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ORIGINAL RESEARCH

The Immunomodulatory Effects of Dexamethasone on Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer

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ABSTRACT

Introduction: The immunomodulatory impact of corticosteroids and concurrent chemotherapy is poorly understood within triple-negative breast cancer (TNBC). On a biochemical level, steroids have been linked to the signaling of chemotherapy-resistant pathways. However, on a clinical level, steroids play an essential role in chemotherapy tolerance through the prevention of chemotherapy-induced nausea and vomiting (CINV) and hypersensitivity reactions. Given these conflicting roles, we wanted to evaluate this interplay more rigorously in the context of early-stage TNBC.

Methods: We performed a retrospective analysis of patients with operable TNBC who received neoadjuvant chemotherapy (NAC) between January 2012 and November 2018, with the primary goal of examining the dose-dependent relationship between pathological complete response (pCR) rates and corticosteroid use. Secondary endpoints included the impact of

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steroid dosing on overall survival (OS) and recurrence-free survival (RFS), along with a breakdown in pCR rates based on steroid doses provided during each chemotherapy phase. Further adjusted analyses were performed based on patient age, diabetic status, and anatomical stage. Finally, we explored the relationship between tumor-infiltrating lymphocytes (TILs) seen on tissue samples at baseline and dexamethasone doses in terms of pCR rates.

Results: In total, of the 174 patients screened within this study period, 116 met full eligibility criteria. Of these eligible patients, all were female, with a median age of 51.5 years (27.0 to 74.0) and a mean body mass index (BMI) of 29.7 [standard deviation (SD) 7.04]. The majority were nondiabetic (80.2%). For cancer stage, 69.8% ($n = 81$) had stage 2 breast cancer. We found no statistically significant association between pCR rates and dexamethasone use, both in terms of the total dose ($p = 0.55$) and mean dose per NAC cycle ($p = 0.74$). Similarly, no difference was noted when adjusting for diabetic status, metformin use, or age at diagnosis, regardless of the total steroid dose provided ($p = 0.72$) or mean dose per cycle ($p = 0.49$). No meaningful changes to pCR rate were seen with higher mean or higher total steroid doses during the paclitaxel (T) phase (adjusted $p = 0.16$ and $p = 0.76$, respectively) or doxorubicin and cyclophosphamide (AC) phase (adjusted $p = 0.83$ and $p = 0.77$, respectively). Furthermore, we found no clinically significant association between dexamethasone dose and either RFS ($p = 0.45$) or OS ($p = 0.89$). Of the 56 patients who had available pre-treatment biopsy tissue samples, 27 achieved pCR, with higher TILs at baseline being associated with higher pCR rates, regardless of the mean dexamethasone dose used.

Conclusion: Our findings demonstrate that dexamethasone has no clinically significant impact on pCR, RFS, or OS when given concurrently with NAC in patients with curative TNBC, regardless of diabetic status.

Keywords: Triple-negative breast cancer (TNBC); Pathological complete response (pCR); Steroids; Neoadjuvant chemotherapy; Taxane; Anthracycline; Tumor-infiltrating lymphocytes (TILs)

Key Summary Points

Why carry out this study?

Preclinical studies suggest that glucocorticoids may negatively impact the effectiveness of cancer therapies in patients with breast cancer. This would suggest that dexamethasone exposure during neoadjuvant chemotherapy (NAC) may confer a negative effect on treatment outcomes.

We reviewed relevant institutional clinical outcome data for patients with early-stage triple-negative breast cancer (TNBC) receiving NAC to determine the impact of dexamethasone administration on key endpoints including pathological complete response (pCR), recurrence-free survival (RFS), and overall survival (OS).

What was learned from the study?

We found no statistically significant association between pCR rates and dexamethasone use, in terms of both the total dose ($p = 0.55$) and mean dose per NAC cycle ($p = 0.74$).

The study demonstrated that use of dexamethasone during NAC has no obvious impact on clinical outcomes. This was a confirmatory finding but will be helpful to know as future research weighs in on whether this result still holds true in the era of neoadjuvant/adjuvant immunotherapy.

INTRODUCTION

Steroids have been widely used within oncology for decades. This is in part due to their capacity to prevent adverse effects such as chemotherapy-induced nausea and vomiting (CINV) and

hypersensitivity reactions [1–4]. Furthermore, they play a supportive role in the management of cancer symptoms, including cerebral edema, cancer-related pain, fatigue, cachexia, and dyspnea [5, 6]. However, steroids come with their own unique set of adverse effects. Short-term steroid use is associated with insomnia, weight gain, hyperglycemia, hyperlipidemia, amenorrhea, and edema. Long-term use can lead to increased risk of osteoporosis, glaucoma, cataracts, gastrointestinal ulcerations, nonalcoholic fatty liver disease, adrenal insufficiency, and cardiovascular events [7–10].

