SIMPOSIO LABORATOIRES GENOPHARM

Il ruolo dell'amifostina nel trattamento dei tumori testa e collo

Moderatori: R.J. Bensadoun (Poitiers - F), R. Corvò (Genova)

Five years experience of treatment with Amifostine in head & neck (H&N) cancer

Giovanni Silvano

S.C. Radioterapia Oncologica, Ospedale S. G. Moscati – ASL Taranto

Radiotherapy (RT) in H&N cancer

- RT plays a main role in the management of H&N cancer as single modality or concurrent with chemotherapy or Cetuximab (RCT)
- RT and RCT can be given as primary treatment modality or after surgery
- RT and RCT cause acute mucositis and acute and chronic xerostomia
- Amifostine can ameliorate these side effects without compromising treatment effectiveness *(Brizel DM, JCO 2000)*

Amifostine and RT in H&N cancer

Amifostine can ameliorate RT side effects without compromising treatment effectiveness

JCO, 2000;18:3339

Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer

By David M. Brizel, Todd H. Wasserman, Michael Henke, Vratislav Strnad, Volkar Rudat, Alain Monnier, Francois Eschwege, Jay Zhang, Lesley Russell, Wolfgang Oster, and Rolf Sauer

IJROBP, 2002; 52: 739

CLINICAL INVESTIGATION Head and Neck

PROPHYLACTIC USE OF AMIFOSTINE TO PREVENT RADIOCHEMOTHERAPY-INDUCED MUCOSITIS AND XEROSTOMIA IN HEAD-AND-NECK CANCER

Dosia Antonadou, M.D., Marizenia Pepelassi, M.D., Maria Synodinou, M.D., Maria Puglisi, M.D., and Nicolas Throuvalas, M.D.

IJROBP, 2006;64:684

CLINICAL INVESTIGATION Head and Neck

INTRAVENOUS AMIFOSTINE DURING CHEMORADIOTHERAPY FOR HEAD-AND-NECK CANCER: A RANDOMIZED PLACEBO-CONTROLLED PHASE III STUDY

Jens Buentzel, M.D.,* Oliver Micke, M.D.,† Irenaus A. Adamietz, M.D.,‡ Alain Monnier, M.D.,§ Michael Glatzel, M.D.,‖ and Alexander de Vries, M.D.¶

RT: Chronic xerostomia ≥ 2

57% vs 34% p= 0.002

Acute mucositis: n.s.

RCT: Chronic xerostomia ≥ 2
30% vs 5% p= 0.047

G4 Acute mucositis:
52% vs 5% p=0.0006

RCT randomized trial:

Acute mucositis: n.s.

Chronic xerostomia ≥ 2 n.s.

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Our experience with Amifostine

- 243 pts with H&N cancer treated with 3D RT o RCT Between 2005 and 2010
- Dose prescription:
  - 70 Gy were prescribed to tnPTV for definitive RT;
  - 60Gy after R0 surgery (66 - 70Gy to R1-2 pts)
  - 50Gy to pnPTV
- 170/243 pts received a radiation dose ≥ 50Gy on both parotid glands *(standard fractionation)*
- Amifostine (200mg/m^2) was daily administered i.v. to
  - 86/170 pts 15-30 minutes before RT: RTA group
  - 84/170 pts did not received Amifostine: RT group

Patients distribution and characteristics

	RTA group	RT group	Tot pts (86+84)
mean age (yrs)	59 (37-84)	62 (31-84)	60.5
PS 0/1	82/4	68/16	150/20
Gender m/f	74/12	74/10	148/22
Definitive RT	45	32	77
RT for local relapse	8	13	21
Post-operative RT	33	39	72
Surgery: R1	10	8	18
Surgery: pT3-4	16	29	45
Surgery: pN2-3	23	17	40
CDDP 100/30	39/27	15/19	54/46
Cetuximab	2	4	6
No Chemo	18	46	64

Amifostine not administered	84 pts
Physician decision	47 pts
hypotension	19 pts
comorbidities	16 pts
allergies	1 pt
patient refusal	1 pt

