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Prospective study on the role of cytidine deaminase activity in lung cancer patients treated with gemcitabine-platinum-based chemotherapy

Dr. Carmelo Tibaldi

Scientific Coordinator of GOIRC

Division of Medical Oncology

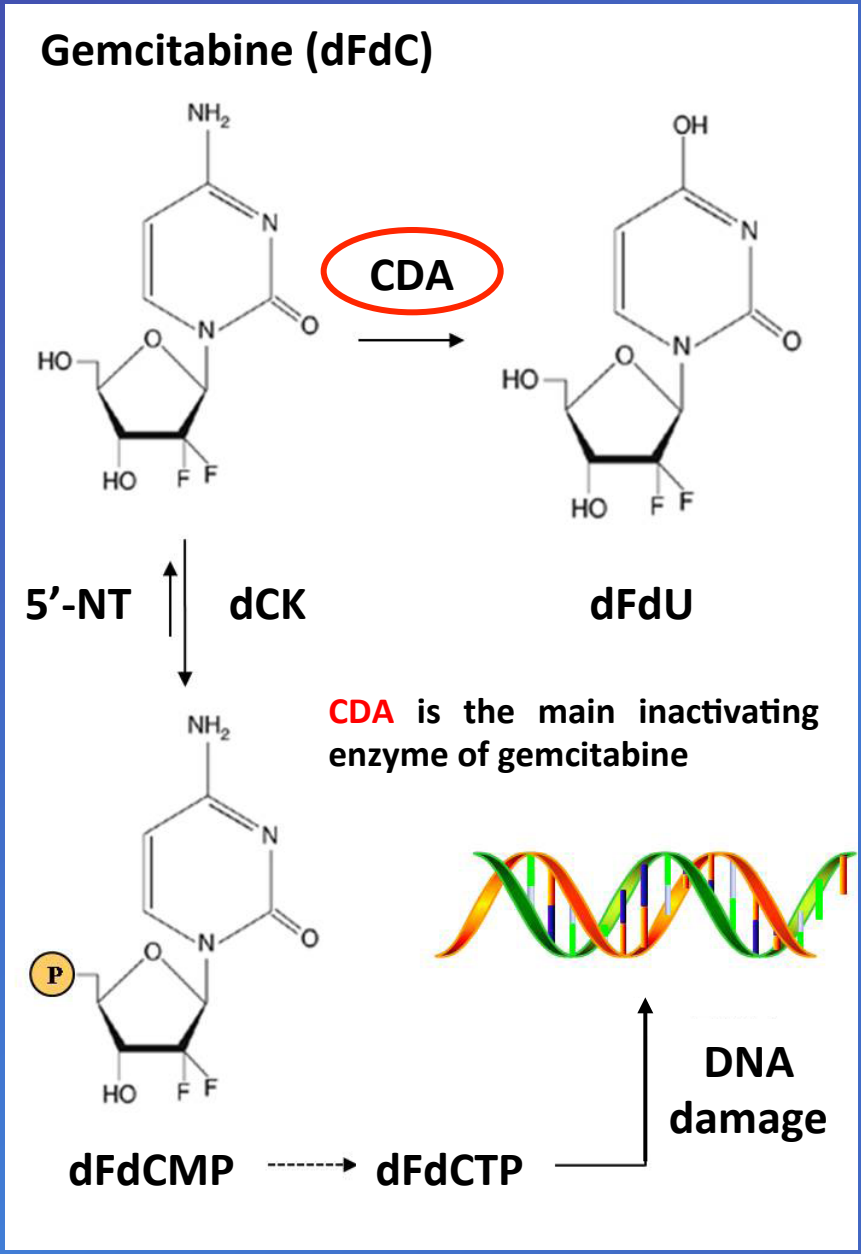
S. Luca Hospital, Lucca, Italy

Carmelo.tibaldi@uslnordovest.toscana.it

Background

- There are no predictive biomarkers of activity and/or efficacy of chemotherapy in NSCLC
- Platinum/gemcitabine is one of the most common regimens used in clinical practice

Background:Cytidine deaminase



- CDA-*A79C* SNP was significantly correlated with clinical benefit, TTP and OS (Tibaldi *et al*, Clin Cancer Res, 2008)
- CDA enzymatic activity appears to be the strongest candidate biomarker of activity and efficacy (Tibaldi *et al*, Ann Oncol, 2011)