In terms of its impact on chemotherapy effectiveness, dexamethasone has been shown within in vitro and in vivo solid tumor models to confer chemotherapy resistance, leading to tumor growth and metastasis [11–16]. However, on a clinical scale, results are often mixed and inconclusive [17, 18]. Although its proapoptotic and antiproliferative effects have been well studied in lymphoid cells, preclinical studies suggest that glucocorticoids may negatively impact the effectiveness of cancer therapies in solid tumor lines, including hepatocellular, colorectal, prostate, ovarian, breast, neuroblastoma, cervical, osteosarcoma, and melanoma [19, 20].

At the cellular level, the effect of steroids on chemotherapy response has been linked to a variety of mechanisms. In particular, the expression of mitogen-activated protein kinase (MAPK) phosphatase 1 (MKP1), a stress- and growth factor-inducible protein that is upregulated by glucocorticoids, plays an important role in the inactivation of p38 and Jnk kinases, resulting in inhibition of stress-induced apoptosis [21]. Another key effector that is upregulated by glucocorticoids is serum and glucocorticoid-induced protein kinase 1 (SGK1). SGK1 signaling is known to play a critical role in tumorigenesis, tumor cell proliferation, tumor migration, and metabolism, as it is a key regulator in several downstream pathways [22]. SGK1 negatively regulates transcription factors and cell cycle inhibitors such as FOXO3a and p27Kip1 [22]. Finally, dexamethasone use upregulates the expression of Krüppel-like factor 5 (KLF5), a key contributor to chemoresistance to docetaxel and cisplatin [23]. Additionally, expression of the antiapoptotic protein clusterin has been shown to be increased after treatment with dexamethasone [24]. Treatment resistance due to steroids has also been documented with radiation therapy, with multiple solid tumor cell line models demonstrating reduced therapeutic effect, though this finding is less consistent [25, 26].

Focusing on estrogen receptor (ER)-negative breast cancer, xenograft models have been able to demonstrate that increased receptor tyrosine kinase-like orphan receptor 1 (ROR1) expression through glucocorticoid receptor (GR) activation can subsequently increase cancer colonization and reduce overall survival (OS), with the subsequent ablation of ROR1 kinase allowing for a partial reversal of these effects [27, 28]. The GR antagonist mifepristone has been studied in multiple solid tumor xenograft models, including triple-negative breast cancer (TNBC) cell line MDA-MB-231, and has been shown to downregulate both SGK1 and MKP1, while also augmenting paclitaxel-induced tumor cell death [20, 22]. A separate GR antagonist, relacorilant, has provided similar findings in ovarian and pancreatic cancer models [29].

On an immunological level, glucocorticoids work as lymphodepleting agents. TNBC is often characterized by the increased presence of tumor-infiltrating lymphocytes (TILs), occurring in approximately 10–20% of TNBC tumors; these have long been established as a prognosticator in both the metastatic and operable settings [30, 31]. Most notably, tumors with higher TILs have better responses to neoadjuvant systemic therapy, including newer immunotherapy options [32, 33]. Thus, one might speculate that a reduction in TILs through corticosteroid use might hinder the response to systemic treatments.

When put together, these data would suggest that dexamethasone exposure during neoadjuvant chemotherapy (NAC) may confer a negative effect on treatment outcomes. To evaluate this hypothesis, we reviewed relevant institutional clinical outcome data for patients with early-stage TNBC to determine the impact of dexamethasone administration on key endpoints including pathological complete

response (pCR), recurrence-free survival (RFS), and OS.

METHODS

Study Design

This was a single-institutional retrospective analysis of patients ≥ 18 years of age with TNBC who received NAC with doxorubicin (A), cyclophosphamide (C), and paclitaxel (T) at the Stefanie Spielman Comprehensive Breast Center, The Ohio State University (OSU), between January 1, 2012, and November 30, 2018. Patients who received additional cytotoxic chemotherapy agents such as carboplatin in the neoadjuvant setting or experimental medications in the neoadjuvant or adjuvant setting were excluded to maximize the homogeneity of the sample population. Due to the retrospective nature of this study, it was not feasible to obtain informed consent from patients. For this reason, a waiver of informed consent was obtained from The Ohio State University Institutional Review Board. All patient data were collected from patient electronic medical records following approval by The Ohio State University Institutional Review Board (IRB protocol number 2017C0195). Data were abstracted to determine patient characteristics at the date of diagnosis, including age, race, gender, body mass index (BMI), tumor histology, tumor grade, cancer stage, ER expression, progesterone receptor (PR) expression, human epidermal growth factor receptor 2 (HER2) status, diabetic status, and medication administration data, including receipt of dexamethasone, metformin, and NAC.

