Primary-Chemotherapy against Triple Negative & Luminal B Operable Breast Cancer

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Randomised clinical studies addressing the sequence of anthracyclines and taxanes in early BC

	Setting	Number of patients	Chemotherapy regimens	Results
Puhalla et al (2008)[2]	Adjuvant	28 28	AC→Doc (DD) Doc→AC* (DD)	RDI of AC 0·98, Doc 0·82 RDI of AC 0·95, Doc 0·96
Wildiers et al (2009)[3]	Adjuvant	58 59	FEC→Doc (±DD) Doc→FEC (±DD)	Doses reduced: FEC 5%, Doc 17% Doses reduced: FEC 5%, Doc 3%†
Piedbois et al (2007)[4]	Adjuvant	31 34	EC→Doc (DD) Doc→EC* (DD)	RDI of E 0·97, Doc 0·81 RDI of E 0·96, Doc 0·96‡
Cardoso et al (2001)[5]	Adjuvant	20 14	A→Doc (→CMF) Doc→A (→CMF)	RDI 100% for both drugs and for both groups
Earl et al (2009)[6]	Neoadjuvant	813 (total)	EC→Pac (±G) (DD) Pac (±G)→EC (DD)	pCR 15% pCR 20%†
Miller et al (2005)[7]	Neoadjuvant	35 34	A→Doc (DD) Doc→A* (DD)	pCR 8·6%; RDI of A 0·95, Doc 0·89 pCR 17·1%; RDI of A 0·94, Doc 0·97

A=doxorubicin. C=cyclophosphamide. Doc=docetaxel. DD=dose dense. RDI=relative dose intensity. F=fluorouracil. E=epirubicin. M=methotrexate. Pac=paclitaxel. G=gemcitabine. pCR=pathological complete response rate. *Leucocyte growth factors were administered in both groups of the study. †Statistically significant. ‡Grade 4 toxicity occurred in 18% of patients in the Doc→EC group versus 40% in the EC→Doc group.

Wildiers et al. Lancet oncology(2010) 11:219-220

Primary treatment against operable breast cancer in Kyoundo

	premenopausal	postmenopausal
Luminal A	CEF100x4	AI TAM (CYP2D6 wt)
HER2	Doc75+Tmab x4 → CEF100x4	
Luminal B	Doc75x4→CEF100x4	
Basal like	Doc75x4→CEF100x4	

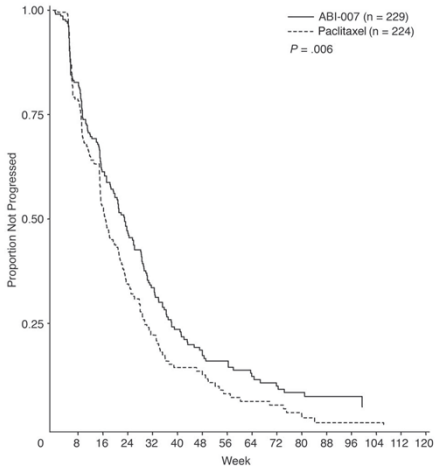
Which is the best sequence?

Taxane → Anthracycline

- Weekly PTX 80
- Doc 100 q3wks
- Doc 75 q3wks
- Abraxane 260 q3wks
- Abraxane 100-150 qwk

- AC(60/600)
- EC(90/830)
- CEF(500/100/500)

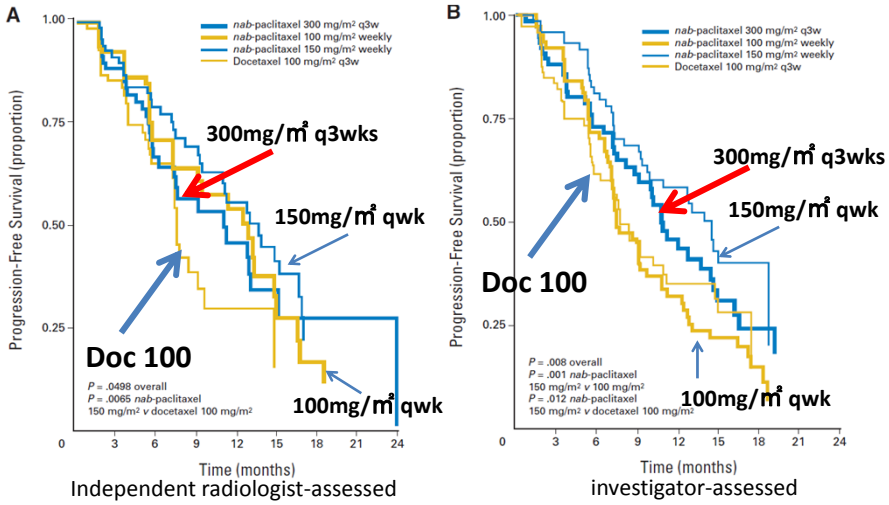
PTX 175 q3wks vs Abraxane 260 q3wks
MBC 1st line



