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*Research article*

# Comparison of Inhibitory Effects between Cetuximab and Cisplatin on Colon Cancer SW480 Cell Line

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**Abstract:** Cancer is still one of the more severe diseases that endangers the life of a human being, especially in the present day. Globally, colorectal cancer is a very predominant cancer and the second principal contributor to cancer-related fatalities across all ages, both adults and children. Currently available treatments include surgery, radiotherapy, chemotherapy, and immunotherapy. Chemotherapy is an established modality in the therapy of cancer, and platinum-based drugs demonstrated activity against several tumours. Here, cancer cell lines were grown in ELISA plates in media until ~80% monolayer confluence. Cetuximab (Cetx) was tested for cytotoxicity on the SW480 colon cancer cell line at six serial concentrations ranging from 2.5 to 0.0781 µg/mL. Similarly, the same cell line was exposed to six serial levels of cisplatin (Cisp.), varying from 100 to 3.125 µg/mL, for 24 hours. Cells without any treatment served as controls. Cell viability was monitored by measuring OD with an ELISA reader after staining with crystal violet. The findings revealed a significant result at the statistical level ($P < 0.05$). in the cell-killing impacts of cetuximab and cisplatin in colon cancer cells. These findings emphasize the potential value of cetuximab's anti-tumour activity when used alongside traditional platinum-based chemotherapy and support its use in targeted cancer therapy.

**Keywords:** Cetuximab; cisplatin; colorectal cancer; SW480 cell line; cytotoxicity

## 1. Introduction

Colon and rectal disease originate in the colon's tissue, the longest segment of the internal organ. The majority of colon cancers arise in the submucosal layer of the digestive system. Several studies say that lifestyle choices like eating high-fat foods and smoking are to blame, but research has found that inherited traits also play a role in about 25% of cases. Colon cancer is a major contributor to well-known types of cancer internationally and represents the third leading cause of cancer deaths in the US [1, 2]. Its therapy necessitates a multi-methodology model, which involves carefully resecting the growth subsequently treated with chemotherapy and radiotherapy. Notwithstanding significant advances in the treatment of colorectal cancer, there is a need for more advanced therapies and novel approaches that incorporate targeted inhibition of signaling pathways [3]. For people with head and neck cancer, Cetx. Moreover, in general, radiotherapy made them more likely to live for five years than people who had radiotherapy alone [4]. The endurance benefits are related

to Cetx's expansion. Administered as frontline chemotherapy for cutting-edge non-small-cell lung carcinoma in individuals with undeniable EGFR mutations was likewise announced [5].

Moreover, some preclinical investigations propose that Cetx. restrains reduces the expansion of EGFR-positive colorectal cancer cells while enhancing the therapeutic impact of chemo- and radiotherapy [6]. Although these therapy blend choices have worked on the patient's endurance, extra nontoxic designated therapy choices are required in the unmanageable treatment setting of cutting-edge colon cancer. There are many different cis-Diamminedichloroplatinum(II) (Cisp.), but it is one of the most powerful anti-tumour agents. It has many anti-tumour uses, covering clinical management of colorectal pathology [7]. Cellular toxicity arises from its binding to DNA and subsequent generation of DNA damage, which activates various signaling cascades culminating in apoptotic cell death [8, 9]. Be that as it may, it likewise has extremely unfavorable impacts, associated with renal injury, peripheral nerve damage, and auditory toxicity [8, 9,10]. Therefore, continued advancement in innovative drugs and treatment modalities for colorectal cancer is essential. Current investigations largely emphasize combination chemotherapeutic approaches designed to mitigate adverse effects and enhance clinical outcomes [11].

## 2. Materials and Methods

### 2.1 Cell Line and Culture Conditions

The College of Medicine, Cancer Research Laboratory, University of Babylon, provides the SW480 cell line, a human colorectal adenocarcinoma cell line. The study involved all cells present in passages 15-25 to make the experiment homogeneous. The cells were grown in RPMI-1640 medium (Gibco, Thermo Fisher Scientific, USA) containing 10% (v/v) fetal bovine serum and penicillin (100 U/mL) and streptomycin (100 μg/mL). Cultures were preserved at 37 °C in a humid atmosphere containing 5% CO2. The medium was refreshed every 2–3 days. When the confluence reached around 8090 percent, cells were dislodged with a 0.25 percent trypsinEDTA solution and then subcultured.