PS = performance status

RTA = treated with Amifostine

RT = treated without Amifostine

CDDP100 = 100mg/m^2 3wks

CDDP30 = 30 mg/m^2 weekly

Distribution of PTV50 mean volume (cc) according to cancer site, CT and Amifostine administration

Site	RTA + RCTA 86 pts	RT + RCT 84 pts	RTA mean cc (min-max)	RT mean cc (min-max)	RCTA mean cc (min-max)	RCT mean cc (min-max)
Oral cavity	22	24	586 (337-831)	865 (340-1355)	773 (329-1217)	726 (349-1180)
Nasopharynx	20	4	750 (1pt)	975 (1pt)	1200 (738-1572)	983 (839-1128)
Oropharynx	21	13	691 (397-1084)	802 (340-1355)	827 (341-1320)	764 (399-1087)
Hypopharynx	6	8	651 (585-717)	659 (530-784)	778 (393-1098)	880 (599-1176)
Larynx	15	30	655 (484-826)	574 (134-1090)	828 (367-1332)	784 (253-1100)
Miscellaneous	2	5	==	307 (170-430)	745 (526-965)	==

pts =number of patients; RTA =RT + amifostine; RCTA= RT+CT+Amifostine

CDDP Dose-Intensity (DI) ac
Amifostine administra

CDDP DI: 100mg/m² RTA < RT 30 mg/m² RTA > RT

Treatment	DI RTA group	DI RT group	Total DI
Definitive RCT			
CDDP 100mg/m²	0.64	0.91	0.69
CDDP 30mg/m²	0.48	0.56	0.51
Induction CT & definitive RCT			
CDDP 100mg/m²	0.75	0.83	0.77
CDDP 30mg/m²	0.87	0.29	0.62
RCT for local relapse			
CDDP 100mg/m²	0.46	No pts	0.46
CDDP 30mg/m²	0.28	0.89	0.77
Post-operative RCT			
CDDP 100mg/m²	0.70	0.88	0.82
CDDP 30mg/m²	0.80	0.60	0.76

CDDP DI has been calculated as ratio of CDDP given on planned

Amifostine Dose-Intensity (DI) according to CDDP/CTX administration

Amifostine DI	pts	100 mg/m² 3wks (n. pts)	30 mg/m² weekly (n. pts)	CTX (n. pts)	RT only (n. pts)
pts tot	86	37	29	2	18
0.9 – 1.0	34 (40%)	30% (11)	48% (14)	0	50% (9)
0.80 – 0.89	4	2% (1)	3% (1)		
0.70 – 0.79	4	2% (1)	7% (2)		
0.60 – 0.69	16	16% (6)	28% (8		
< 0.60	28	50% (18)	14% (4		

CDDP = Cisplatin; CTX= Cetuximab

Amifostine DI has been calculated as ratio of Amifostine a
radiotherapy fractions

Amifostine:	DI%	pts %
CDDP 100	≥ 80%	32%
“” “”	< 60%	50%
CDDP 30	≥ 80%	51%
“” “”	< 60%	14%
RT only	≥ 80%	55%
“” “”	< 60%	33%

Amifostine Dose-Intensity (DI) according to CDDP/CTX administration

definitive *vs* post-operative RT

Amifostine DI	pts	100 mg/m2 3wks % (n. pts)		30 mg/m2 weekly % (n. pts)		CTX % (n. pts)		RT only % (n. pts)	
tot	86	(28)	PORT (9)	(15)	PORT (14)	(2)	P (0)	(8)	P(10)
0.9 – 1.0	34	37 (10)	11 (1)	53 (8)	43 (6)	0	0	62 (5)	40 (4)
0.80 – 0.89	4	0	11 (1)	0	7 (1)	50 (1)	0	0	10 (1)
0.70 – 0.79	4	3 (1)	0	7 (1)	7 (1)	0	0	12 (1)	0
0.60 – 0.69	16	14 (4)	22 (2)	33 (5)	21 (3)	50 (1)	0	0	10 (1)
< 0.60	28	46 (13)	55 (5)	7 (1)	21 (3)	0	0	25 (2)	40 (4)