J Clin Oncol 23: 7794, 2005

Doc100 vs Abraxane
MBC 1st line

300mg/㎡ q3wks
100mg/㎡ qwk
150mg/㎡ qwk

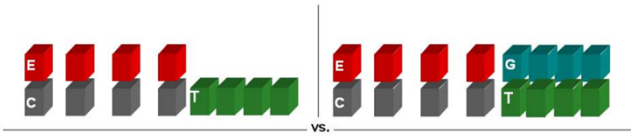


J Clin Oncol 27: 3611, 2009

Neo-tAnGo Treatment Schema

2009 ASCO

2 x 2 factorial design



Epirubicin 90mg/m²
Cyclophosphamide 600mg/m²
Q 21 days

Primary endpoint: pCR rates

- A 2-reader review of pathology reports, blinded to treatment, was undertaken (812 pts)
- pCR defined as
  - pCR in all breast tumours　AND
  - absence of disease in AxLNs in all breast tumours

Component qn	EC & T (n=404)	EC & TG (n=408)	p
pCR rate (95% CI)	17% (14-21)	17% (14-21)	0.98

Sequencing qn	EC→T±G (n=406)	T±G→EC	p
pCR rate (95% CI)	15% (11-18)	20% (16-24)	0.03

Adjustment for stratification variables does not alter results
(Age, ER status, Tumour size, Nodal status, Inflammatory / Locally advanced disease)

Primary treatment against operable breast cancer in Kyoundo

	premenopausal	postmenopausal
Luminal A	CEF100x4	AI TAM (CYP2D6 wt)
HER2	Doc75+Tmab x4 → CEF100x4	
Luminal B	Abraxane →CEF100x4	
Basal like	Abraxane→CEF100x4	

pCR rate↑25～30%?

original article

Annals of Oncology 20: 1185–1192, 2009
doi:10.1093/annonc/mdn748
Published online 13 February 2009

Preoperative weekly cisplatin–epirubicin–paclitaxel with G-CSF support in triple-negative large operable breast cancer

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Received 3 November 2008; accepted 18 November 2008

Background: Findings from our previously published phase II study showed a high pathologic complete remission (pCR) rate in patients with triple-negative large operable breast cancer after the administration of eight cisplatin–epirubicin–paclitaxel (PET) weekly cycles. The safety and efficacy data of the initial population were updated, with inclusion of additional experience with the same therapy.

Methods: Patients with triple-negative large operable breast cancer (T2–T3 N0–1; T > 3 cm) received eight preoperative weekly cycles of cisplatin 30 mg/m^2, epirubicin 50 mg/m^2, paclitaxel (Taxol) 120 mg/m^2, with granulocyte colony-stimulating factor (5 μg/kg, days 3–5) support.

Results: Overall 74 consecutive patients (T2/T3 = 35/39; N0/N+ = 26/48) were treated, from May 1999 to May 2008. At pathological assessment, 46 women (62%; 95% confidence interval 50–73) showed pCR in both breast and axilla. At a 41-month median follow-up (range 3–119), 13 events (nine distant metastases) had occurred, 5-year projected disease-free survival (DFS) and distant disease-free survival being 76% and 84%, respectively. Five-year DFS was 90% and 56% in pCRs and non-pCRs, respectively. Severe neutropenia and anemia occurred in 23 (31%) and eight (10.8%) patients, respectively. Severe non-hematological toxicity was recorded in <20% of patients. Peripheral neuropathy was quite frequent but never severe.

Conclusions: Eight weekly PET cycles are a highly effective primary treatment in women with triple-negative large operable breast cancer. This approach results in a very promising long-term DFS in this poor prognosis population. This triplet regimen is worthy of evaluation in phase III trials.

Key words: cisplatin, epirubicin, operable breast cancer, paclitaxel, triple negative, weekly administration

pCR 62% !!