### 2.2 Reagents and Materials

Cisplatin (cis-Diamminedichloroplatinum (II)) was purchased from a local pharmacy and dissolved in sterile saline to prepare stock solutions. Cetuximab was obtained from the Science Laboratories at the Belarusian State University (College of Belarus). All tissue culture consumables, including 96-well microculture plates, serological pipettes, and cell culture flasks, were obtained from local scientific suppliers. PBS solution and RPMI-1640 growth medium, trypsin-EDTA, crystal violet, paraformaldehyde, methanol, and acetic acid were of analytical grade.

### 2.3 Cytotoxicity Assay

The crystal violet staining technique was used to assess cell viability. SW480 cells were plated in 96-well culture plates at a cell concentration of 1×10^4 cells per plate in 200 μL of complete, supplemented RPMI-1640 medium. The plates were subsequently preserved at 37 0 C in a humidity-controlled incubator supplemented with 5% $CO_2$ to allow cell adhesion and the development of an approximately 80% confluent monolayer.

#### *2.3.1 Drug Treatment*

After the initial 24-hour incubation period, the cultivation medium was discarded and replaced with a medium containing the test compounds. Cells were treated with cetuximab at six serial values: 2.5, 1.25, 0.625, 0.3125, 0.156, and 0.0781 μg/mL. In parallel experiments, cells were exposed to cisplatin at six values: 100, 50, 25, 12.5, 6.25, and 3.125 μg/mL. All treatments were performed in triplicate. Negative controls were made of untreated cells (culture medium only). The plates were cultured for 24 and 48 h under the same conditions.

#### *2.3.2 Crystal Violet Staining*

The drug-containing medium was carefully aspirated after the treatment period (24 and 48 hours), and the cells were washed twice with PBS to remove non-adherent cells and residual medium. To fix the cells, 4% paraformaldehyde (100 μL/well) was added and maintained for 15 minutes at 25°C. Cells were then rinsed with the fixative, followed by incubation with 100 μL/well of 0.1% crystal violet solution solubilized in 20%

methanol at 25°C for 20 minutes. The remaining stain was removed by rinsing the plates with distilled water (3-4 times) until no stain appeared in the wash solution. Plates were put inverted and left to dry overnight at 25°C.

#### *2.3.3 Colorimetric Quantification*

The crystal violet retained by the cells was eluted by adding 100 µL of 10% acetic acid to the wells and incubating the wells for 20 minutes with gentle shaking on an orbital platform. Readings were taken at 570 nm and recorded using a microplate ELISA reader (model to be specified if needed). The rate of inhibition (IR%) was computed using the following equation.

$$IR\% = \frac{OD_{control} - OD_{treated}}{OD_{control}} \times 100$$

Where $OD_{control}$ represents the average optical density of untreated control cells, and $OD_{treated}$ represents the mean optical density of drug-treated cells.

### 2.4 Statistical Analysis

Each experimental procedure was conducted three times, and the findings are reported as mean ± SD. The SPSS software (V 26.0) was used for statistical analysis. The unpaired Student t-test was conducted to compare the cetuximab- and cisplatin-treated groups simultaneously. ANOVA was used to test dose-dependent effects within each treatment group, and the test was examined using post hoc multiple comparisons with the Tukey test. Further, a two-way ANOVA was employed to assess the effects of drug type, drug concentration, and exposure duration on cell viability, along with their interactions. The variation was deemed relevant when the P value was less than 0.05. The graphic representations were produced in Microsoft Excel (Microsoft, USA) and GraphPad Prism software (V 9.0).

## 3. Results and Discussion

### 3.1 Cytotoxic Effect of Cetuximab on SW480 Cells

The cytotoxicity of Cetuximab on SW480 colon cancer cells was tested in six serial concentrations (0.07812.5 -3) in 24 and 48 hours of exposure. Cell survival was measured using the crystal violet assay, and the results revealed a clear dose-dependent suppressive effect of cetuximab on the progression of SW480 cells.

