACT

Objective: To evaluate the effects of the measles virus (MV) in combination with standard therapeutic agents cetuximab and chemotherapy on colon tumor cells.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the College of Medicine, University of Babylon, Iraq from 1st December 2024 to 30th May 2025.

Methods: Cells were exposed to various doses of attenuated MV, cetuximab, 5-fluorouracil, and cisplatin. Viability, apoptosis (caspase-3 levels), and immune markers (IFN-γ, TGF-β, IL-10, TNF-α) were assessed using biochemical assays to identify optimal therapeutic ratios.

Results: Cetuximab alone increased caspase-3 levels, while combination therapies induced greater cell death through alternative mechanisms. MV markedly elevated IFN-γ (55.50±12.10 vs. 24.15±3.73, $P < 0.001$). Combination treatments suppressed immunosuppressive cytokines; TGF-β was significantly reduced in the measles virus cisplatin group (0.161±0.001 vs. 0.182±0.002, $P = 0.005$), and IL-10 and TNF-α levels were lowered dose-dependently, with triple combinations achieving near-complete suppression (5.00±0.80 vs. 203.63±22.19, $P < 0.001$).

Conclusion: Measles virus based combination therapy produces potent immunomodulatory effects, enhancing anti-tumor action beyond apoptosis by reducing immunosuppressive cytokines and controlling inflammation. Optimizing dose ratios and ensuring clinical safety remain crucial for future applications.

Key Words: Oncolytic virus, Measles virus, Cetuximab, Combination therapy, Colon cancer, Immunomodulation

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INTRODUCTION

Currently, colorectal cancer is one of the most common causes of cancer death globally, with around 1.9 million new cases of colorectal cancer diagnosed each year.[1] Despite significant advances in surgical techniques, as well as chemotherapy treatments and targeted therapies, the five-year survival rate for metastatic colorectal cancer has not improved and continues to be under 15%. This highlights the need for new, innovative therapies.[2]

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Oncolytic viruses are classified as cancer-targeted viruses that can occur naturally or be engineered.[3]

Oncolytic viruses selectively replicate in and kill cancer cells while leaving normal tissues unharmed. There are several benefits of using oncolytic virus therapies over conventional treatment, including the possibility of tumor selectivity, the systematic recruitment of the immune system, and the chance to circumvent drug resistance mechanisms.[4] Measles virus (MV) is one of the several natural or engineered oncolytic viruses constructed, tested, and studied for oncolytic virotherapy in a variety of cancers and is the most promising oncolytic virus for use due to its excellent safety profile, characterized biology, and potent oncolytic activity.[5]

The vaccine strain of the measles virus (MV) preferentially targets cancer cells through several mechanisms. Cancer cells frequently over express CD46, which is the cellular receptor for measles virus and also serves as a regulatory protein in the complement system.[6] Moreover, many cancer cell lines exhibit aberrant interferon responses and defective DNA repair pathways, which promote viral replication and hinder the clearance of viral infections.[3] When considering direct oncolytic effects, measles virus (MV) infection can induce strong anti-tumor immune

responses by activating both innate and adaptive immune responses.[7]

The basis of combination therapy in oncological settings is that multiple therapeutic modalities can act synergistically to produce superior outcomes than single-modality therapies.[8] The use of oncolytic viruses in combination with chemotherapy and targeted agents offers several benefits, including complementary mechanisms of action, a decreased likelihood of resistance, and the potential to reduce the dose of individual agents while maintaining or increasing efficacy.[9]

Cetuximab is a chimeric monoclonal antibody that targets the epidermal growth factor receptor (EGFR) andis efficacious in managing colorectal cancer, particularly in tumors harboring wild-type KRAS.[2] There is overexpression of EGFR in approximately 60-80% of colorectal cancers, and EGFR encourages tumor proliferation, survival, and metastasis.[10] Combination chemotherapy with cetuximab has shown improved outcomes in metastatic colorectal cancer, suggesting that additional combination strategies can be explored.