Efficacy of Neoadjuvant Cisplatin in Triple-Negative Breast Cancer

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A B S T R A C T

Purpose
Cisplatin is a chemotherapeutic agent not used routinely for breast cancer treatment. As a DNA cross-linking agent, cisplatin may be effective treatment for hereditary *BRCA1*-mutated breast cancers. Because sporadic triple-negative breast cancer (TNBC) and *BRCA1*-associated breast cancer share features suggesting common pathogenesis, we conducted a neoadjuvant trial of cisplatin in TNBC and explored specific biomarkers to identify predictors of response.

Patients and Methods
Twenty-eight women with stage II or III breast cancers lacking estrogen and progesterone receptors and HER2/Neu (TNBC) were enrolled and treated with four cycles of cisplatin at 75 mg/m^2 every 21 days. After definitive surgery, patients received standard adjuvant chemotherapy and radiation therapy per their treating physicians. Clinical and pathologic treatment response were assessed, and pretreatment tumor samples were evaluated for selected biomarkers.

Results
Six (22%) of 28 patients achieved pathologic complete responses, including both patients with *BRCA1* germline mutations; 18 (64%) patients had a clinical complete or partial response. Fourteen (50%) patients showed good pathologic responses (Miller-Payne score of 3, 4, or 5), 10 had minor responses (Miller-Payne score of 1 or 2), and four (14%) progressed. All TNBCs clustered with reference basal-like tumors by hierarchical clustering. Factors associated with good cisplatin response include young age ($P = .001$), low *BRCA1* mRNA expression ($P = .03$), *BRCA1* promoter methylation ($P = .04$), p53 nonsense or frameshift mutations ($P = .01$), and a gene expression signature of E2F3 activation ($P = .03$).

Conclusion
Single-agent cisplatin induced response in a subset of patients with TNBC. Decreased *BRCA1* expression may identify subsets of TNBCs that are cisplatin sensitive. Other biomarkers show promise in predicting cisplatin response.

J Clin Oncol 28:1145-1153. © 2010 by American Society of Clinical Oncology

The Breast xxx (2010) 1–3

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Short Report

Cisplatin–gemcitabine therapy in metastatic breast cancer: Improved outcome in triple negative breast cancer patients compared to non-triple negative patients

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ARTICLE INFO

Article history:
Received 28 October 2009
Received in revised form
22 January 2010
Accepted 8 February 2010

Keywords:
Triple negative
Cisplatin and gemcitabine chemotherapy
Metastatic breast cancer

ABSTRACT

Triple negative or basal-like breast cancers lack expression of estrogen, progesterone and HER2*neu* receptors. There are no specific treatment guidelines for this group of patients, however, it has been postulated that their phenotypic and molecular similarity to BRCA-1 related cancers would confer sensitivity to certain cytotoxic agents like cisplatin (CDDP). The aim of the study was to retrospectively examine the clinical outcome at our institution of patients with metastatic breast cancer treated with CDDP and gemcitabine combination chemotherapy who had triple negative breast cancer compared to non-triple negative breast cancer. Thirty-six patients with metastatic breast cancer were treated with CDDP and gemcitabine combination chemotherapy, 17 of whom were triple negative (47%) and 19 were non-triple negative (53%). The median progression free survival for triple negative and non-triple negative metastatic breast cancer patients were 5.3 months and 1.7 months respectively ($p = 0.058$). By multivariate Cox proportional hazard model after adjusting for age, race and menopausal status the risk of progression was reduced by 47% for triple negative compared to non-triple negative metastatic breast cancer patients (HR = 0.53, $p = 0.071$).

Conclusions: Our results suggest an improved outcome for metastatic triple negative breast cancer patients compared to non-triple negative breast cancer patients when treated with cisplatin and gemcitabine combination chemotherapy.

Efficacy of gemcitabine and cisplatin (GP) as first-line combination therapy in patients with triple-negative metastatic breast cancer: Preliminary results report of a phase II trial.

J Clin Oncol 28:15s, 2010 (suppl; abstr 1100)

Background: Triple-negative breast cancer (TNBC) contributes to the poor prognosis. Only a few studies have revealed that cisplatin-based therapy may be effective for this subtype of breast cancer. The objective of this study was to evaluate doublet with gemcitabine/cisplatin (GP) as first-line therapy in patients with metastatic TNBC.

