



INSTITUT ZA ONKOLOGIJU  
I RADIOLOGIJU SRBIJE

NATIONAL CANCER RESEARCH CENTER

# INDUCTION THERAPY WITH CYTARABINE POTENTIATED 5FU-CDDP REGIMEN IN ADVANCED HEAD AND NECK CANCER (HNC); A REPORT OF 538 PATIENTS

Svetislav Jelic, Miroslav Kreacic, Slavko Vucicevic, Natasa Jovanovic, Tamara Ursulovic,  
Dusica Gavrilovic, Nada Babovic

## INTRODUCTION

After our first randomized study demonstrating response and survival benefit for short infusional Cytarabine (CAR) 1000 mg/m<sup>2</sup> applied 6 hours before Cisplatin in order to potentiate its cytotoxicity in the standard 5FU-CDDP regimen in locally advanced HNC pts (unresectable T4, N2c-3), two additional studies were done. One compared potentiation with CAR 500 mg/m<sup>2</sup> vs. CAR 1000 mg/m<sup>2</sup> and the other the 5FU-CDDP regimen with 4h infusion 5FU versus continuous infusional 5FU, in both arms CDDP being potentiated with CAR 500 mg/m<sup>2</sup>. A meta-analysis of the 3 trials was performed in order to assess response (important for downstaging or downsizing nodal disease with better prospect for radiotherapy) and survival in three Cohorts in which all patients from the 3 studies could be allocated.

## THE THREE LOCAL TRIALS INCLUDED IN THE PRESENT META-ANALYSIS

- Randomized study comparing the classical 5FU-CDDP regimen with the same regimen but with Cisplatin potentiation by Cytarabine 1000 mg/m<sup>2</sup> applied 6 hours before Cisplatin
  - Randomized study comparing Cisplatin potentiation in the same regimen by either Cytarabine 1000 mg/m<sup>2</sup> or Cytarabine 500 mg/m<sup>2</sup>
  - Randomized study with both arms receiving potentiation of Cisplatin by Cytarabine 500 mg/m<sup>2</sup> but with 5FU being applied either as a continuous infusion or a 4-hour infusion
- Irradiation in all 3 trials = 66-70 Gy, 2 Gy per day, 5 days per week

## SUMMARY OF RESULTS IN INDIVIDUAL STUDIES

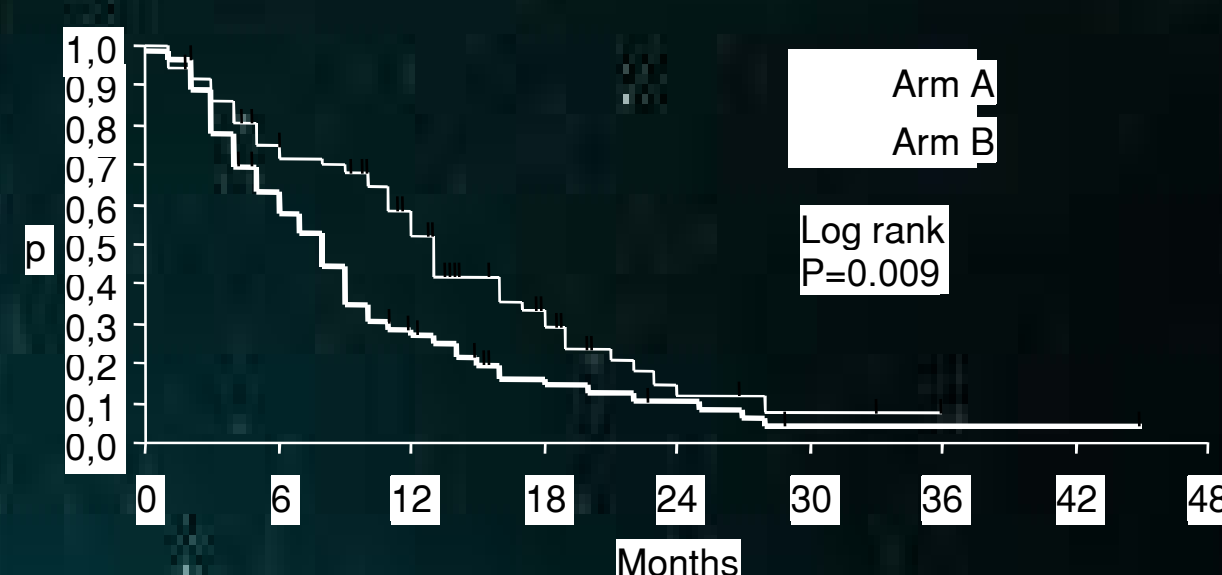
- Both response rate, downstaging and survival are positively affected when Cisplatin in the 5FU-CDDP regimen is potentiated with Cytarabine 1000 mg/m<sup>2</sup>; some excess toxicity is observed
- No difference in RR and survival between arms receiving Cisplatin potentiation with either Cytarabine 1000 mg/m<sup>2</sup> or 500 mg/m<sup>2</sup>
- No difference in RR and survival between arms receiving potentiation of Cisplatin by Cytarabine 500 mg/m<sup>2</sup>, with 5FU applied either as a continuous infusion or a 4-hour infusion