Endpoints

- **Co-primary endpoints:**

- To demonstrate a response rate of 40% in the group of pts with low CDA enzymatic activity versus 14% in the group of pts with high CDA enzymatic activity
- To demonstrate a relative reduction of progression or death by at least 50% (HR=0.5)

Secondary endpoints:

Overall survival

Toxicity

Patient Selection Criteria/Treatment

Chemotherapy-naive NSCLC patients; EGFR WT;

Clinical Stage IIIB-IV

ECOG Performance Status <2

Cisplatin 80 mg/m^2 i.v. day 1
Gemcitabine 1200 mg/m^2 i.v. days 1, 8
q 21days

Carboplatin AUC 5
Gemcitabine 1000 mg/m^2 i.v. days 1, 8
q 21days

Methods/Evaluation Criteria

- **CDA enzymatic activity** was evaluated by spectrophotometric assay (Peters et al, Nucleosides Nucleotides Nucleic Acids, 2014)

  Median 7.2 (1.37-37.5)

  8.35 (1.37-37.5) Contal & O' Quigley test

- **Responses** were assessed by CT scan every 3 cycles using RECIST mod 1.1 version criteria
- **Toxicities** were assessed using NCI-CTC 3.0 version. The worst toxicity grade for each patient was reported

Patients' characteristics

		Patients n(%)
N. Pts		121
Age median yrs		70 (49-87)
Male		94 (77.6)
Female		27 (22.4)
Stage III B		26 (21.5)
IV		95 (78.5)
ECOG PS:	0	48 (39.6)
	1-2	64-9 (60.4)
Adenocarcinoma		28 (23.1)
Squamous		75 (62.0)
NSCLC		18 (14.9)
CDDP-Gem		48 (39.6)
Carbo-Gem		73 (60.4)

CDA enzymatic activity: response

	RESPONSE %	95% Exact Confidence Limits	P
Low ≤ 7.2	54.1	40.85%-66.94%	0.0015 *
High > 7.2	25.0	14.72%-37.86%	