Conventional chemotherapeutic agents, such as 5-fluorouracil (5FU) and cisplatin, remain the primary agents in colorectal cancer management. 5-FU is a fluoropyrimidine analogue that interferes with DNA synthesis and repair, while cisplatin forms DNA cross-links to induce apoptosis.[11] The immunomodulatory effects, particularly the induction of immunogenic cell death, make cytotoxic agents attractive collaborators with oncolytic virus therapy.[12]

Despite the potential advantages of combination approaches, the ideal combination and use of an oncolytic viral therapy with conventional therapies have not been elucidated. The interplay between viral replication, immunogenicity, immune activation, and drug-induced cytotoxicity should be further explored to identify synergistic combinations and to reduce (or avoid) those that appear antagonistic.[13]

This study evaluated measles virus with cetuximab and chemotherapy in SW480 cells to assess cytotoxicity, apoptosis, immune modulation, and optimal dosing.

METHODS

This study was conducted at College of Medicine, University of Babylon, Iraq from 1st December 2024 to 30th May 2025 vide letter No. 314 dated 25th November 2024. Human SW480 colon cancer cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 μg/ml streptomycin. Cells were cultured at 37°C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using the trypan blue exclusion method, and only cultures with viability greater than 95% were used for experiments.

Measles Virus: Live attenuated measles virus vaccine strain (Edmonston-Zagreb) was obtained from the Iraqi Ministry of Health vaccine repository. Working concentrations of 10 μg/ml were used based on preliminary dose-response studies.

Cetuximab: Cetuximab (Erbitux®) was obtained as a clinical-grade formulation and used at a concentration of 100 μg/ml based on published literature and preliminary optimization studies.

Chemotherapeutic Agents: 5-fluorouracil (Sigma-Aldrich) and cisplatin (Sigma-Aldrich) were prepared as stock solutions in dimethyl sulfoxide (DMSO) and phosphate-buffered saline (PBS), respectively. Working concentrations ranged from 15-500 μg/mL,as determined by dose-response characterization.

Experimental Design: SW480 cells were seeded in 96-well plates at a density of 5×10^3 cells per well and allowed to adhere for 24 hours. Cells were then treated with various combinations of therapeutic agents according to the following experimental groups:

1. **Single Agent Studies:** Control (untreated), measles virus alone, cetuximab alone, 5FU alone, cisplatin alone
2. **Dual Combination Studies:** MV + cisplatin, MV + 5FU, cetuximab + cisplatin, cetuximab + 5FU
3. **Triple Combination Studies:** MV + cetuximab + cisplatin, MV + cetuximab + 5FU

Each treatment condition was evaluated at multiple time points (24, 48, and 72 hours) with at least six replicates per condition. Dose-response relationships were established for chemotherapeutic agents using concentrations of 15, 31, 62, 125, 250 and 500 μg/ml.

Cell viability was assessed using the crystal violet (CV) assay. Following treatment, cells were fixed with 4% paraformaldehyde for 15 minutes, washed with PBS, and stained with 0.1% crystal violet solution for 30 minutes. After washing and drying, bound dye was solubilized with 10% acetic acid, and absorbance was measured at 590 nm using a microplate reader (BioTek Instruments, Winooski, VT, USA).

Caspase-3 levels were determined using a commercial ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instruction. Briefly, cells were lysed using the provided lysis buffer, and protein concentrations were normalized using the Bradford assay. Cell lysates were then incubated in ELISA plates coated with anti-caspase-3 antibodies, followed by detection using horseradish peroxidase-conjugated secondary antibodies and the development of a colorimetric substrate.

Cytokine Analysis: Culture supernatants were collected at specified time points and stored at -80°C until analysis. Cytokine levels (IFN-γ, TGF-β, IL-10, and TNF-α) were measured using commercially available ELISA kits (R&D Systems) according to the manufacturer's protocols. All samples were analyzed in

duplicate, and cytokine concentrations were calculated based on standard curves generated using recombinant proteins.

IFN-γ Measurement: IFN-γ levels were determined using a human IFN-γ quantikine ELISA kit with a detection limit of 8 pg/ml and an inter-assay coefficient of variation <10%.

TGF-β Analysis: TGF-β1 levels were measured using a human TGF-β1 quantikine ELISA kit following acid activation to convert latent TGF-β to its active form. The detection limit was seven pg/mL.

IL-10 Quantification: IL-10 concentrations were determined using a human IL-10 quantikine ELISA kit with a sensitivity of 3.9 pg/ml and intra-assay precision <5%.

TNF-α Assessment: TNF-α levels were measured using a human TNF-α quantikine ELISA kit with a minimum detectable dose of 0.18 pg/ml.

The data was entered and analyzed through SPSS-25. Statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. Differences were considered statistically significant at $P<0.05$.