All study data were collected and managed using REDCap electronic data capture tools supported by The Ohio State University Center for Clinical and Translational Science [34–36]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

The analysis of TILs was performed on a subset of the patients' core biopsy samples that were collected prior to NAC and were available through our institutional tumor bank. Whole tissue sections from archived hematoxylin and eosin (H&E)-stained glass slides were scanned using the Philips Ultra Fast Scanner at ×40 magnification with a single focus layer. TIL scoring was performed according to guideline recommendations from the International TILs Working Group (2014) [52].

The primary endpoint was evaluating the association between pCR and dexamethasone exposure during NAC. Secondary endpoints included RFS and OS in relation to steroid doses received. Additionally, further investigation of pCR rates was performed based on the dexamethasone doses administered during either the doxorubicin-cyclophosphamide or paclitaxel portions of NAC. A post hoc analysis examining the relationship between the likelihood of steroid administration and chemotherapy dose density was also performed. Finally, baseline TIL levels were analyzed to assess their impact on achieving a pCR. pCR is defined as the absence of invasive breast cancer in both the primary breast mass and the lymph nodes while allowing for the presence of in situ carcinoma where applicable (ypT0/Tis). OS is defined as the time from diagnosis to the time of death from any cause. RFS is defined as the time from diagnosis to the time of breast cancer recurrence or death from any cause. For "high" versus "low" dexamethasone use subgroups in our analysis, we used the median dose of dexamethasone administered as a cutoff.

Since 2012, our institutional practice for preventing CINV during NAC has involved the use of olanzapine-containing regimens. As such, only 12 mg of oral dexamethasone is given on day 1 for each cycle. If olanzapine was contraindicated, 12 mg of dexamethasone is given on day 1, followed by 8 mg on days 2, 3, and 4. During the paclitaxel chemotherapy stage, 12–20 mg of dexamethasone is given intravenously prior to each paclitaxel dose, although this may be discontinued if hypersensitivity is not observed following 2–3 initial doses.

Statistical Analysis

Demographic and baseline clinical information was tabulated overall and by pCR. Total dose and average dose per cycle of dexamethasone were analyzed in relation to (1) any qualifying NAC, (2) paclitaxel, and (3) doxorubicin and cyclophosphamide. The outcome variable was pCR. For each exposure summary, a logistic regression model was fit with dexamethasone exposure as the only covariate for unadjusted summaries and with the addition of diabetes classification (none, prediabetes, type 1, type 2), age at diagnosis, and receipt of metformin (yes/no) for the adjusted summaries. Nominal p values are provided for the unadjusted and adjusted associations of pCR with each exposure summary. Models were adjusted for age, cancer stage, and diabetes mellitus history to reduce the potential confounding effect on the outcomes, as dexamethasone would likely be reduced in patients with diabetes due to severe hyperglycemia.

To evaluate the relationship between dexamethasone dose and survival outcomes, we performed Cox proportional hazards regression without additional covariates, as well as adjusting for age and cancer stage at diagnosis. Logistic regression was used to test for differences in TILs by pCR status. TIL percentage was represented as log(TILs + 1).

RESULTS

Patient Characteristics

Between January 1, 2012, and November 30, 2018, 174 patients with TNBC received NAC with AC-T, and 116 met the study eligibility criteria (see Study Design for inclusion and exclusion criteria). All participants were female, with a median age of 51.5 years (range 27.0–74.0). At diagnosis, 11.2% had stage 1 disease, 69.8% had stage 2 disease, and 19.0% had stage 3 disease. In terms of comorbidities, we found that 19.8% of participants had a diagnosis of diabetes mellitus. Baseline characteristics are further summarized in Table 1.

Dexamethasone Administration

Regarding dexamethasone exposure, the mean total amount received with NAC was 239 mg (SD 40–600 mg). Additionally, the median dose of dexamethasone provided per cycle was 33.7 mg. This median value was used as our threshold for categorizing "high" versus "low" steroid exposure cohorts for secondary endpoints, with $\geq$ 33.5 mg representing the high category and $<$ 33.5 mg representing the low category.