#### *3.1.1 Effect at 24 Hours*

Cetuximab showed high cytotoxicity against SW480 cells after 24 hours of treatment at all concentrations tested (Table 1; Figure 1). The rate of inhibition increased gradually with increasing drug concentration. A low level of inhibition (13.21) was observed at the lowest concentration (0.0781 µg/mL). The inhibitory effect was significantly higher at higher concentrations, reaching 57.30% at 0.3125 µg/mL and 85.12% at 0.625 µg/mL. The highest reduction rate of 91.24% was observed at 1.25 µg/mL. The maximum concentration tested (2.5 µg/mL) showed a slightly lower inhibition rate (90.82%), suggesting that, in these experimental conditions, the maximum cytotoxic effect was achieved at 1.25 µg/mL.

**Table 1.** SW480 **cell response to cetuximab after 24 hours.**

| Concentration (µg/mL) | Control | 0.0781 | 0.156 | 0.3125 | 0.625 | 1.25 | 2.5 |
|---|---|---|---|---|---|---|---|
| Mean OD | 0.719 | 0.624 | 0.537 | 0.307 | 0.107 | 0.063 | 0.066 |
| IR (%) | — | 13.21 | 25.31 | 57.30 | 85.12 | 91.24 | 90.82 |

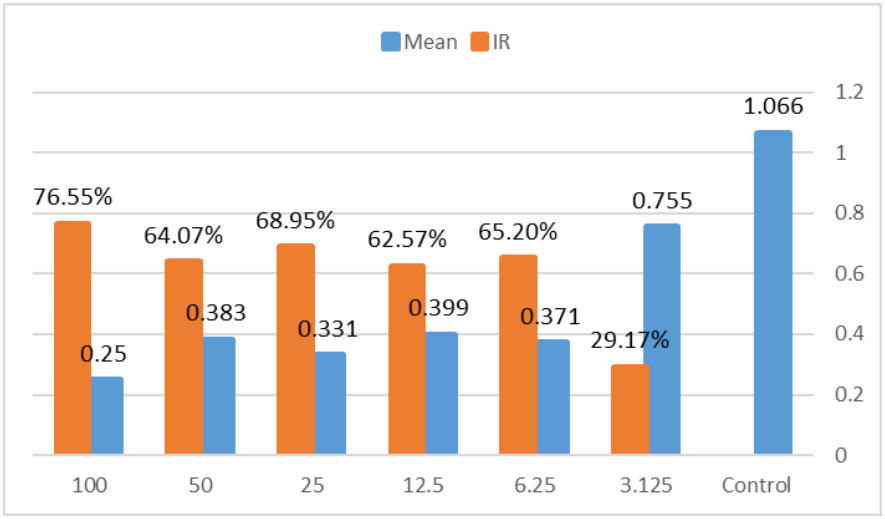


**Figure 1**. Cetuximab Impact on cell viability of SW480 colon cancer cells in 24 hours. Different concentrations of cetuximab (0.07812.5 µg/mL) were administered to the cells and incubated for 24 hours. The crystal violet assay was used to determine cell viability. Blue bars are the mean optical density (OD 5 0) and orange bars show the inhibition rate (percent). The findings are displayed as the mean ± SD (n = 3).

### *3.1.2 Effect at 48 Hours*

The 48-hour exposure of cetuximab produced better cytotoxicity than the 24-hour exposure (Table 2; Figure 2). The inhibition rates obtained were usually higher across all concentrations tested. The lowest concentration (0.057 µg/mL) showed an inhibition rate of 36.06%, which was significantly higher than the rate at 24 hours. There was a significant cytotoxicity at 0.143 µg/mL (87.13% inhibition) and a maximum cytotoxicity of 97.77 at 0.286 µg/mL. The greater the concentration level (0.625, 1.25, and 2.5 µg/mL), the higher the inhibition rates: 89.79, 93.72, and 93.83, respectively. These findings suggest that the antiproliferative effect of Cetuximab on SW480 cells is enhanced with long-term exposure.