RESULTS

The cell viability was significantly reduced after the treatment with Cisplatin and 5-FU at all concentrations (500-31.25 µg/ml) compared to the control group. Cisplatin exhibited greater cytotoxicity than 5-FU, which demonstrated a dose-dependent effect (Fig. 1).

Cancer cells treated with cetuximab (100 µg/mL) and varying doses of 5-FU or cisplatin (500–31.25 µg/mL) showed reduced viability versus controls. Only 5-FU + cetuximab at 62.5 µg/mL differed significantly; cisplatin + cetuximab showed no significant change across concentrations (Fig. 2).

Tretatment with anticancer drugs combined with Cetuximab and Measles virus significantly reduced the cell population. Cisplatin treatment was more cytotoxic than 5-Fu at all concentrations tested (Fig. 3).

Combination treatments markedly reduced caspase-3 levels compared to cetuximab alone. In 5-FU–cetuximab and cisplatin-cetuximab groups, caspase-3 decreased dose-dependently ($P<0.001$). The triple combination with measles virus caused the greatest reduction across all concentrations, indicating alternative, non-apoptotic cell death mechanisms enhancing cytotoxic efficacy (Fig. 4).

Measles virus markedly increased IFN-γ production (55.503±12.109 vs. 24.147±3.730; $P<0.001$), confirming strong immune activation. Adding 5-FU or cisplatin caused dose-dependent attenuation of IFN-γ, while triple combinations with cetuximab and chemotherapy yielded intermediate but still elevated IFN-γ levels, indicating balanced immunomodulatory effects (Fig. 5).

The cisplatin–measles virus combination significantly suppressed TGF-β levels ($P = 0.002$, power = 0.939), while other treatments showed no notable effects. Several cisplatin concentrations (31–500 µg/mL) markedly reduced TGF-β compared with controls, suggesting a unique synergistic immune-modulating interaction between cisplatin and the measles virus (Fig. 6).

Combination treatments significantly reduced IL-10 levels compared with controls across all protocols. Cetuximab and 5-FU combinations showed gradual dose-dependent decreases, while cisplatin–measles virus combinations achieved the strongest IL-10 suppression. Triple therapy with cisplatin, cetuximab, and MV also markedly lowered IL-10, confirming enhanced immunomodulatory synergy across treatment regimens (Fig. 7).

Combination treatments caused strong, dose-dependent reductions in TNF-α levels. In the 5-FU–cetuximab study, TNF-α significantly decreased from 200.4±10.3 in controls to 60.6 ± 5.3 at 500 µg/mL ($P<0.001$). Cisplatin-based combinations produced even greater suppression, while the triple therapy (cisplatin-cetuximab -MV) achieved near-complete inhibition, reducing TNF-α to 5.0±0.8 at 500 µg/mL ($P<0.001$). These results demonstrate a potent, concentration-dependent anti-inflammatory effect across regimens, with the triple combination exhibiting the most profound cytokine suppression, suggesting a strong therapeutic synergy in modulating tumor-promoting inflammation and enhancing anticancer efficacy (Fig. 8).

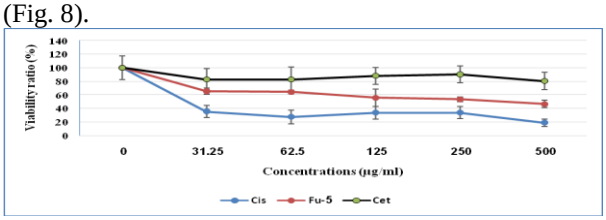

Figure No. 1: Cytotoxicity of cisplatin, 5-fluorouracil, and cetuximab on SW480 colon cancer cells

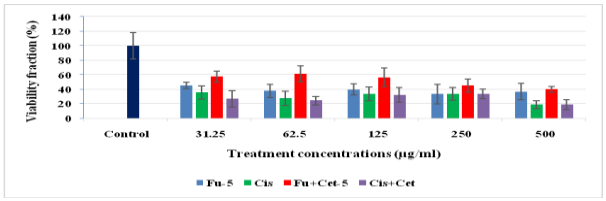

Figure No. 2: Effect of cetuximab in combination with cisplatin and 5-fluorouracil on SW480 colon cancer cells