## THE COHORTS

- Cohort 1: 5FU-CDDP only  
Intent-to-treat: 83 patients  
Evaluable: 81 patient
- Cohort 2: 5FU-CDDP + CAR 1000 mg/m<sup>2</sup>  
Intent-to-treat: 153 patients  
Evaluable: 141 patient
- Cohort 3: 5FU-CDDP + CAR 500 mg/m<sup>2</sup>  
Intent-to-treat: 246 patients  
Evaluable: 212 patients

**STATISTICAL ANALYSIS:** Response rates and PD rates calculated on evaluable patient basis; survival data calculated on intent-to-treat basis; toxicities calculated per number of cycles; chi-square used for detecting differences in RR, PDR, toxicity; log-rank used for detecting difference in survival; death hazard ratio and 95% CI was determined; Cox regression analysis used for assessment of survival predictors; Cut-off significance level with the Bonferroni correction fixed at p=0.02

## RESULTS OF FIRST TRIAL DEMONSTRATING BENEFIT OF CAR POTENTIATED REGIMEN OVER 5FU-CDDP ALONE



Median survival with CAR = 13 months, without CAR = 8 months

## THE RESPONSE RATES

Parameter	Cohort 1 N patients	Cohort 2 141	Cohort 3 212
CR	7 (9%)	13 (9%)	10 (5%)
PR	29 (36%)	74 (53%)	130 (61%)
SD	10 (12%)	23 (16%)	41 (19%)
PD	35 (43%)	31 (22%)	31 (15%)
RR	36 (45%)	87 (62%)	140 (66%)
PDR	35 (43%)	31 (22%)	31 (15%)