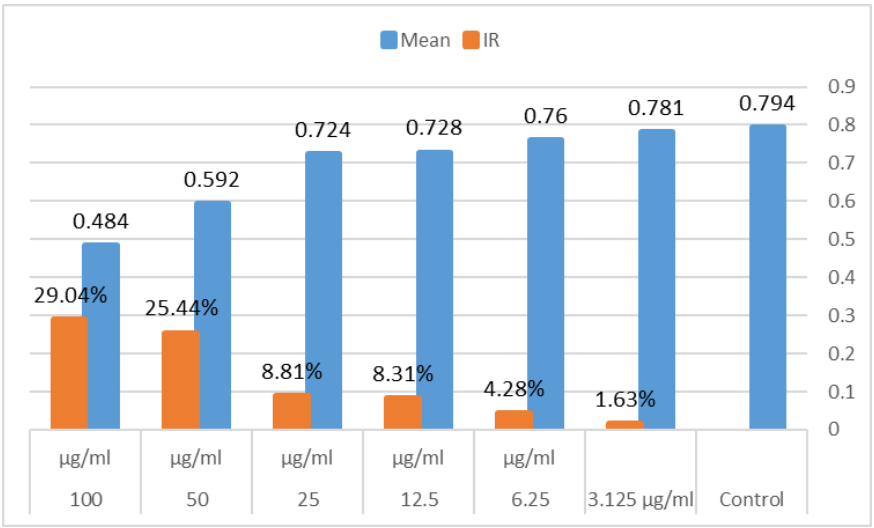


**Figure 2.** SW480 colon cancer cell viability affected by cisplatin after 24 hours. Different concentrations of cisplatin (3.125-100 mu g/mL) were added to the cells and cultured for 24 h. Cell survival was determined using a crystal violet assay. Blue bars indicate the mean optical density (OD 070 ) and orange bars indicate the rate of inhibition (percentage ). The data are presented as mean ± SD (n = 3).

**Table 2.** Effects of cisplatin on SW480 cells in 24 hours.

| Concentration (µg/mL) | Control | 3.125 | 6.25 | 12.5 | 25 | 50 | 100 |
|---|---|---|---|---|---|---|---|
| Mean OD | 0.794 | 0.781 | 0.760 | 0.728 | 0.724 | 0.592 | 0.484 |
| IR (%) | — | 1.64 | 4.28 | 8.31 | 8.82 | 25.44 | 39.04 |

### 3.2 Cytotoxic Effect of Cisplatin on SW480 Cells

The cytotoxic activity of cisplatin on SW480 cells was tested at six serial doses (3.125-100 µg/mL) after 24 and 48 hours to allow comparison with Cetuximab treatment.

#### *3.2.1 Effect at 24 Hours*

The cytotoxicity of cisplatin on SW480 cells was relatively lower after 24 hours of exposure than that of Cetuximab (Table 3; Figure 3). The lowest concentration (3.125 µg/mL) resulted in the lowest inhibition percentage (1.64%), indicating that cell viability was not significantly affected. The concentration of the inhibitory effect rose slowly to 8.31 percent at 12.5 mol/L and 25.44 percent at 50 mol/L. The highest test concentration (100 µg/mL) yielded the highest inhibition rate (39.04%). All these findings imply that, with a shorter incubation period, cisplatin has a lower short-term cytotoxic effect on SW480 cells than cetuximab.

**Table 3.** Cetuximab effect on the SW480 cells after 48 hours.

| Concentration (µg/mL) | Control | 0.057 | 0.143 | 0.286 | 0.625 | 1.25 | 2.5 |
|---|---|---|---|---|---|---|---|
| Mean OD | 0.94 | 0.601 | 0.121 | 0.021 | 0.096 | 0.059 | 0.058 |
| IR (%) | — | 36.06 | 87.13 | 97.77 | 89.79 | 93.72 | 93.83 |