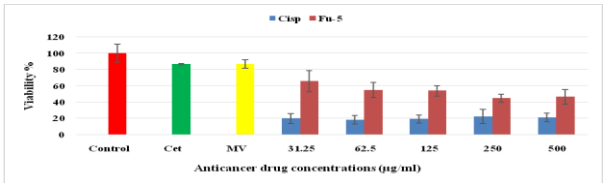

Figure No. 3: Effect of oncolytic measles virus treatment combined with anticancer drugs Cisplatin (Cisp) and 5 5-Fluorouracil (5-Fu) in the presence of Cetuximab monoclonal antibody (Cet) on the viability of SW480 colon cancer

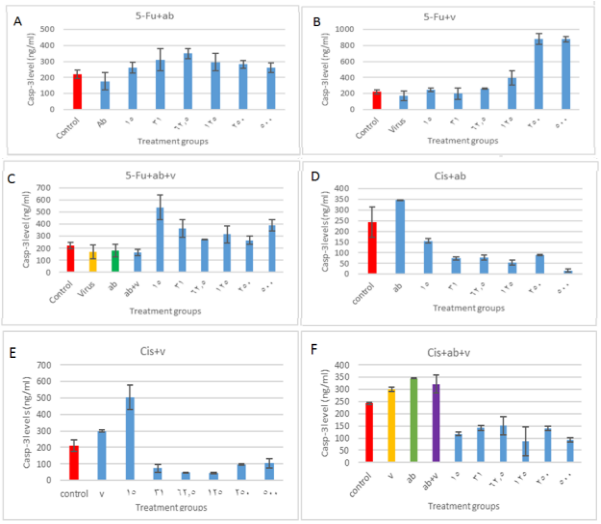

Figure No. 4: Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C), Cisplatin-Cetuximab(D), Cisplatin-MV (E), and Cisplatin-Cetuximab-MV (F) on caspase-3 levels in SW480 colon cancer cells

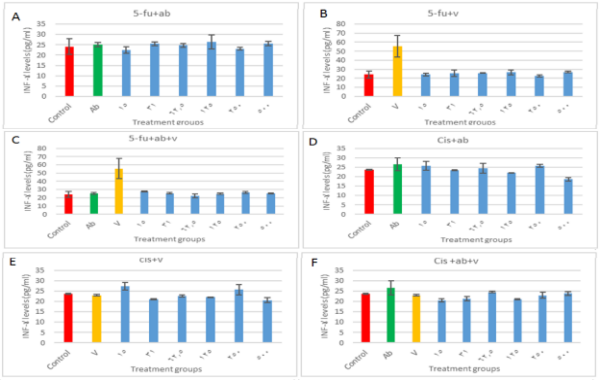

Figure No. 5: Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the INF gamma levels in SW480 colon cancer cells

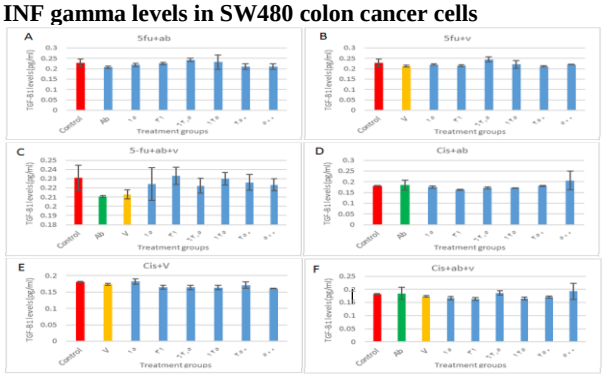

Figure No. 6: Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab (D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the TGF-b levels in SW480 colon cancer cells

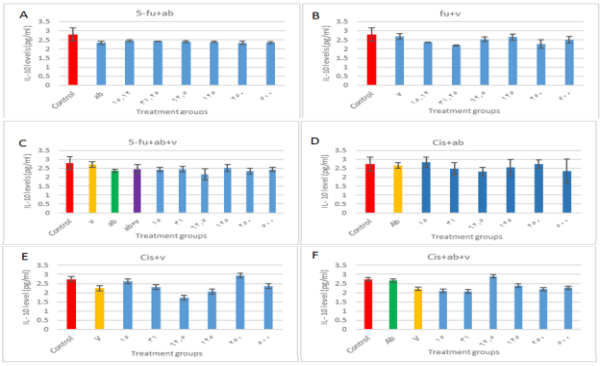

Figure No. 7: Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the IL10 levels in SW480 colon cancer cells