The median dose of dexamethasone administered per cycle of chemotherapy was 33.7 mg. The median dose of dexamethasone administered per cycle during the doxorubicin-cyclophosphamide phase was 47.0 mg, whereas the dose per cycle during the paclitaxel phase was 118.5 mg.

Dexamethasone Dose and pCR

For our primary endpoint, we found no statistically significant association between pCR rate and dexamethasone dose, in terms of either total dose (odds ratio [OR] 1.0, 95% confidence interval [CI] 1–1.01, $p = 0.55$) or mean dose per NAC cycle (OR 1.0, 95% CI 0.97–1.02, $p = 0.74$), as shown in Table 2. Even when adjusting for diabetic status, tumor stage and age at diagnosis, no difference in pCR rates was noted, regardless of the total steroid dose provided (OR 1.0, 95% CI 0.97–1.02, $p = 0.72$) or mean dose per cycle (OR 1.0, 95% CI 1–1.01, $p = 0.49$). This is illustrated in Fig. 1.

Furthermore, differences in mean steroid doses per cycle during paclitaxel (unadjusted $p = 0.19$, adjusted $p = 0.16$) or doxorubicin-cyclophosphamide therapy (unadjusted $p = 0.91$, adjusted $p = 0.83$) did not alter pCR rates. Similarly, differences in total steroid doses during paclitaxel therapy (unadjusted $p = 0.78$, adjusted 0.76) or doxorubicin-cyclophosphamide therapy (unadjusted $p = 0.85$, adjusted $p = 0.77$) did not meaningfully influence pCR rates.

To assess whether dose-dense administration of chemotherapy influenced steroid dosing, we performed an ad hoc analysis, which found that higher steroid doses were provided to those on

Table 1 Baseline demographics and characteristics

	pCR (*n* = 51)	Non-pCR (*n* = 65)	Overall (*n* = 116)
Age—mean (SD)	51.0 (11.1)	52.0 (10.9)	51.6 (11.0)
Age—median [Min, Max]	52.0 [27.0, 72.0]	51.0 [31.0, 74.0]	51.5 [27.0, 74.0]
Female	51 (100%)	65 (100%)	116 (100%)
Race			
Asian	2 (3.9%)	2 (3.1%)	4 (3.4%)
Black	9 (17.6%)	8 (12.3%)	17 (14.7%)
White	40 (78.4%)	54 (83.1%)	94 (81.0%)
Other	0 (0%)	1 (1.5%)	1 (0.9%)
BMI			
Mean (SD)	28.1 (6.44)	31.0 (7.27)	29.7 (7.04)
Median [Min, Max]	27.1 [17.2, 48.6]	29.0 [18.7, 53.1]	28.5 [17.2, 53.1]
Diabetes			
Type 1	1 (2.0%)	1 (1.5%)	2 (1.7%)
Type 2	9 (17.6%)	11 (16.9%)	20 (17.2%)
Prediabetic	0 (0%)	1 (1.5%)	1 (0.9%)
Stage			
1	8 (15.7%)	5 (7.7%)	13 (11.2%)
2	33 (64.7%)	48 (73.8%)	81 (69.8%)
3	10 (19.6%)	12 (18.5%)	22 (19.0%)
Grade			
2	8 (15.7%)	7 (10.8%)	15 (12.9%)
3	43 (84.3%)	58 (89.2%)	101 (87.1%)
HER2-negative	50 (98.0%)	65 (100%)	115 (99.1%)
HER2-equivocal	1 (2.0%)	0 (0%)	1 (0.9%)
ER-negative	51 (100%)	65 (100%)	116 (100%)
PR-negative	51 (100%)	65 (100%)	116 (100%)
Mean dexamethasone dose in mg (SD)	37.2 (13.8)	38.0 (14.2)	37.7 (13.9)
Median dexamethasone dose in mg [Min, Max]	32.0 [11.0, 75.0]	36.0 [5.00, 69.6]	33.7 [5.00, 75.0]

BMI body mass index, *ER* estrogen receptor, *mg* milligrams, *pCR* pathological complete response, *PR* progesterone receptor