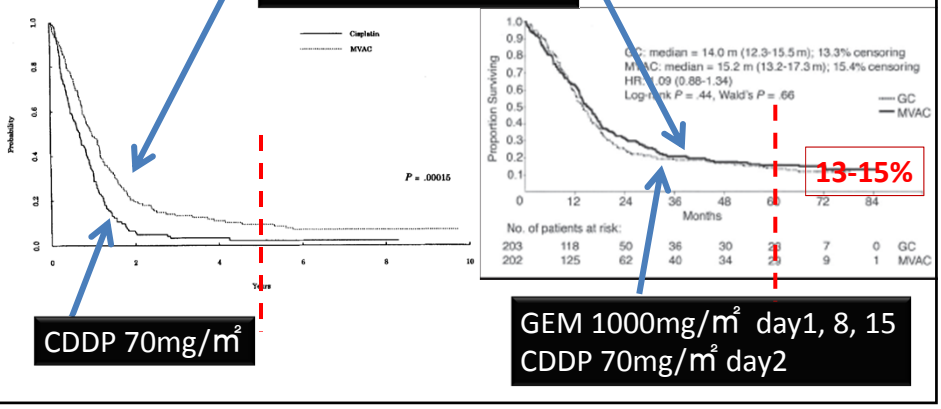
Methods: This is a single-institutional phase II trial. The primary endpoint was progression-free survival (PFS). Eligible subjects were aging from 18 to 75 years old, **with no prior chemotherpay for MBC**, with tumors negative for ER, PR, or HER2, with at least one measurable disease according to the RECIST criteria, with ECOG PS of 0-1, and with adequate organ function. Patients received 21-day cycles of **gemcitabine (1,000mg/m^2) on days 1, 8 and cisplatin (25 mg/m^2) on days 1-3.** Treatment was continued until disease progression or unacceptable toxicity or up to 8 cycles. Response rate was evaluated every six weeks.

Results: As of Nov. 2009, 65 patients had been enrolled with a planned sample size of 80 patients. The first 45 patients had completed the treatment and were analyzed. A median age was 48 years. 42 patients had received adjuvant chemotherapy (39 patients with anthracycline and/or taxane). The median number of GP treatment cycles was six. The median PFS was 6.2 months (95% CI: 5.0-7.3). **The response rate was 62.2% (28/45, 95% CI: 47.5%-77%);** stable disease was 31.1% (14/45); progressive disease was 6.7% (3/45). G3/4 toxicities were neutropenia 40% (18pts); thrombocytopenia 33.3% (15pts); fatigue 17.8% (8pts); anorexia 15.6% (7pts); anemia 13.3% (6pts); nausea/vomiting 8.9% (4pts). The chemotherapy doses were reduced in 13.3% (6 pts) because of toxicity.

Conclusions: This preliminary analysis demonstrated that GP regimen as first-line chemotherapy is **highly effective** and safe in patients with TNBC.

CDDP < MVAC = GC
against advanced urothelial carcinoma

MTX 30mg/㎡ day1, 15, 22
VCR 3mg/㎡ day2, 15, 22
ADM 30mg/㎡ day2
CDDP 70mg/㎡ day2

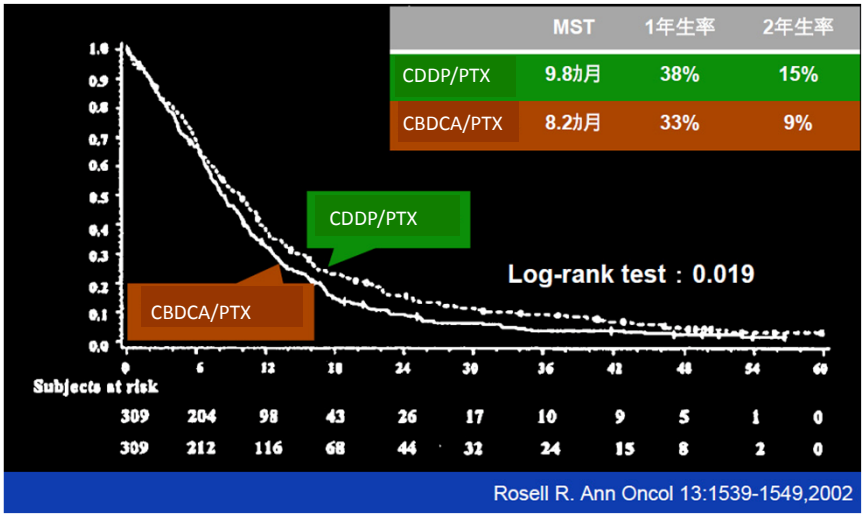


CDDP 70mg/㎡

GEM 1000mg/㎡ day1, 8, 15
CDDP 70mg/㎡ day2

CDDP or CBDCA ?

