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# MECHANISMS OF DRUG RESISTANCE IN CANCER CHEMOTHERAPY: AN OBSERVATIONAL STUDY FROM A TERTIARY CARE HOSPITAL IN NORTH INDIA

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## ABSTRACT

**Background:**Drug resistance remains a major barrier to effective cancer chemotherapy, contributing to treatment failure and disease progression. Understanding its underlying mechanisms is essential for improving outcomes, especially in resource-limited settings.

**Objectives:**To assess the mechanisms of drug resistance in cancer chemotherapy and examine their association with clinical and demographic factors among patients at a tertiary care hospital in North India.

**Methods:**This hospital-based observational analytical study was conducted from June to October 2021 among 40 patients with histopathologically confirmed malignancies receiving chemotherapy. Demographic, clinical, and treatment-related data were collected using a semi-structured proforma. Drug resistance was assessed using clinical response criteria, and resistance mechanisms were identified from available laboratory and clinical records. Data were analyzed using SPSS version 22.0, with $p<0.05$ considered statistically significant.

**Results:**Drug resistance was observed in 55% of patients. Advanced cancer stage was significantly associated with resistance ($p<0.05$), with the highest rate among Stage IV patients. Age, gender, and cancer type showed no significant association. Drug efflux was the most common mechanism (40.9%), followed by altered drug targets (18.2%) and apoptosis evasion (18.2%). Multiple mechanisms were identified in a small proportion of cases.

**Conclusion:**Drug resistance is common among cancer patients receiving chemotherapy, particularly in advanced disease. The predominance of efflux-mediated resistance underscores the need for targeted therapeutic strategies. Early detection, personalized treatment, and stronger diagnostic infrastructure are essential to overcome chemoresistance and improve patient outcomes.

**Keywords:** Cancer chemotherapy; Drug resistance; Efflux mechanisms; Apoptosis; Tumor stage; North India

## INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide, accounting for a substantial proportion of global disease burden despite advances in early detection and therapeutic strategies [1]. Chemotherapy continues to be a cornerstone in the management of many malignancies; however, its effectiveness is frequently compromised by the development of drug resistance, which poses a major obstacle to successful treatment outcomes [2]. Drug resistance can be intrinsic, where tumor cells are inherently non-responsive, or acquired, where resistance develops after initial sensitivity to therapy [3]. Understanding the underlying mechanisms is therefore essential for improving therapeutic efficacy and patient survival.

At the molecular level, resistance to anticancer drugs is a multifactorial phenomenon involving diverse cellular and microenvironmental processes. One of the most well-characterized mechanisms is the overexpression of efflux transporters such as ATP-binding cassette (ABC) proteins, which actively pump chemotherapeutic agents out of cancer cells, reducing intracellular drug concentrations [4]. Additionally, alterations in drug targets, enhanced DNA repair capacity, and evasion of apoptosis contribute significantly to chemoresistance [5]. Cancer cells may also undergo epigenetic changes and phenotypic transitions, including epithelial–mesenchymal transition (EMT), which are associated with increased invasiveness and resistance to therapy [6].

Tumor heterogeneity further complicates treatment, as genetically diverse subclones within the same tumor may respond differently to chemotherapy, leading to selective survival of resistant populations [7]. Moreover, the tumor microenvironment plays a critical role in modulating drug response. Factors such as hypoxia, acidic pH, and interactions with stromal cells can promote resistance by altering drug penetration and cellular sensitivity [8].

Recent studies have also highlighted the role of cancer stem cells, a subpopulation of tumor cells with self-renewal capacity, which are inherently resistant to conventional therapies and contribute to relapse and metastasis [9].

In the Indian context, cancer incidence is steadily rising, with increasing numbers of patients requiring systemic chemotherapy. However, variability in treatment response and limited access to advanced molecular diagnostics pose challenges in effectively managing drug resistance [10]. In North India, tertiary care hospitals cater to a large and diverse patient population, providing an opportunity to study real-world patterns of chemoresistance and associated mechanisms. Despite growing global literature, there remains a paucity of region-specific clinical data correlating molecular mechanisms of resistance with patient characteristics and treatment outcomes.

