Adverse Events in Neoadjuvant Therapy for Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis of Phase III Trials

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Abstract

Background: Neoadjuvant therapy (NAT) is standard treatment for triple-negative breast cancer (TNBC) but toxicity is a major concern. This study aimed to assess the incidence and risk of grade ≥3 adverse events (AEs) associated with NAT in non-metastatic TNBC. **Methods:** We performed a systematic review and meta-analysis registered in PROSPERO (CRD42024562785). Four databases were searched for randomized controlled trials (RCTs) from 2010–2025 reporting grade ≥3 AEs in TNBC. Pooled prevalence and risk ratios (RRs) were estimated using random-effects models. **Results:** Six RCTs including 3,316 patients were analyzed. Neutropenia was the most common severe AE, with pooled prevalence of 33.5% for ICIs, 23.7% for PARP inhibitors, and 16.0% for platinum regimens. PARP inhibitors significantly increased neutropenia (RR 1.84) and anemia (RR 2.08), while thrombocytopenia risk was also higher (RR 3.56). ICIs were associated with more febrile neutropenia (14.9%) but without significant risk increase. ALT elevation was more frequent with platinum regimens (6.4%). Fatal AEs were rare (<1%). **Conclusions:** NAT improves outcomes in TNBC but is associated with substantial severe toxicity. PARP inhibitors carry the greatest hematologic risks, ICIs add immune-related AEs, and platinum regimens showed the lowest AE burden. Biomarker-driven patient selection and vigilant monitoring are essential to optimize safety.

Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast carcinoma that predominantly affects younger women and certain racial and ethnic groups, including African American and Hispanic populations. Defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, TNBC accounts for approximately 15-20% of all breast cancers and is associated with higher rates of recurrence, early visceral metastases, and lower overall survival (OS) compared to hormone receptor-positive or HER2-positive subtypes. The biological complexity of TNBC encompasses several distinct molecular subtypes—including basal-like, mesenchymal, immunomodulatory, and luminal androgen receptor-positive tumors—each with differing prognoses and therapeutic susceptibilities, necessitating individualized, biomarker-driven treatment strategies.

A substantial proportion of TNBC cases—particularly those with basal-like features—harbor germline BRCA1 or BRCA2 pathogenic variants, which confer homologous recombination deficiency and render tumors more susceptible to DNA-damaging agents. This intrinsic vulnerability provides the rationale for incorporating poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, into systemic treatment strategies. Olaparib induces synthetic lethality by inhibiting DNA repair in BRCA-mutated cells while minimizing harm to normal tissue, demonstrating clinical efficacy in advanced breast cancer and, more recently, in patients with early-stage, high-risk HER2-negative disease carrying germline BRCA mutations. Although emerging evidence suggests that BRCA-mutated patients may enhance response to DNA-damaging agents, the use of PARP inhibitors in the neoadjuvant setting is still under active investigation.

Neoadjuvant therapy (NAT) has become a standard approach for early-stage TNBC, facilitating breast-conserving surgery and providing an opportunity to assess tumor chemosensitivity. Achieving pathological complete response (pCR) is strongly associated with improved disease-free survival (DFS) and OS in TNBC, reinforcing its role as a surrogate endpoint for long-term benefit. However, conventional NAT based on anthracyclines and taxanes has limited efficacy in some patients, prompting the exploration of novel therapeutic approaches.

Objective: To conduct a systematic review and meta-analysis evaluating treatment outcomes and toxicity profiles in TNBC patients receiving neoadjuvant chemotherapy.

Methods and Materials

Study Design and Registration

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (24) guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024562785.

Eligibility Criteria

Eligible studies enrolled adult women with histologically confirmed, previously untreated, non-metastatic TNBC and reported on grade ≥3 adverse events. We included randomized controlled trials published between January 1, 2010, and June 30, 2025. Although our primary focus was on phase 3 trials, phase 2 randomized trials were also eligible if they enrolled a substantial sample size, employed a rigorous randomized controlled design, and reported detailed grade ≥3 toxicity outcomes comparable to phase 3 standards. We excluded trials that were single-arm, retrospective, non-randomized, limited to metastatic disease, or lacked toxicity data stratified by severity.