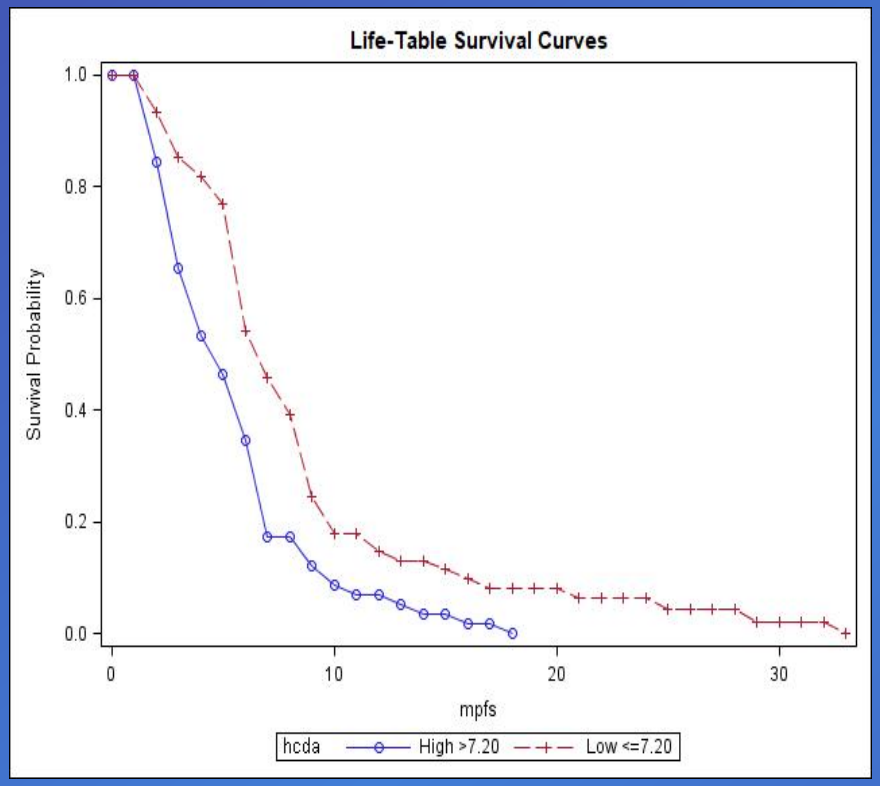
* Statistically significant

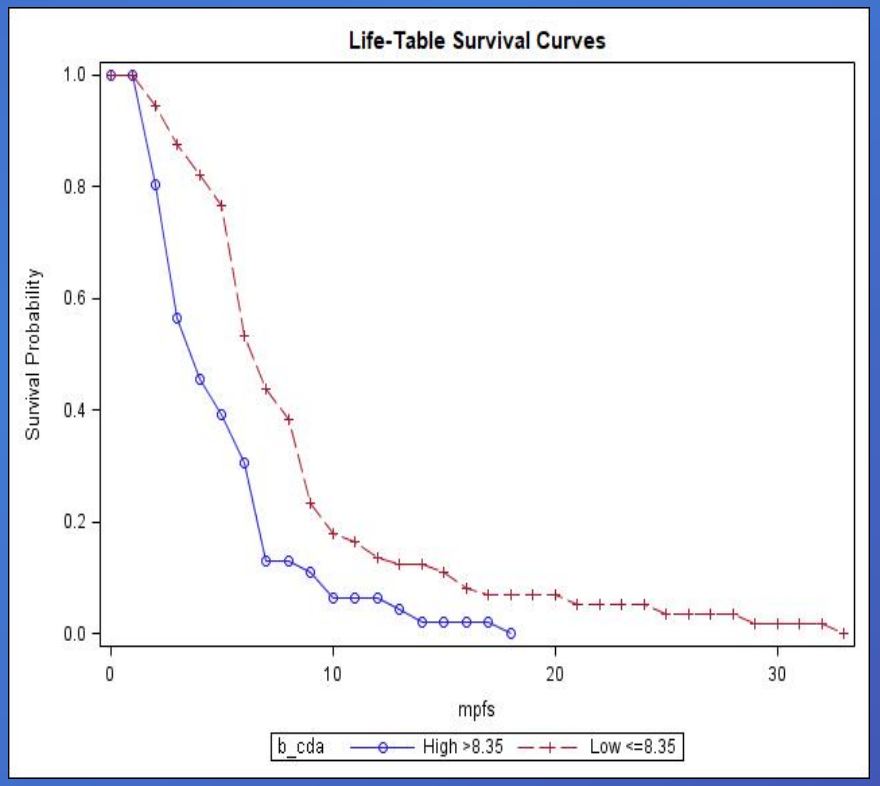
Progression-Free Survival and Overall Survival CDA enzymatic activity

	PFS (95% CI)	P	OS (95% CI)	P
Low ≤7.2	7.5 (6.0-9.0)	<0.001*	13.9 (12.5-23.7)	<0.001*
High >7.2	5.5 (4.5-6.5)		9.4 (7.6-11.5)	