Table 2 The odds ratio between dexamethasone dosage and pCR rate

	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Dex dose per NAC cycle (per 10 mg)	OR 0.96 [0.73–1.25]	OR 0.95 [0.72–1.25]
Dex dose per AC cycle (per 10 mg)	OR 1.01 [0.90–1.28]	OR 1.01 [0.80–1.28]
Dex dose per T cycle (per 10 mg)	OR 0.97 [0.92–1.02]	OR 0.96 [0.91–1.02]
Total dex dose during NAC (per 10 mg)	OR 1.01 [0.97–1.06]	OR 1.02 [0.97–1.06]
Total dex dose during AC cycles	OR 1.01 [0.95–1.07]	OR 1.01 [0.95–1.07]
Total dex dose during T cycles (per 10 mg)	OR 1.01 [0.95–1.07]	OR 1.01 [0.95–1.07]

AC Adriamycin and cyclophosphamide, *CI* confidence interval, *Dex* dexamethasone, *NAC* neoadjuvant chemotherapy, *OR* odds ratio, *pCR* pathological complete response, *T* paclitaxel

Statistical significance ($p < 0.05$) was not reached in any of the categories above

dose-dense paclitaxel therapy compared to weekly dosing ($p = 0.02$), but not for those who received dose-dense doxorubicin-cyclophosphamide compared to Q3 week dosing ($p = 0.5$). Even after adjusting for doxorubicin-cyclophosphamide and paclitaxel dose intensities, no statistically significant association between average dexamethasone dose during NAC and pCR rates was observed (OR 1.0, 95% CI of 0.99–1, $p = 0.58$).

Dexamethasone Dose and Survival Outcomes

We found no statistically significant difference between the high and low mean per-cycle dexamethasone dose groups in terms of hazard ratio for OS (HR 1.0, 95% CI 0.96–1.03, $p = 0.89$). Similarly, across these dexamethasone exposure subgroups, RFS was not associated with the degree of dexamethasone exposure (HR 0.99, 95% CI 0.96–1.02, $p = 0.45$) (Fig. 2). After a median follow-up period of 50 months, the 5-year OS rate was 79.9% (95% CI 67.7–94.2%) among the high-exposure group versus 82.6% (95% CI 71.9–94.9%) among low-exposure patients. For 5-year RFS, this was 81.4% (95% CI 71.6–92.7%) versus 72.6% (95% CI 61.1–86.2%), respectively.

TILs and pCR

Approximately half of patients ($n = 56$) had baseline biopsies available to evaluate TILs, of which 27 achieved pCR. The median TIL percentage was 30% among those who achieved pCR versus 17.5% among those who did not (Fig. 3). Higher TIL percentages were associated with a higher probability of pCR overall (logistic regression $p = 0.04$). The associations between average dexamethasone dose per NAC cycle were not statistically significantly different between patients with TIL percentages above and below the median ($p = 0.48$) (Fig. 4). In the multivariate logistic regression interaction models using TIL percentage as continuous rather than grouped, there was still no statistically significant interaction with dexamethasone dose, either adjusting for diabetes status, age at diagnosis, and metformin use ($p = 0.64$) or without adjustment ($p = 0.49$).

DISCUSSION

Our study was able to highlight that the dose of dexamethasone used for supportive care during curative chemotherapy in TNBC did not have a statistically significant impact on clinical outcomes, including pCR, RFS, and OS. These findings were confirmed when adjusted for patient age, tumor stage, and diabetic status. Further testing related to doses of dexamethasone per cycle and doses provided during either AC or T chemotherapy resulted in similar findings. Overall, this would suggest that dexamethasone is a safe option for symptom control given its apparent lack of impact on clinically relevant recurrence or survival outcomes. Additional testing performed included baseline