Given this background, there is a clear need to investigate the mechanisms of drug resistance in cancer patients within a tertiary care setting in North India. Such insights can contribute to the development of targeted therapeutic strategies and optimize existing treatment protocols. Therefore, the present study aims to evaluate the key mechanisms of drug resistance in patients undergoing cancer chemotherapy and to analyze their association with clinical and demographic factors.

## METHODOLOGY

**Study Design:**This study was designed as a hospital-based observational analytical study, conducted to evaluate the mechanisms of drug resistance among patients receiving cancer chemotherapy.

**Study Setting:**The study was conducted in the Department of Oncology of a tertiary care hospital in North India, which caters to a large population from both urban and rural backgrounds and provides comprehensive cancer care, including chemotherapy, diagnostic, and supportive services.

**Study Duration:**The study was carried out over a period of five months, from June 2021 to October 2021.

**Study Population:**The study population included patients diagnosed with various types of malignancies who were undergoing chemotherapy at the study center during the study period.

### Inclusion Criteria

Patients aged ≥18 years

Histopathologically confirmed diagnosis of cancer
Patients receiving at least one cycle of chemotherapy
Patients who provided written informed consent

**Exclusion Criteria**

Patients who had not yet initiated chemotherapy
Patients receiving only surgical or radiotherapy treatment
Critically ill patients unable to participate in the study
Patients unwilling to provide consent

**Sample Size:**The sample size was calculated based on the expected proportion of drug resistance among cancer patients. Assuming a prevalence (p) of 50% (due to lack of precise regional estimates), a confidence level of 95% (Z = 1.96), and an absolute precision (d) of 15%, the sample size was calculated using the formula:
$n = Z^2 \times p \times (1 - p) / d^2$
Substituting the values: $n = (1.96)^2 \times 0.5 \times 0.5 / (0.15)^2 \approx 42.7$
The calculated sample size was approximately 43. Considering feasibility constraints, a final sample size of 40 patients was included in the study.

**Sampling Technique:**A consecutive sampling technique was employed, wherein all eligible patients presenting during the study period and fulfilling the inclusion criteria were recruited until the required sample size was achieved.

**Data Collection Tools & Procedure:**Data were collected using a predesigned, semi-structured case record form. Information regarding demographic details (age, sex), clinical characteristics (type and stage of cancer, prior treatment history), and chemotherapy regimen was recorded. Assessment of drug resistance was performed based on clinical response criteria, including lack of tumor regression, disease progression, or recurrence after initial response. Where feasible, laboratory parameters and available molecular markers (such as expression of efflux proteins or biomarkers indicative of apoptosis resistance) were reviewed from patient records. Data collection was conducted by trained investigators to ensure uniformity and accuracy.

**Study Variables:**Independent variables included demographic factors (age, sex), clinical parameters (type of malignancy, stage of disease), and treatment-related variables (type of chemotherapy regimen, number of cycles). The dependent variable was the presence or absence of drug resistance, categorized based on clinical and, where available, laboratory evidence. Additional variables included specific mechanisms of resistance such as drug efflux, altered drug targets, enhanced DNA repair, and apoptosis evasion.

**Statistical Analysis:**Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Descriptive statistics were used to summarize the data, with categorical variables expressed as frequencies and percentages, and continuous variables as mean ±standard deviation. Inferential statistics, including Chi-square test or Fisher's exact test, were applied to assess associations between categorical variables. A p-value of less than 0.05 was considered statistically significant.

**Ethical Considerations:**Written informed consent was obtained from all participants prior to enrollment. Confidentiality and anonymity of patient information were strictly maintained. The study adhered to the ethical principles outlined in the Declaration of Helsinki for biomedical research involving human subjects.