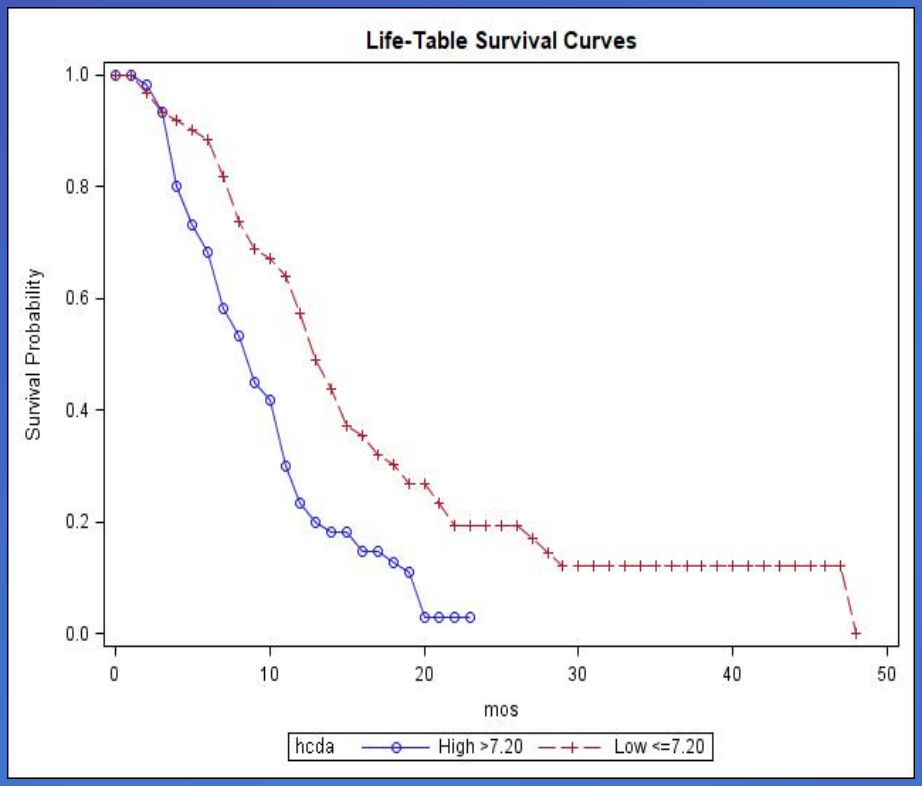
*Statistically significant

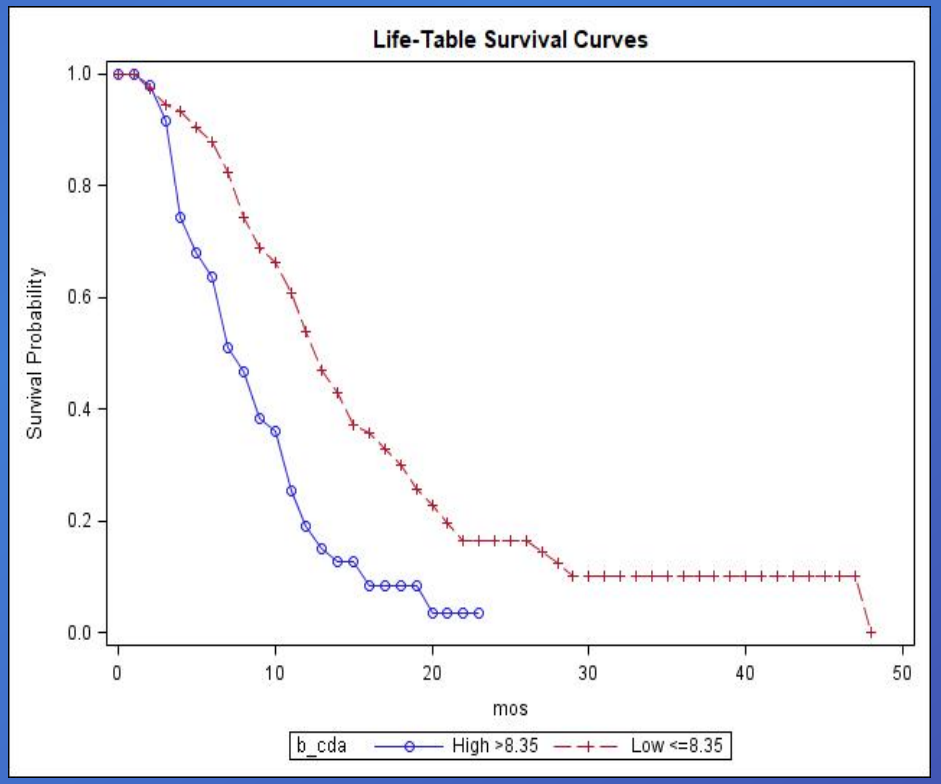
Progression-Free Survival and CDA enzymatic activity





Overall Survival and CDA enzymatic activity





Conclusions I

- CDA-enzymatic activity evaluated by spectrophotometric assay is confirmed to be, in a multicenter prospective study, a strong prognostic marker of activity and efficacy in patients treated with platinum/gemcitabine

- This marker should be validated as predictive biomarker in a phase III clinical study

Conclusions II

Platinum/gemcitabine:

- Nasopharynx cancer
- NSCLC:adjuvant and neoadjuvant settings
- Ovarian carcinoma
- Triple negative breast cancer
- Bladder carcinoma
- Bile duct cancer

Gemcitabine-combinations:

- Pancreatic carcinoma
- Sarcomas of soft tissue

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