PDR = progressive disease rate

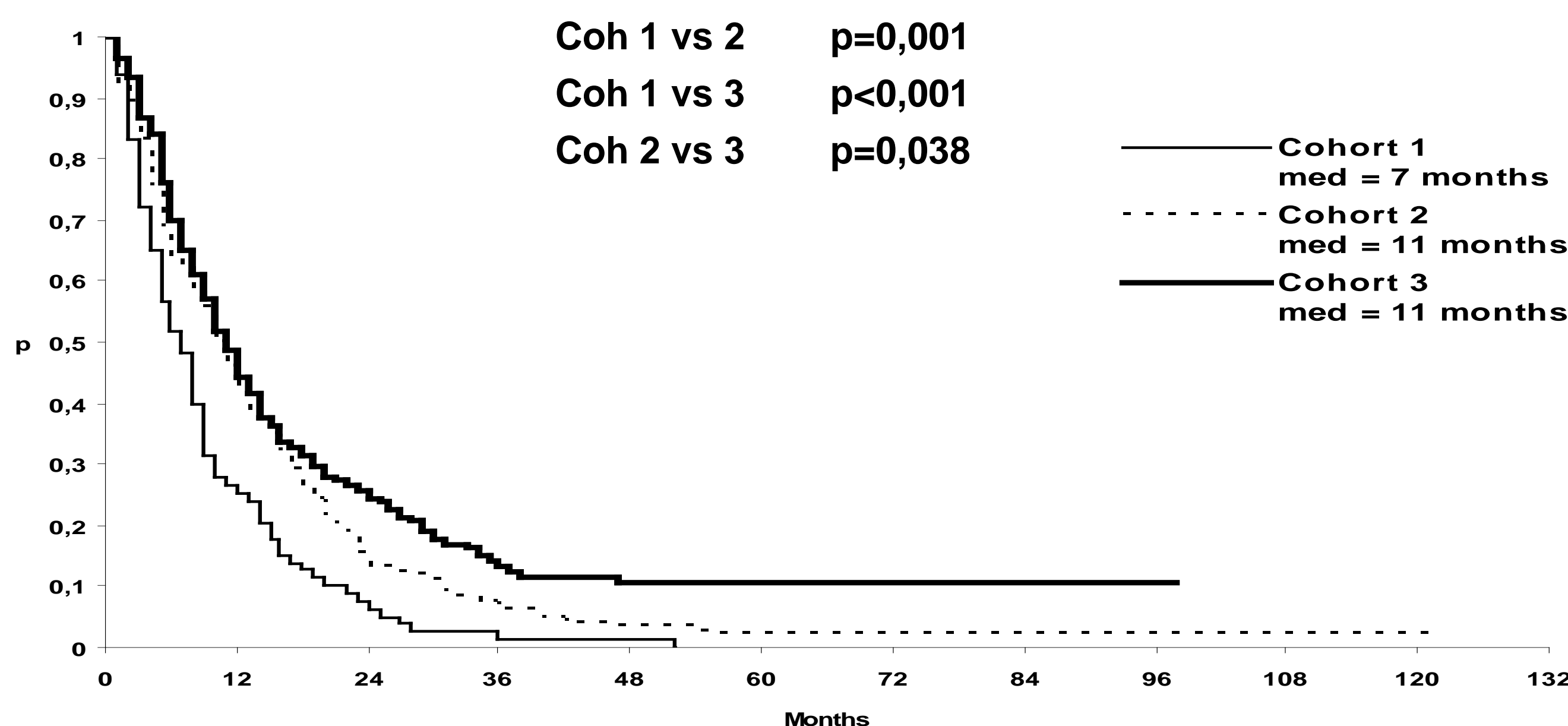
## TOXICITIES

Parameter	Cohort 1 N cycles	Cohort 2 555	Cohort 3 848
Granulocytes IV14	12 (4%)	77 (14%)	82 (10%)
Platelets IV	8 (2%)	22 (4%)	11 (1%)
HB III-IV	89 (27%)	147 (29%)	166 (20%)
Nausea any	19 (6%)	18 (4%)	35 (4%)
BUN any	27 (8%)	33 (6%)	67 (8%)

## SUMMARY OF ACTIVITY AND TOXICITY DATA

- No statistically significant difference for RR and PDR between Cohorts 2 and 3
- Cohort 2 vs. Cohort 1: difference in RR p=0.012, in PDR p=0.001
- Cohort 3 vs Cohort 1: difference in RR p<0.001, in PDR p<0.001
- Non-hematological toxicities identical in all three Cohorts
- Granulocytopenia gr IV significantly more frequent in Cohorts 2 and 3 but with no excess infections
- Thrombocytopenia gr IV significantly more frequent in Cohort 2; no difference in platelet toxicity between Cohorts 1 and 3

## Overall survival



## COX REGRESSION MODEL FOR OVERALL SURVIVAL (Likelihood ratio test: p < 0.001)

Actual treatment	Cohort 2 : Cohort 1 Cohort 3 : Cohort 1	HR = 0,60 HR = 0,56
Performance status	PS 2+3 : PS 0+1	HR = 1,25
Primary tumor localization	Mesopharynx : Hypopharynx + Larynx	HR = 1,06

## CONCLUSIONS:

1. Potentiation of Cisplatin by Cytarabine in the 5FU-CDDP regimen results in both response and survival benefit in locally advanced head and neck cancer patients
2. Potentiation of Cisplatin by Cytarabine in the 5FU-CDDP regimen in the Cox model appears as the strongest factor that positively affects survival in dismal prognosis head and neck cancer patients