## RESULTS

A total of 40 patients were included in the study, with the majority belonging to the 41–60 years age group and a slight male predominance (Table 1)

**Table 1: Demographic Characteristics of Study Participants (n = 40)**

| Variable | Category | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Age (years) | 18–40 | 10 | 25.0 |
| | 41–60 | 18 | 45.0 |
| | >60 | 12 | 30.0 |
| Gender | Male | 22 | 55.0 |
| | Female | 18 | 45.0 |

Breast cancer was the most common malignancy, followed by head and neck cancers, with most patients presenting in Stage III and IV disease (Table 2)

**Table 2: Clinical Profile of Patients**

| Variable | Category | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Type of Cancer | Breast | 10 | 25.0 |
| | Lung | 8 | 20.0 |
| | Colorectal | 7 | 17.5 |
| | Head & Neck | 9 | 22.5 |
| | Others | 6 | 15.0 |
| Stage of Cancer | Stage II | 8 | 20.0 |
| | Stage III | 18 | 45.0 |
| | Stage IV | 14 | 35.0 |

The overall prevalence of drug resistance was found to be 55%. A higher proportion of resistance was observed among patients aged above 60 years and in males; however, these associations were not statistically significant. A statistically significant association was observed between advanced stage of cancer and drug resistance ($p = 0.03$), with the highest resistance seen in Stage IV patients (Table 3)

**Table 3: Prevalence of Drug Resistance and Associated Factors**

| Variable | Category | Drug Resistance Present (n, %) | Drug Resistance Absent (n, %) | p-value |
|---|---|---|---|---|
| Overall | — | 22 (55.0) | 18 (45.0) | — |
| Age Group | ≤60 years | 14 (50.0) | 14 (50.0) | 0.41 |
| | >60 years | 8 (66.7) | 4 (33.3) | |
| Gender | Male | 13 (59.1) | 9 (40.9) | 0.62 |
| | Female | 9 (50.0) | 9 (50.0) | |
| Stage | Stage II | 2 (25.0) | 6 (75.0) | 0.03* |

| | | | | |
|---|---|---|---|---|
| | Stage III | 10 (55.6) | 8 (44.4) | |
| | Stage IV | 10 (71.4) | 4 (28.6) | |

*Statistically significant ($p < 0.05$)

Among patients exhibiting drug resistance, drug efflux mediated by transport proteins was the most common mechanism, followed by altered drug targets and apoptosis evasion. A small proportion of patients demonstrated multiple resistance mechanisms (Table 4)

**Table 4: Distribution of Mechanisms of Drug Resistance (n = 22)**

| Mechanism of Resistance | Frequency (n) | Percentage (%) |
|---|---|---|
| Drug Efflux (ABC transporters) | 9 | 40.9 |
| Altered Drug Targets | 4 | 18.2 |
| Enhanced DNA Repair | 3 | 13.6 |
| Apoptosis Evasion | 4 | 18.2 |
| Multiple Mechanisms | 2 | 9.1 |

No statistically significant association was observed between the type of cancer and the presence of drug resistance, although relatively higher resistance rates were noted in head and neck and lung cancers (Table 5)

**Table 5: Association Between Type of Cancer and Drug Resistance**

| Type of Cancer | Drug Resistance Present (n, %) | Drug Resistance Absent (n, %) | p-value |
|---|---|---|---|
| Breast | 5 (50.0) | 5 (50.0) | 0.58 |
| Lung | 5 (62.5) | 3 (37.5) | |
| Colorectal | 4 (57.1) | 3 (42.9) | |
| Head & Neck | 6 (66.7) | 3 (33.3) | |
| Others | 2 (33.3) | 4 (66.7) | |

## DISCUSSION

The present study evaluated the mechanisms of drug resistance in cancer chemotherapy among patients attending a tertiary care hospital in North India. The findings demonstrated that more than half of the patients (55%) exhibited drug resistance, with a statistically significant association between advanced stage of cancer and resistance. Among the identified mechanisms, drug efflux mediated by transporter proteins emerged as the most prevalent, followed by altered drug targets and evasion of apoptosis.

The observed prevalence of drug resistance in this study is consistent with previous reports indicating that a substantial proportion of cancer patients eventually develop resistance to chemotherapy [2,3]. The slightly higher prevalence noted in the present study may be attributed to the inclusion of a greater proportion of patients in advanced stages (Stage III and IV), which are known to be associated with more aggressive tumor biology and reduced responsiveness to treatment. Similar findings have been reported by Vasan et al., who highlighted tumor evolution and clonal selection as key contributors to resistance in advanced malignancies [7].