CDDP+Paclitaxel vs CBDCA+Paclitaxel in NSCLC



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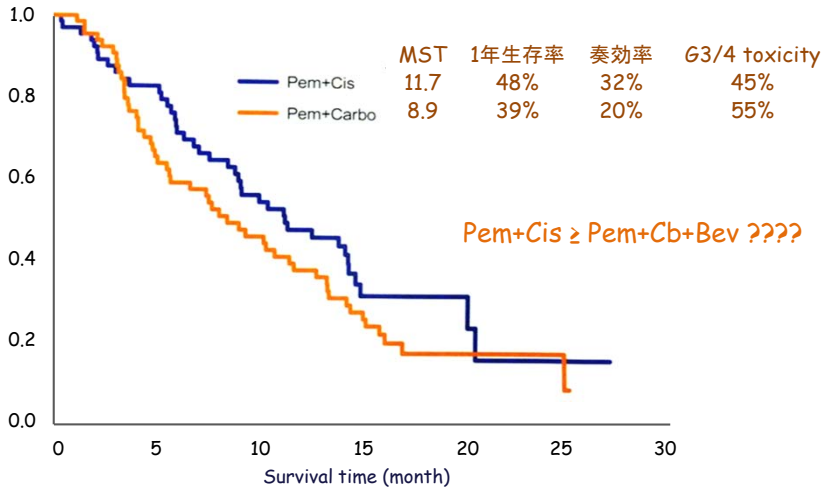
CDDP + Pem vs CBDCA + Pem

Randomized phase II study n=130
NSCLC(Non-sq 80%) stage IIIB/IV PS 0-1 median age 64



Nagel et al. ASCO 2010

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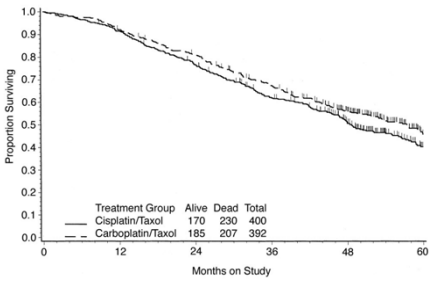
CDDP vs CBDCA in other cancers

Ovarian Cancer
PTX+CDDP vs PTX+CBDCA (AUC 7.5)



CDDP=CBDCA

Germ Cell Tumor
BEP vs CEB (AUC 5)

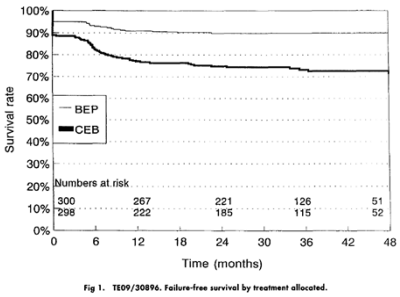


Fig 1. TE09/30896. Failure-free survival by treatment allocated.

CDDP>>CBDCA

Neoadjuvant platinum-based chemotherapy (CT) for triple-negative locally advanced breast cancer (LABC): Retrospective analysis of 125 patients.