## INTERIM REPORT OF INDUCTION CHEMOTHERAPY PRECEEDING CHEMORADIOTHERAPY

### TREATMENT SCHEDULE

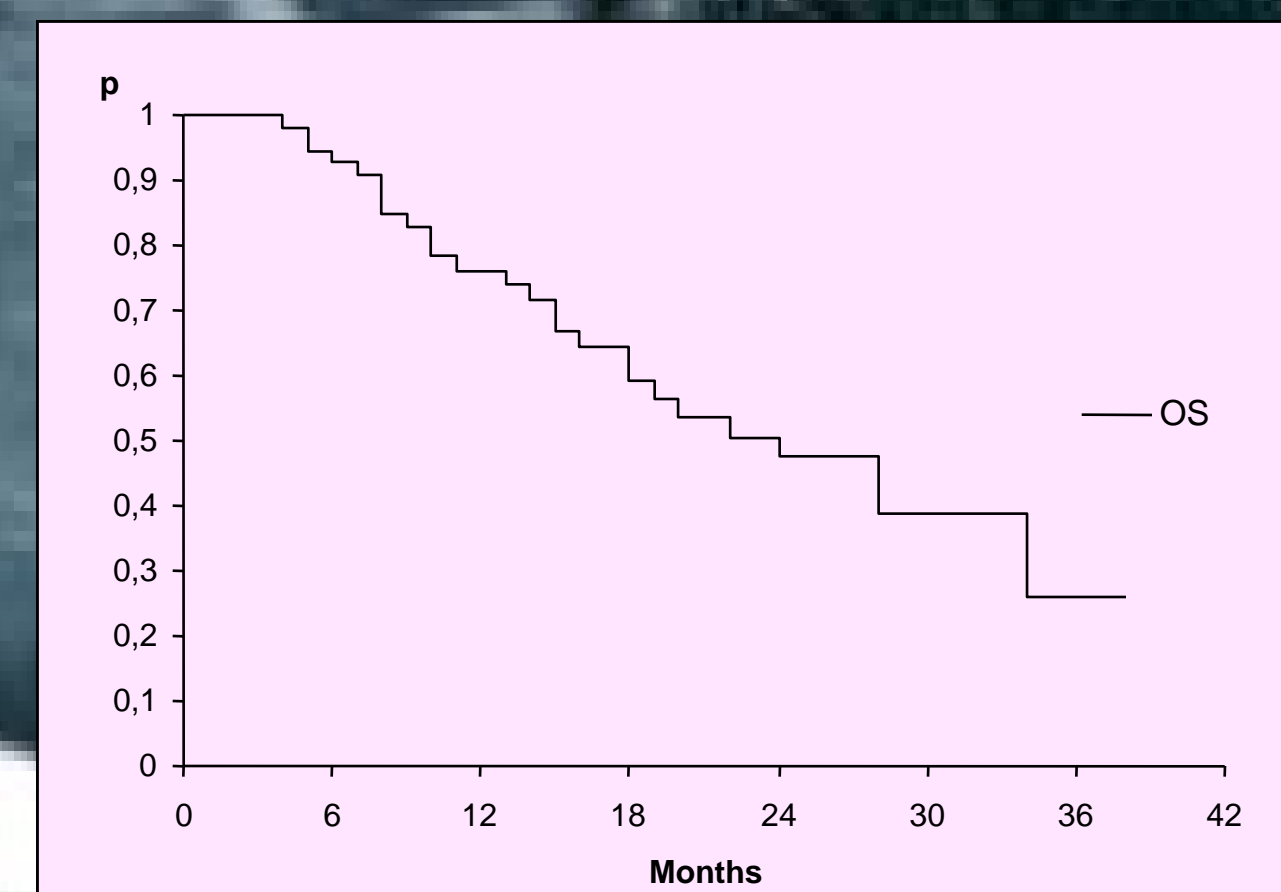
Neoadjuvant chemotherapy  
Day 1: Cytarabine 500 mg/m<sup>2</sup>, one hour infusion in 250 ml 0,9% NaCl at 9h 00 Cisplatin 120 mg/m<sup>2</sup> with forced osmotic and saline diuresis at 15h 00 5-FU 750 mg/m<sup>2</sup>/24h as continuous infusion  
Days 2-5: 5-FU 750 mg/m<sup>2</sup>/24h as continuous infusion  
total number of cycles is 3 Intercycle interval is 21 days  
B) Chemoradiotherapy  
Starts 3 to 4 weeks after the end of the 3rd chemotherapy cycle 2 Gy per day, 5 days per week, total dose 66-70 Gy  
Cisplatin 60 mg/m<sup>2</sup> on days 1, 22 and 43 of irradiation treatment

### ANALYSIS OF TIMING AND SCHEDULE OF TREATMENT MODALITIES

“Regular patients”  
3 cycles of neoadjuvant chemotherapy, 3 cycles of concomitant chemotherapy, full irradiation dosage, right timing  
N = 33  
“Irregular patients”  
N = 23  
- incomplete radiotherapy ..... 5  
- neoadjuvant chemotherapy interrupted because of toxicity ..... 6  
- less than 3 cycles of concomitant chemotherapy with radiotherapy delays ..... 12

**POTENTIATION OF CDDP BY CAR IN 5FU-CDDP INDUCTION TREATMENT PRECEEDING RADIOTHERAPY OR CHEMORADIOTHERAPY IMPROVES BOTH RR AN SURVIVAL. HOWEVER, ANY IRREGULARITIES IN THE SCHEDULE OR TIMING IN THE COMBINED REGIMEN HAVE A DELETERIOUS EFFECT ON SURVIVAL**

Survival for the whole group. After a median follow-up of 20 months the median survival is 24 months



The median survival for “ Irregular patients“ is 14 months. The median survival for “Regular patients“ has not been reached and is at the moment 28+ months (p=0.019)