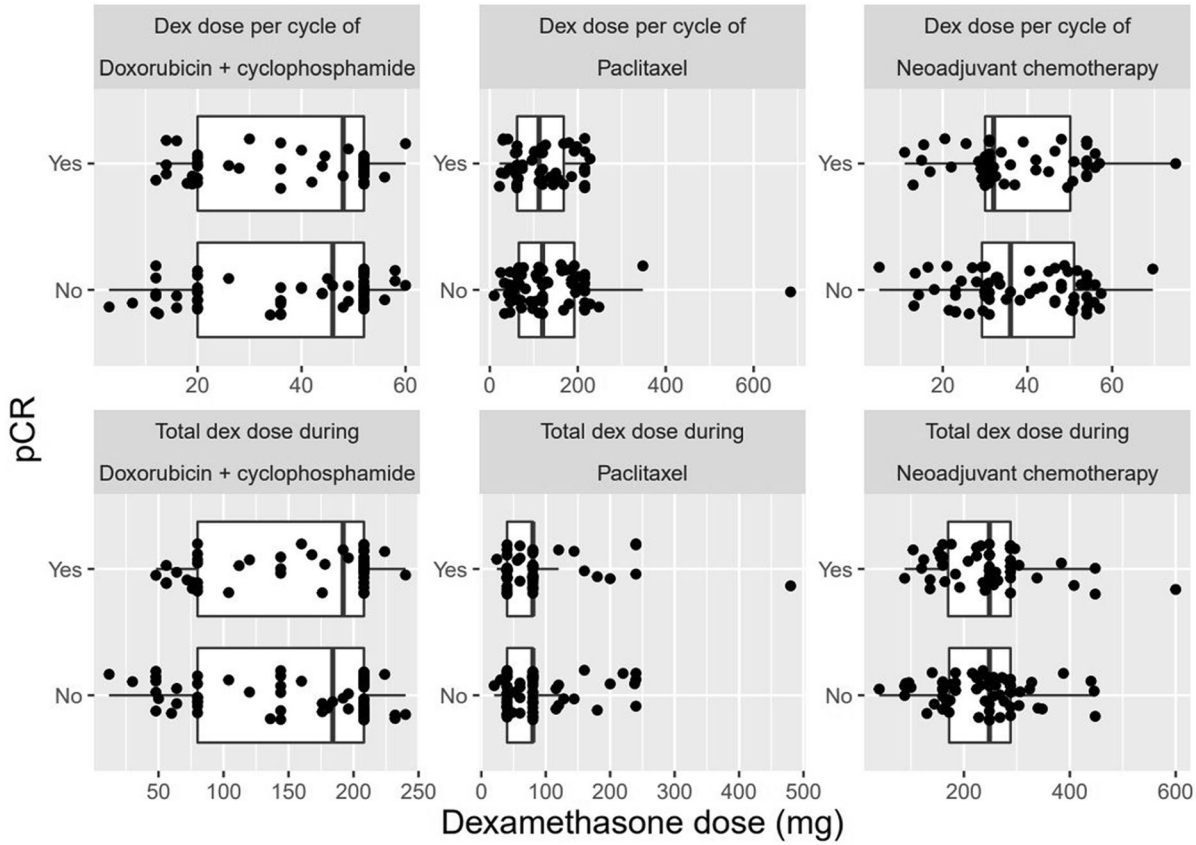

Fig. 1 Relationship between pCR status and dexamethasone dose. This figure compares the relationship between pCR status and dexamethasone dose, in terms of both dexamethasone dose per cycle and total dexamethasone dose throughout the completion of NAC. Dexamethasone dose has no impact on pCR rates for patients who receive NAC when assessed by dexamethasone dose per cycle of chemotherapy (top row) or by overall dexamethasone dose during NAC (bottom row). Abbreviations: dex, dexamethasone; mg, milligrams; pCR, pathological complete response; NAC, neoadjuvant chemotherapy

TIL testing, which was found to be at significantly higher levels in those who had achieved pCR following NAC. This falls in line with known prognostic data within TNBC as discussed earlier [30–33, 37–39].

Though there are preclinical studies mentioned earlier suggesting that glucocorticoids may impact the effectiveness of systemic chemotherapy, this finding is not universal, with few examples demonstrating a neutral or synergistic effect [40, 41]. For example, within breast cancer models, both in vivo and in vitro models (4T1) have shown that pretreatment with dexamethasone enhances the effects of doxorubicin in relation to its impact on cell death, apoptosis, tumor regression, and cytokine profile [41]. Similarly for cisplatin, dexamethasone has been found to amplify the antitumor and antiangiogenic effects of the chemotherapy when used on tumor-inoculated (EAC) mouse models [42].

Outside of breast cancer, some studies have similarly concluded that dexamethasone exposure may not be as clinically harmful and detrimental as previously hypothesized. One of the few randomized clinical trials to examine the impact of dexamethasone on clinical efficacy was a phase 2 study involving stage IV non-small cell lung cancer (NSCLC) where patients received carboplatin and gemcitabine with or without pretreatment dexamethasone [43]. No statistically significant difference was