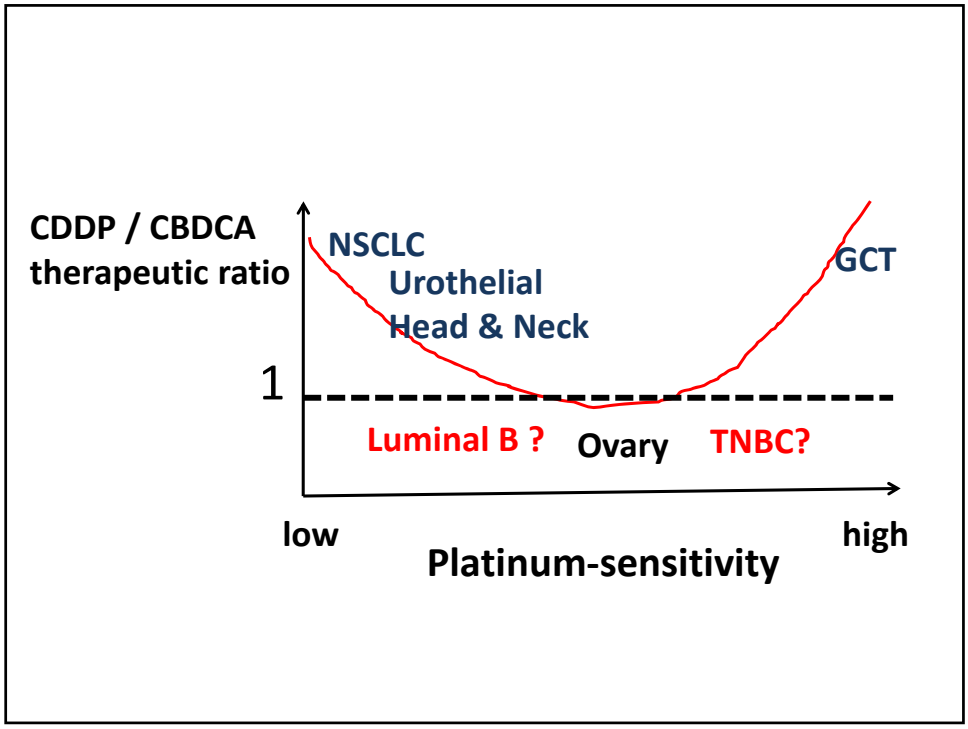
J Clin Oncol 27:15s, 2009 (suppl; abstr 625)

Background: Triple-negative breast cancer (TNBC), defined by lack of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, accounts for 15-20% of all breast cancers and is associated with poor prognosis. There is no consensus regarding optimal CT for treatment of such patients. Preclinical data suggests TNBC may be sensitive to platinums because of deficiencies in BRCA-associated DNA repair. The aim of this study was to evaluate pathologic complete response (pCR) and overall survival (OS) in patients with TNBC treated with neoadjuvant platinum-based CT.

Methods: We identified 674 patients with LABC who received neoadjuvant CT between January 1999 and June 2008 at University of Miami. Of these, 125 (18.5%) had histopathologic confirmation of TNBC. All patients received neoadjuvant platinum salts + docetaxel. 76 (61%) also received neoadjuvant AC, while 42 (34%) received adjuvant AC. pCR was defined as no residual invasive disease in breast and axilla. OS was calculated according to Kaplan-Meier.

Results: Demographics: median age 50 (28-86 years). 60% premenopausal. TNM stage distribution: T1 0.9%, T2 5.2%, T3 53.4%, T4 40.5%, N0 25.0%, N1 36.2%, N2 35.4%, N3 3.4%, M0 100%, inflammatory 11%, median tumor size = 9.5 cm. Follow up duration ranged from 0.3 to 8.9 years. pCR was observed in 42 of 125 patients (34%; 95% CI 26-43%). Among patients receiving neoadjuvant AC, 30 of 76 (40%; 95% CI 28-51%) had pCR, while amongst those receiving adjuvant AC, 12 of 42 (29%, 95% CI 16-45%) had pCR at the time of definitive surgery. Patients achieving pCR had significantly higher OS (5-yr rate = 73% in pCR, vs. 49% in non-pCR; $p < 0.001$). **OS in TNBC patients receiving cisplatin/docetaxel was significantly superior to those receiving carboplatin/docetaxel (11 mortality events out of 78 patients receiving cisplatin based CT vs 24 out of 47 receiving carboplatin based CT logrank p = 0.001).**

Conclusions: To date, this is the largest single institution cohort of locally advanced TNBC uniformly treated with platinum+docetaxel-based CT regimens. Platinum/docetaxel-based neoadjuvant CT provided high rates of pCR and excellent OS for women with locally advanced TNBC.



Which is the best sequence?

Gemcitabine
Platinum

➡

Anthracycline

- GEM+CDDP ?