Data Sources and Search Strategy

A comprehensive search was conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), Google Academic from January 2010 through December 2024. Search terms included combinations of "triple-negative breast cancer", "neoadjuvant chemotherapy", "immune checkpoint inhibitors", "PARP inhibitors", "platinum", and "adverse events". Controlled vocabulary (MeSH/Emtree) and Boolean operators were used. The complete search strategy is presented in Supplementary Appendix A. Reference lists of included articles and relevant reviews were also screened manually.

Study Selection

Two reviewers independently screened titles and abstracts. Full-text evaluation was conducted for potentially eligible studies. Disagreements were resolved by consensus or arbitration by a third reviewer. The selection process was documented using a PRISMA flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized form. Extracted data included trial identifiers (authors, year, journal), sample size, treatment regimens, study duration, inclusion/exclusion criteria, patient characteristics, follow-up, and the incidence of grade ≥3 adverse events. Toxicities were classified using CTCAE v5.0.(25) When absolute numbers were not provided, event counts were estimated from reported percentages and sample sizes.

Outcomes and Statistical Analysis

The primary outcome was the incidence of grade ≥3 adverse events. Meta-analyses were conducted for toxicities reported in ≥3 studies using a random-effects model (DerSimonian and Laird method). For each event, we calculated pooled proportions and odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity was evaluated using the I^2 statistic, with values above 50% considered substantial.

Pre-specified subgroup analyses were planned to compare regimens containing platinum agents, PARP inhibitors, and ICIs versus control. Sensitivity analyses included leave-one-out methods and exclusion of studies at high risk of bias. Publication bias will be assessed using funnel plots and Egger's test.

Results

A total of 4,096 records were retrieved through systematic database searches. After removing duplicates and screening titles and abstracts, 22 full-text articles were assessed for eligibility. Of these, ten publications reporting on six unique RCT met the inclusion criteria and were incorporated into the final analysis. A PRISMA (32) flow diagram outlining the selection process is provided in Figure 1.

The six included trials were conducted between 2013 and 2024 and collectively enrolled 3,316 women with newly diagnosed, non-metastatic TNBC. (8, 9, 17-19, 27-31) All patients received NAT, either alone or in combination with additional agents such as platinum compounds, PARP inhibitors, or ICIs. Patient eligibility generally required ECOG performance status 0–1, and median age across the trials ranged from 48 to 51 years.

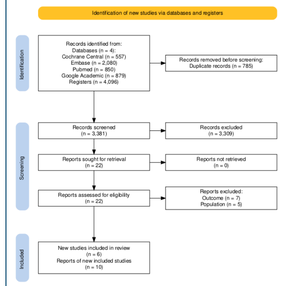


Figure 1. Prisma Flowchart.

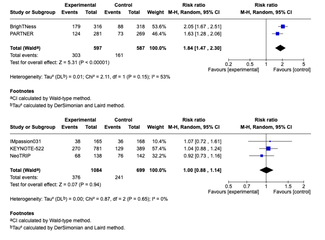


Figure 2. Risk Ratio of Grade ≥3 Neutropenia in TNBC Patients Receiving Neoadjuvant Therapy .

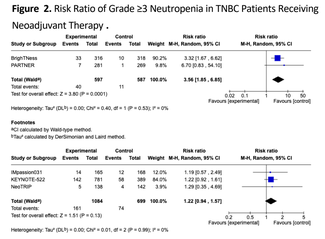


Figure 4. Risk Ratio of Grade ≥3 Thrombocytopenia in TNBC Patients Receiving Neoadjuvant Therapy

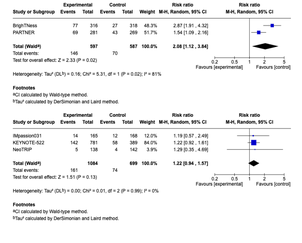


Figure 3. Risk Ratio of Grade ≥3 Anemia in TNBC Patients Receiving Neoadjuvant Therapy