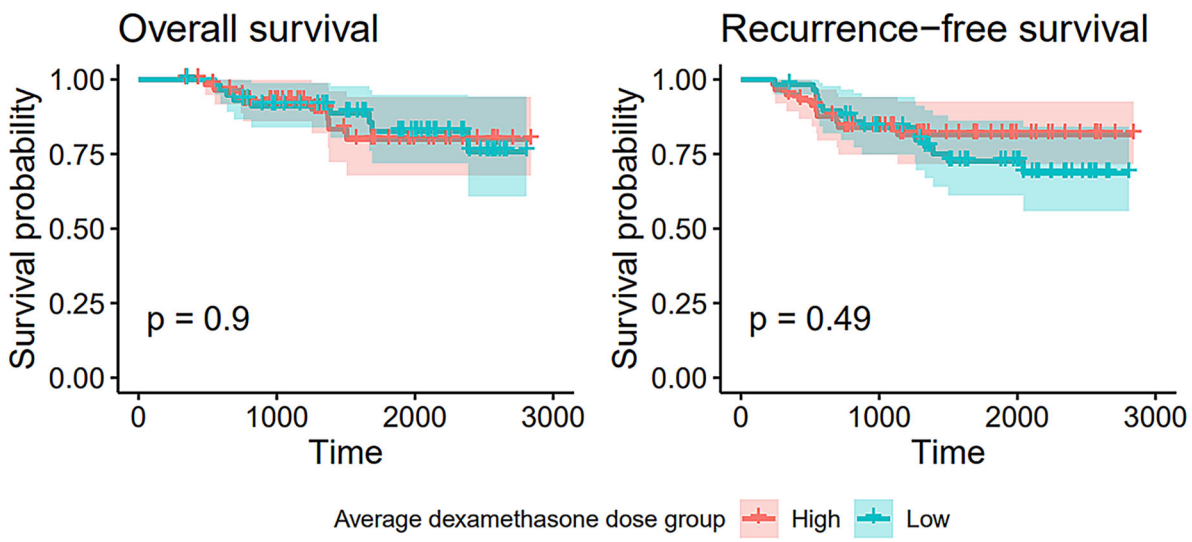

Fig. 2 Dexamethasone group (high vs. low) versus overall survival (OS) and recurrence-free survival (RFS). Kaplan–-Meier curves depicting the relationship between dexamethasone group (high vs. low) versus OS and RFS. A median dose cutoff of 33.5 mg was used to separate groups into high vs. low categories. No statistically significant difference in OS or RFS was noted

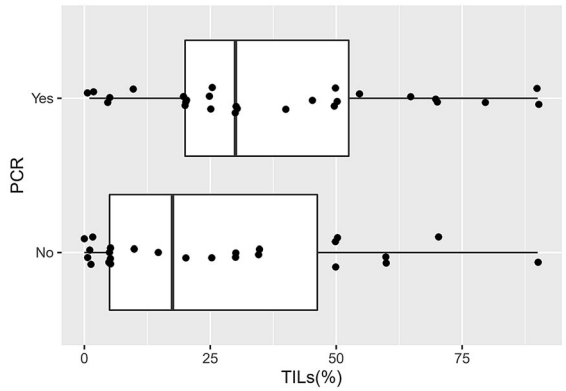

Fig. 3 Percentage of TILs at baseline and pCR following NAC. Relationship between the total percentage of TILs at baseline and pCR status following NAC. Abbreviations: pCR, pathological complete response; TILs, tumor-infiltrating lymphocytes

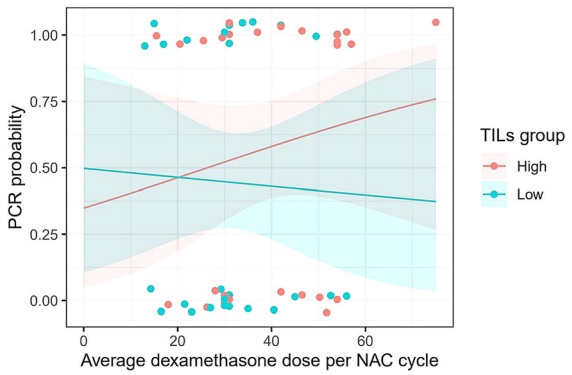

Fig. 4 pCR probability based on TILs and dexamethasone dose. Representation of pCR probability based on TILs at baseline and average dexamethasone dose received throughout each cycle of NAC. Abbreviations: Dex, dexamethasone; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; TILs, tumor-infiltrating lymphocytes

seen in terms of objective response rates or survival, though a threefold advantage in partial response rates was seen with the dexamethasone arm (26% vs. 8%), along with a 3-month improvement in OS (378 vs. 291 days). Though focused on intrahepatic therapy, a separate randomized controlled trial involving intrahepatic fluorodeoxyuridine with or without dexamethasone in patients with colorectal cancer and liver metastases reached a similar conclusion, with a trend toward increased survival with the addition of dexamethasone (23 months vs. 15 months, $p = 0.06$) and a statistically significant improvement in the objective response rate (36% vs. 4%,