- AC(60/600)
- EC(90/830)
- CEF(500/100/500)

Example of recommended hydration

NCCN Chemotherapy Order Template™ 2009

60 min	Pre hydration 500ml	20% mannitol 62.5-125mL
15 min	Mannitol 12.5-25g	
60 min	CDDP	5% dextrose 0.45% NaCL Total 1000mL KCL 20mEq MgSO4 8mEq(1g)
60 min	Post hydration 500ml	

Day 2以降は補液なし

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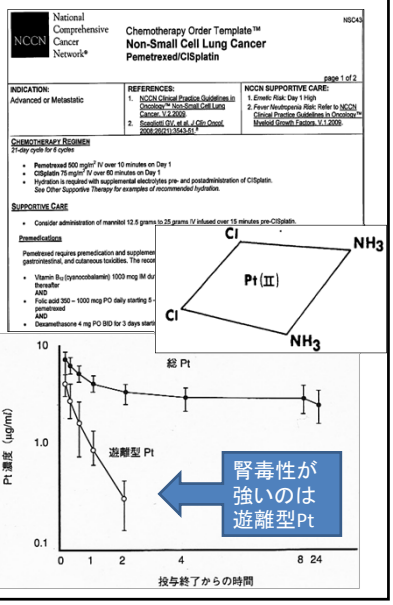
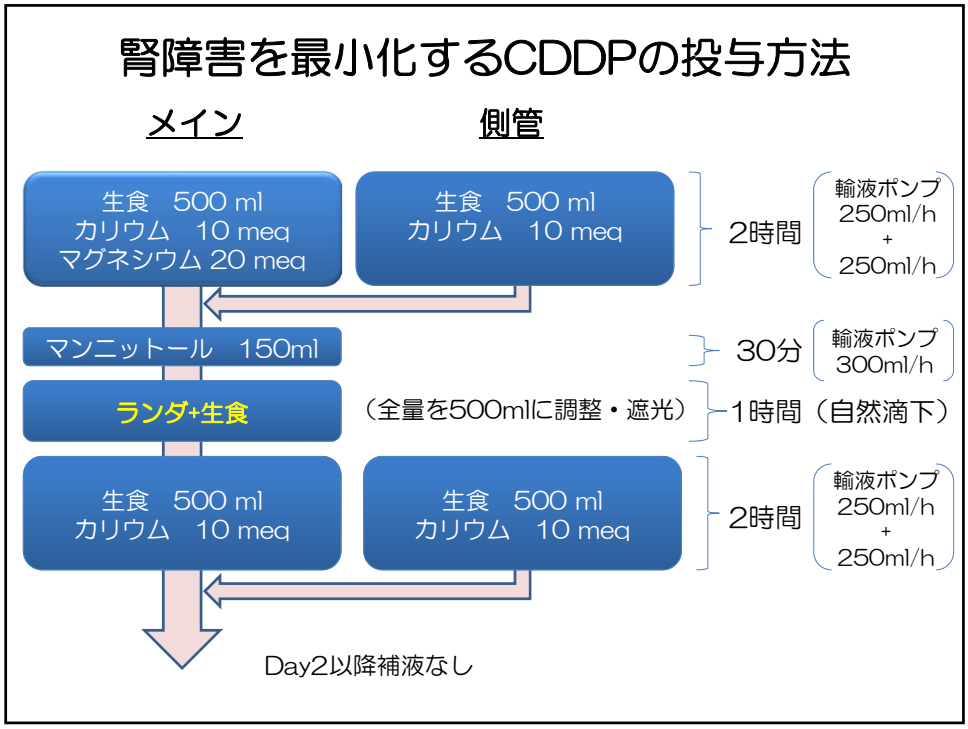
シスプラチン(ランダ®)を含むレジメンにおける輸液の標準化

- NCCNのオーダーテンプレートに準拠
- 前後の補液は生食としシスプラチンの-Cl基が-OH基に変換されにくくすることで腎毒性を軽減
  (Ann Inter Med 100: 19, 1984)
- マグネシウムによる腎保護効果
  (Br J Cancer 54: 19, 1986, Eur J Cancer 44: 2608, 2008)
- 生食急速投与とマンニットール投与により投与前後4時間の尿量を最低100ml/h以上に保つ
  (Tumori 93: 138, 2007, Cancer Chemother Pharmacol 23: 243, 1989, 腫瘍内科 5(3): 347, 2010)




腎障害を最小化するCDDPの投与方法
メイン
側管
生食　500 ml
カリウム　10 meq
マグネシウム 20 meq
生食　500 ml
カリウム　10 meq
2時間
輸液ポンプ
250ml/h
+
250ml/h
マンニットール　150ml
30分
輸液ポンプ
300ml/h
ランダ+生食
（全量を500mlに調整・遮光）
1時間（自然滴下）
生食　500 ml
カリウム　10 meq
生食　500 ml
カリウム　10 meq
2時間
輸液ポンプ
250ml/h
+
250ml/h
Day2以降補液なし