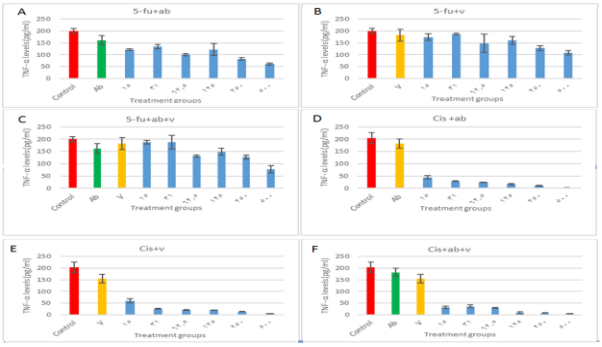

Fig. 8: Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on TNF levels in SW480 colon cancer cells

DISCUSSION

This study compared the cytotoxic and immunomodulatory effects of cisplatin, 5-fluorouracil (5-FU), cetuximab, and measles virus (MV) combinations on colon cancer cells. Cisplatin exhibited superior cytotoxicity to 5-FU, aligning with previous studies showing that platinum agents cause more severe and irreparable DNA damage than the metabolic interference caused by 5-FU.[14] The dose-dependent cytotoxicity observed for both agents matched earlier pharmacodynamic data, confirming their reproducibility across colorectal cancer models. While both drugs were effective individually, cisplatin demonstrated higher potency across all concentrations tested (500-31.25 µg/ml).

The mechanism of 5-FU involves inhibition of thymidylate synthase and disruption of RNA/DNA synthesis, leading to apoptosis.[15] However, its cytotoxicity is also time-dependent.[16] Interestingly, cisplatin-5-FU combinations sometimes show reduced efficacy compared to monotherapy due to complex interactions affecting the cell cycle.[17] The addition of cetuximab (100 µg/ml) modestly enhanced 5-FU effects but did not significantly improve cisplatin activity, possibly because cetuximab efficacy depends on KRAS

wild-type status.[18] The limited response in this study may therefore reflect intrinsic resistance due to KRAS mutations or other downstream alterations.[19]

The most promising outcome emerged from the triple combination of MV, cetuximab, and chemotherapy especially MV + cetuximab + cisplatin which resulted in the most pronounced tumor cell reduction. The measles virus preferentially targets tumor cells expressing high CD46 receptor levels, leading to oncolysis and immune activation.[20] MV can also induce immunogenic cell death (ICD), stimulating long-term anti-tumor immunity.[21]

Interestingly, although cetuximab alone increased caspase-3 (apoptosis marker), combination therapies reduced caspase-3 levels despite higher overall cytotoxicity. This suggests that alternative regulated cell death pathways such as necroptosis, pyroptosis, or ferroptosis may predominate, offering advantages in overcoming apoptosis resistance and promoting immunogenicity.[22] The reduced caspase-3 may thus indicate a shift toward ICD, wherein tumor cells release danger signals (DAMPs) that activate adaptive immunity.

MV treatment significantly elevated IFN-γ levels, activating both innate and adaptive immune responses.[23] IFN-γ promotes MHC class I expression, cytotoxic T-cell activation, and macrophage polarization. Combination therapies also reduced TGF-β levels especially with cisplatin-MV suggesting a shift from an immunosuppressive to an immunostimulatory tumor microenvironment.[24] This reprogramming could transform "cold" immune-resistant tumors into "hot" responsive ones.[25]

Furthermore, IL-10 suppression across treatment groups reduced anti-inflammatory signaling, enhancing anti-tumor activity.[26] The most striking immunologic outcome was near-complete TNF-α suppression in high-dose triple therapy. Although TNF-α contributes to anti-tumor immunity, chronic elevation supports tumor progression and angiogenesis.[19] Its down-regulation may therefore disrupt inflammatory circuits that sustain colorectal tumor growth.[27]

CONCLUSION

Combining oncolytic virotherapy with chemotherapy and cetuximab provides superior anti-tumor activity through complex immune modulation beyond classical chemotherapy effects. The treatment shifted cancer cell death from apoptosis to alternative, more effective mechanisms while enhancing immune activation via IFN-γ production. It also suppressed key immunosuppressive mediators (TGF-β, IL-10) and inflammatory cytokines (TNF-α), reprogramming the tumor microenvironment. These dose-dependent effects highlight the need for rational, immune-targeted combination design.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Reyam Abdul Khuder Mohammed, Kaiser N. Madlum
Drafting or Revising Critically:	Reyam Abdul Khuder Mohammed, Zaytoon Abdulrida Al-Khafaji
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

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