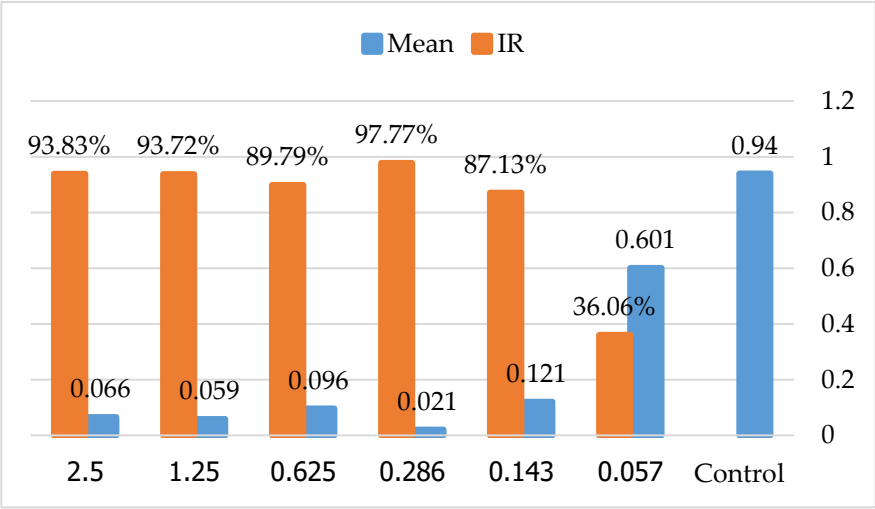


**Figure 3.** Cetuximab Effect on SW480 colon cancer cell viability after 48 hours. Cells were incubated with different cetuximab (0.057-2.5 µg/mL) concentrations over a period of 48 hrs. The crystal violet assay was used to measure cell viability. Blue bars mean optical density (OD 5 0), and orange bars mean inhibition rate (percent). Statistical values are presented as the mean ± SD (n=3).

#### *3.2.2 Effect at 48 Hours*

There was a significant increase in cytotoxicity with extended cisplatin exposure from 24 to 48 hours (Table 4; Figure 4). The lowest inhibition rate (3.125 µg/mL) was 29.17, which is significantly higher than the rate of 1.64 at 24 hours. The antiproliferative activity was enhanced, with inhibition rates of 62.57-68.95 at intermediate concentrations. The highest inhibition percentage, 76.55%, occurred at a concentration of 100 µg/mL. Cisplatin still showed better efficacy at 48 hours, but the maximum inhibition rate (76.55) was still lower than that of cetuximab (97.77) under similar conditions.

**Table 4.** Effect of Cisplatin on SW480 cells (48 hours).

| Concentration (µg/mL) | Control | 3.125 | 6.25 | 12.5 | 25 | 50 | 100 |
|---|---|---|---|---|---|---|---|
| Mean OD | 1.066 | 0.755 | 0.371 | 0.399 | 0.331 | 0.383 | 0.250 |
| IR (%) | — | 29.17 | 65.20 | 62.57 | 68.95 | 64.07 | 76.55 |

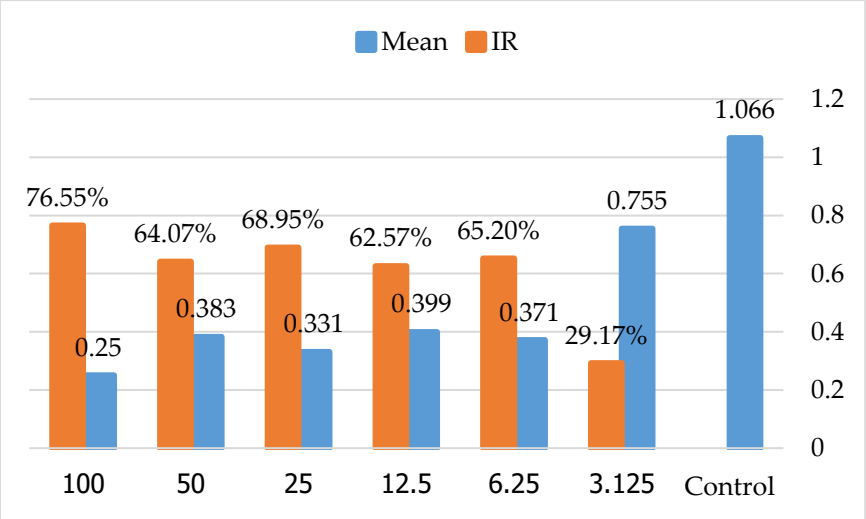


**Figure 4.** Treatment of SW480 cells in colon cancer with cisplatin after 48 hours. Cells were incubated with different dosages of cisplatin (3.125-100 µg/ml) for 48 hours. The crystal violet assay was used to measure cell viability. Blue bars are the mean optical density (OD 5 ), and orange bars are the rate of inhibition (percent). The findings are presented as mean ± SD (n = 3).

### 3.3 Comparative Analysis of Cetuximab and Cisplatin

Statistical analysis revealed a marked variation in the cytotoxic efficacy of cetuximab and cisplatin against colon cancer cells SW480 ($P < 0.05$). Table 5 gives a comparative summary of the major findings.