$p = 0.03$) [44]. Retrospectively, a 2004 study by Münstedt et al. involving 245 cases of curative ovarian cancer found that those receiving steroids ($n = 62$) had no meaningful difference in OS from those who avoided steroid therapy ($n = 183$), but did have a meaningful improvement in treatment completion rates (64.5% vs. 44.8%, $p = 0.007$) and complete response rates (58.1% vs. 37.0%, $p = 0.035$) with the administration of glucocorticoids versus without glucocorticoids [45].

These findings may be in part due to the anti-inflammatory effects of glucocorticoids given the close link between inflammation and cancer [46]. However, with the emergence of immune checkpoint inhibitors (ICIs) such as pembrolizumab for the treatment of TNBC, there have been growing concerns regarding concurrent steroid use given its tendency to create an anti-inflammatory or "immunologically inert" environment, particularly as it relates to TILs as mentioned earlier. Interestingly, an in vitro study of TILs within metastatic melanoma found that although dexamethasone pretreatment does decrease TIL activity initially, this effect appears to be easily reversible, often recovering within 72 hours of steroid cessation [47]. Whether these short-lived effects are sufficient to impact clinical outcomes, particularly for those on ICIs, has yet to be clearly demonstrated. One of the frequently cited examples of this effect within TNBC, though highly debated, is the end result of the IMpassion130 and 131 trials, which randomized patients to receive the ICI atezolizumab (PD-L1 inhibitor) or placebo in combination with either nab-paclitaxel or paclitaxel, respectively. While IMpassion130 showed that the addition of atezolizumab to nab-paclitaxel improved progression-free survival (PFS) in patients with metastatic or unresectable TNBC, this was not the case with IMpassion131 when atezolizumab was combined with paclitaxel compared to the paclitaxel alone [48, 49]. One of the differences in trial design involved the incorporation of dexamethasone premedication within IMpassion131 to prevent hypersensitivity reactions to paclitaxel. However, other landmark trials such as KEYNOTE-355 and KEYNOTE-522 were widely successful despite using a similar dexamethasone protocol during infusions of pembrolizumab and chemotherapy [50, 51]. Regardless, until further data emerge, this remains an unanswered question due to the theoretical risk for diminished ICI efficacy.

Reflecting on our own study, we know it is inherently limited by the nature of its retrospective design. As with many retrospective analyses, selection bias impacts our patient population. For example, those with severe or uncontrolled diabetes would likely have minimized steroid use, whereas those with mild disease would be selected for standard steroid therapy. We also lacked a steroid-free control group for comparison. While no obvious difference in steroid exposure was seen with doxorubicin-cyclophosphamide or NAC in general, those on dose-dense paclitaxel received more steroids than their standard-dose counterparts. We attempted to account for this by including results adjusted for dexamethasone dose per cycle rather than the total dexamethasone dose. Finally, sample size limited our ability to perform further subgroup analyses, such as those based on residual cancer burden classifications. With these limitations in mind, this study highlights the disparity between preclinical and clinical data in terms of the possible detrimental impact steroids can have on chemotherapy resistance in TNBC. However, whether these findings can be extrapolated to current TNBC regimens that combine ICI with cytotoxic chemotherapy remains to be seen.

CONCLUSIONS

Our analysis did not find a statistical association between dexamethasone use and clinical outcomes among patients with localized TNBC. This was true in terms of pCR, RFS, and OS, with no impact in terms of diabetic status. Thus, we were able to demonstrate that dexamethasone use has a limited impact on treatment outcomes despite convincing preclinical data. However, given the emerging role of ICIs in the curative and palliative management of TNBC, further efforts are needed to gauge their impact on clinical outcomes for those on combination therapies.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Declaration of Helsinki and ethical approval was obtained from The Ohio State University Institutional Review Board (IRB protocol No. 2017C0195). Due to the retrospective nature of this study, it was not feasible to obtain informed consent from patients. For this reason, a waiver of informed consent was obtained. Individual consent from each subject was not required by the IRB as deidentified data was used. All research was carried out in accordance with these institutional and international guidelines and regulations.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Data only available to OSU IRB approved investigators due to HIPAA restrictions on identified data.

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