A significant association between cancer stage and drug resistance was observed, with Stage IV patients showing the highest prevalence. This aligns with established evidence suggesting that tumor burden, hypoxia, and microenvironmental factors increase with disease progression, thereby promoting resistance mechanisms [8]. Advanced tumors often exhibit increased genetic instability, facilitating the emergence of resistant clones. Additionally, delayed diagnosis and initiation of

treatment, which are common challenges in developing regions, may further contribute to the higher resistance observed in later stages.

In contrast, demographic variables such as age and gender were not significantly associated with drug resistance in this study. This finding is in agreement with earlier research indicating that biological tumor characteristics and molecular pathways play a more critical role in determining chemotherapy response than patient demographics alone [5]. However, the slightly higher resistance observed in older patients may be explained by age-related changes in drug metabolism and immune response, although this did not reach statistical significance.

Regarding the mechanisms of resistance, drug efflux via ATP-binding cassette transporters was the most commonly identified pathway. This is consistent with the work of Robey et al., who emphasized the central role of efflux pumps such as P-glycoprotein in reducing intracellular drug accumulation [4]. Alterations in drug targets and evasion of apoptosis were also notable contributors, reflecting the complexity and multifactorial nature of chemoresistance. These findings corroborate earlier studies demonstrating that cancer cells can adapt through multiple pathways simultaneously, making treatment increasingly challenging [6].

Although variations in resistance patterns were observed across different cancer types, no statistically significant association was found. This may be due to the relatively small sample size and heterogeneous distribution of malignancies. Previous studies have reported variable resistance profiles depending on tumor type, molecular subtype, and treatment regimen, suggesting that larger, site-specific studies are required for definitive conclusions [9].

From a clinical perspective, the findings of this study underscore the importance of early detection and timely initiation of therapy to reduce the likelihood of resistance. Furthermore, the identification of predominant resistance mechanisms highlights the potential role of targeted therapies, such as inhibitors of efflux transporters or agents that modulate apoptotic pathways, in improving treatment outcomes. Incorporating molecular diagnostics into routine clinical practice could facilitate personalized treatment strategies, particularly in resource-limited settings.

The strengths of this study include its real-world clinical setting and focus on a region with limited existing data on chemoresistance. The use of standardized criteria for assessing drug resistance enhances the reliability of findings. However, certain limitations must be acknowledged. The relatively small sample size and short study duration may limit the generalizability of results. Additionally, the reliance on available clinical and laboratory data, with limited access to advanced molecular testing, may have led to underestimation of certain resistance mechanisms. The heterogeneity of cancer types included in the study is another limiting factor.

Future research should focus on larger, multicentric studies with integration of molecular profiling techniques to better characterize resistance mechanisms. Longitudinal studies assessing treatment outcomes and survival in relation to resistance patterns would also provide valuable insights. Overall, addressing drug resistance remains a critical priority in improving the effectiveness of cancer chemotherapy and patient prognosis.

## CONCLUSION

The present study highlights that drug resistance is a significant challenge in cancer chemotherapy, affecting more than half of the patients in the studied population. Advanced stage of cancer was found to be a key factor associated with increased resistance, emphasizing the importance of early diagnosis and timely intervention. Among the various mechanisms, drug efflux mediated by transporter proteins was the most commonly observed, followed by alterations in drug targets and evasion of apoptosis, indicating the multifactorial nature of chemoresistance.These findings underscore the need for integrating molecular insights into routine clinical practice to identify resistance patterns early and tailor treatment strategies accordingly. Strengthening diagnostic capabilities and promoting personalized medicine approaches may improve therapeutic outcomes. Further large-scale and longitudinal studies are recommended to validate these findings and explore targeted interventions to overcome drug resistance in cancer chemotherapy.

## DECLARATIONS

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**Conflict of Interest:**The authors declare no conflict of interest.
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