**Table 5.** Comparative overview of the cetuximab and cisplatin cytotoxicity on the SW480.

| Parameter | Cetuximab | Cisplatin |
|---|---|---|
| Concentration range tested | 0.0781–2.5 µg/mL | 3.125–100 µg/mL |
| Maximum IR% at 24 hours | 91.24% (at 1.25 µg/mL) | 39.04% (at 100 µg/mL) |
| Maximum IR% at 48 hours | 97.77% (at 0.286 µg/mL) | 76.55% (at 100 µg/mL) |
| Dose required for >50% inhibition (24h) | 0.3125 µg/mL | Not achieved |
| Dose required for >50% inhibition (48h) | 0.143 µg/mL | 6.25 µg/mL |

Cetuximab showed more than 90% inhibition at concentrations of 1.25 µg/mL and above, whereas cisplatin showed only 39.04% inhibition at the maximum test concentration (100 µg/mL). This is a significant disparity in cytotoxicity, with cetuximab about 80 times more effective at this concentration. The treatment difference was significant ($P < 0.001$). Both drugs showed increased cytotoxicity at 48 hours, but cetuximab was more effective. The maximum inhibition was almost 100% (97.77%) with cetuximab at 0.286 0mL and 76.55% with cisplatin at 100 0mL. The ANOVA showed significant main effects of drug type and concentration ($P < 0.001$ in both cases) and exposure duration ($P < 0.01$). Moreover, the interactions among these variables were statistically significant ($P < 0.05$).

### 3.4 Discussion

#### *3.4.1 Superior Efficacy of Cetuximab*

The outcomes of this study show that cetuximab is much more cytotoxic on the SW480 colon cancer cells than cisplatin. The rapid mechanism of action of cetuximab, with over 90 percent inhibition within the first 24 hours, suggests a powerful mechanism that can kill cancer cells. This is consistent with previous literature indicating that cetuximab represses the proliferation of EGFR-positive colorectal cancer cell lines. Cetuximab is highly effective due to its highly specific and targeted mechanism of action. Cetuximab, a chimeric monoclonal antibody, specifically binds the extracellular domain of EGFR and, as such, blocks further ligand-receptor interaction. This inhibits downstream signaling pathways, including the most important MAPK and PI3K/AKT, which play essential roles in the development, viability, and metastasis of tumor cells. Conversely, the mechanism of action of cisplatin is non-selective, and it involves the formation of DNA adducts that lead to an apoptotic response in cancer and normal cells, a typical feature of its known toxic profile [7, 8].

#### *3.4.2 Dose-Response Relationships*

The 2 drugs showed similar dose-dependent cytotoxicity, but their dose-response curves were very different. Cetuximab showed a steep relationship between dose and response, with inhibition levels increasing from 0.156 to 0.625 ug/mL, then leveling off at higher concentrations. This plateau effect implies that the balance regarding the number of EGFR binding sites has been achieved, and subsequent drug supplementation plays no important role. The relationship between dose and response was less steep with cisplatin, with the rate of inhibition increasing gradually across the concentration range used (without necessarily reaching a final plateau at 24 hours).

#### *3.4.3 Time-Dependent Effects*

The cytotoxic effects of the two drugs also improved with increasing exposure time, although the rates of increase differed. Cisplatin showed a stronger time-dependent increase in efficacy, with the highest inhibition rates of 39.04% and 76.55% at 24 and 48 hours, respectively. This is consistent with the cisplatin-mediated cytotoxicity mechanism, which involves time to form DNA adducts, interact with cellular repair systems, and activate apoptotic pathways [8, 9]. The improved efficacy of cetuximab was also observed at 48 hours, but the degree of enhancement was not as significant, as the rate of inhibition was high at 24 hours.

#### *3.4.4 Clinical Implications*

The current results indicate that Cetuximab is a promising targeted therapy for colorectal cancer. In addition to panitumumab, cetuximab has been granted FDA approval as an EGFR-targeting monoclonal antibody for metastatic colorectal cancer [12]. They are usually used in conjunction with cytotoxic chemotherapy regimens as first- or second-line agents [13]. Previous clinical trials have established that the Cetuximab–irinotecan combination has a better therapeutic impact than single-agent cetuximab in irinotecan-refractory metastatic colorectal carcinoma [12,14,15]. On the same note, when cetuximab was combined with platinum-based chemotherapy, it improved survival in individuals with advanced EGFR-expressing NSCLC [5]. Our preclinical evidence indicates that cetuximab, when combined with cisplatin, can act synergistically or additively in colon cancer cells, allowing a reduction in the cisplatin dose and the elimination of its inherent toxicities, such as nephrotoxicity, peripheral neuropathy, and ototoxicity [8, 9, 10].