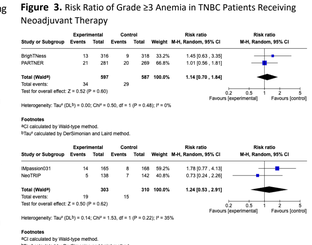


Figure 5. Risk Ratio of Grade ≥3 Leukopenia in TNBC Patients Receiving Neoadjuvant Therapy

Discussion

This study represents the first systematic review and meta-analysis specifically focused on phase 3 studies and high-grade (grade ≥3) adverse events associated with NAT in TNBC. While several prior publications have evaluated the efficacy of NAT strategies in TNBC, no previous synthesis has comprehensively quantified and compared the toxicity burden across contemporary phase 3 RCTs. Our findings provide critical insight into the safety profile of intensified treatment regimens, including those incorporating platinum agents, PARP inhibitors, and ICIs, that are increasingly used in routine clinical practice. Across six trials and over 3,300 patients, we identified hematologic toxicities, particularly neutropenia, anemia, and thrombocytopenia, as the most frequent severe adverse events.

Key Toxicity Patterns

PARP inhibitors demonstrated the highest hematologic risks, significantly increasing neutropenia (RR=1.84), anemia (RR=2.08), and thrombocytopenia (RR=3.56), primarily through DNA repair pathway targeting affecting normal hematopoietic cells. The PARTNER trial's 48-hour interval between carboplatin and olaparib reduced myelosuppression while preserving efficacy, demonstrating how pharmacodynamic scheduling can mitigate toxicity. These findings are consistent with prior studies showing that platinum salts significantly increase severe hematologic adverse events. ICIs did not significantly increase hematologic toxicity risk but introduced immune-related adverse events affecting multiple organ systems. While most irAEs are manageable with corticosteroids, they can be severe and life-threatening, requiring vigilant monitoring protocols.

Biomarker-Driven Selection

PARP inhibitor efficacy is largely restricted to BRCA-mutated patients, yet toxicity occurs regardless of mutation status. The PARTNER trial showed olaparib in BRCA wild-type patients increased toxicity without survival benefit, emphasizing the importance of biomarker-guided selection to avoid exposure and unnecessary harm. The recent integration of ICIs has redefined the therapeutic landscape for TNBC. The KEYNOTE-522 trial demonstrated significant improvement in pCR rates and overall survival with pembrolizumab addition to standard chemotherapy, confirmed by a recent meta-analysis showing that adding ICIs to chemotherapy in early-stage TNBC increases the risk of grade 3-4 toxicities compared to chemotherapy alone.

Clinical Implications

The substantial toxicity burden necessitates: (1) personalized risk assessment incorporating predictive biomarkers (BRCA status, PD-L1 expression) for treatment selection; (2) proactive monitoring and supportive care protocols; (3) appropriate patient counseling regarding risk-benefit trade-offs; and (4) guideline-directed toxicity management, particularly for hematologic and immune-related events.

Conclusions

This meta-analysis demonstrates that NAT for TNBC carries substantial grade ≥3 toxicity burden, particularly hematologic events. PARP inhibitors showed the highest hematologic risks, ICIs added immune-related toxicities without significant hematologic impact, and platinum-based regimens demonstrated the lowest severe adverse event rates.

These findings emphasize the critical importance of biomarker-driven treatment selection, particularly restricting PARP inhibitors to BRCA-mutated patients. Vigilant toxicity monitoring, proactive supportive care, and multidisciplinary management are essential for optimizing outcomes in this curative-intent setting.

As novel agents and combinations continue emerging, balancing efficacy with safety through precision-based approaches will remain central to TNBC care. **The substantial toxicity burden identified here underscores the need for individualized risk-benefit assessment and shared decision-making to ensure optimal patient outcomes while minimizing harm.**

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