#### *3.4.5 Mechanistic Considerations*

The increased cytotoxicity of cetuximab observed may be due to mechanisms beyond pure EGFR blockade. Past research has shown that cetuximab suppresses downstream signaling, including the MAPK/ERK pathway, which is important for cell development and viability [6, 16]. Moreover, cetuximab was shown to increase caspase-3 cleavage, thereby activating apoptotic signaling [16]. The oral squamous cell carcinoma models synergize with cetuximab and other agents such as celecoxib, and it can be projected that the same combination strategies will also be effective in colon cancer [16].

#### *3.4.6 Study Limitations*

There are various limitations of this study. Firstly, the present research was conducted on a single colon cancer cell line (SW480); therefore, the results could not be extended to other colon cancer cell lines with different genetic backgrounds and EGFR expression levels. Second, this was an in vitro study and therefore did not consider pharmacokinetic factors, tumor-microenvironment interactions, or the involvement of the immune system, which determine drug efficacy in in vivo studies. Third, the cetuximab-cisplatin combination was not under investigation in the study; hence, no information would be available on the potential synergistic effect of the combination. Finally, the mechanisms underlying the observed cytotoxicity had not been examined by molecular methods, such as Western blotting or flow cytometry.

#### *3.4.7 Future Directions*

Future research is also needed to evaluate the use of cetuximab at different cisplatin ratios to determine the optimal concentrations of both medications that act synergistically. In addition, experiments across multiple colon cancer cell lines with varying EGFR concentrations would improve the generalizability of these findings. A mechanistic understanding would be gained through molecular analyses of the impact of these therapies on EGFR downstream signaling pathways, and assessment of apoptosis-related and cell cycle–regulatory biomarkers is recommended. Additionally, in vivo xenograft experiments are necessary to substantiate further the therapeutic effectiveness of cetuximab, whether used as a single agent or in combination with platinum-based chemotherapy.

## 4. Conclusions

The present investigation assessed and compared the cytotoxicity of cetuximab and cisplatin in the human SW480 colorectal cancer cell line using the crystal violet assay. The research results indicate that cetuximab has stronger antiproliferative effects than cisplatin against SW480 cells in vitro. At the low value of 1.25 μg/mL and 0.286 μg/mL, cetuximab recorded maximum inhibition rates of 91.24 per cent and 97.77 per cent at 24 and 48 hours, respectively. Conversely, cisplatin achieved only the highest levels of 39.04 and 76.55 at 24 and 48 hours, respectively, despite being used at much higher concentrations (100 μg/mL). The statistical analysis revealed that the two treatments differ ($P < 0.001$), with cetuximab approximately 80-fold more effective at the required concentration. The speed and the strength of the inhibitory effect of cetuximab are sufficient reasons to consider it a high-quality targeted therapy against EGFR-expressing colorectal cancers. These results are consistent with its established mechanism of action, which entails EGFR inhibition, followed by downstream inhibition of the proliferative signaling pathway. The findings do support the preclinical use of cetuximab in combination with conventional platinum-based chemotherapy. This research, however, was limited to a single cell type and in vitro conditions. Future research must determine the effectiveness of cetuximab across various EGFR levels in colorectal cancer cell lines, investigate whether a cetuximab-cisplatin combination is feasible, and validate the findings in xenograft models. Such studies would also justify the therapeutic potential of a particular EGFR inhibitor in the treatment of colorectal cancer.

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**Authors' Contribution:** Conceptualization, [A.A.S.] and [B.A.M.]; methodology, [A.A.S.]; software, [A.A.S.]; validation, [A.A.S.], [B.A.M.] and [Z.A.O.A.]; formal analysis, [A.A.S.]; investigation, [A.A.S.], [B.A.M.]; resources, [Z.A.O.A.]; data curation, [A.A.S.]; writing first draft, [A.A.S.]; review and editing, [B.A.M.] and [Z.A.O.A.]; visualization. Each author has read and agreed to the published version of the manuscript.

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