86 pts: CDDP = Cisplatin; CTX= Cetuximab; PORT = Post-ope

Amifostine DI has been calculated as ratio of Amifostine ad
radiotherapy fractions

Amifostine DI:

No difference between definitive *vs* post operative RT or RCT

RT Dose (D%) according to CDDP and administration in the Amifostine group

RT dose %	100 mg/m2 3wks n. pts (%)	30 mg/m2 weekly n. pts (%)	RT only n. pts (%)
Definitive RT or RCT			
90-100	100	100	100
80-89	0	0	0
< 80	0	0	0
Post-operative RT or RCT			
90-100	100	100	100
80-89	0	0	
< 80	0	0	

RT D% has been calculated as percentage of the planned dose given

All pts received full RT dose also when Amifostina was administered

RT and CDDP/CTX definitive discontinuance according to Amifostine administration

86 + 84 pts	RTA group (%)	RT group (%)	Total (%)
RT discontinuation	0/86	4/84 (5)	4/170 (2.5)
Dose < 50Gy	0	0	0
Dose < 60Gy	0	2 (2.5)	2 (1.2)
Dose < 70Gy	0	2 (2.5)	2 (1.2)
CDDP discontinuation	45/68 (66)	18/38 (47)	63/106 (59)
CDDP 100mg/m2	26/37 (70)	4/16 (25)	30/53 (57)
CDDP 30mg/m2	17/29 (59)	13/18 (7	
CTX discontinuation	2/2 (100)	1/4 (2	

CDDP = Cisplatin; CTX= Cetuximab

RT was not discontinued when Amifostina was administered *vs* 5% in the not Amifostine group
CDDP was discontinued more frequently in RTA group when administered as 100mg/m²

Amifostine definitive discontinuance according to CT schedule

Amifostine G4 Toxicity	No CT	RCT group CDDP 100 mg/m²	RCT group CDDP 30 mg/m²	CTX	total
Pts	18	37	29	2	86
Nausea	0	0	0	0	0
Vomiting	2 (11%)	7 (19%)	1 (3)	0	10 (12)
Hypotension	8 (44%)	22 (59%)	18 (62%)	2 (100)	50 (58)
Allergic reaction	3 (17%)	2 (5)	0	0	5 (6)
Asthenia	0	0	0	0	0
No discontinuance	5 (28)	6 (16)	10 (34)	0	21 (24)

CDDP = Cisplatin; CTX= Cetuximab

Amifostine was discontinued in 75% of pts mainly for hypotension (44-60%) and vomiting (19%)

Compliance

- CDDP DI: 100mg/m^2 RTA < RT
  30 mg/m^2 RTA > RT
- RT Dose: No RT discontinuance in the Amifostine treated pts (RTA group) *vs* 5% in the RT group
- Amifostine DI: according to CDDP schedule
  - ≥ 80 for 32-55% of pts **(100 – 30 mg/m^2)**
  - < 60 for 14-50% of pts **(30 – 100 mg/m^2)**
- Amifostine discontinuance (75%) mainly for hypotension (44-60%)

Acute Toxicity

- toxicity was recorded weekly during RT or RCT
- Mucositis was retrospectively evaluated and graduated according to CTCAE scale (ver 4.0)
- Amifostine, CDDP and RT or RCT discontinuance was recorded on pts medical charts
- Acute toxicity has been evaluated on all pts

G3-4 acute mucositis according to Amifostine Dose-Intensity (DI) and CDDP administration

Amifostine DI 86 pts	100 mg/m2 3wks n. pts (%)	30 mg/m2 weekly n. pts (%)	CTX n. pts (%)	RT only n. pts (%)	Tot. %
Definitive RT/RCT	**28**	**15**	**2**	**8**	**53**
0.81 – 1.0	2/10	3/8	0/1	1/5	6/24 **25%**
0.61 – 0.8	2 (G4 1pt)/5	2/6	1/1	1/1	6/13 **46%**
≤ 0.60	3 (G4 1pt)/13	0/1	0	1/2	4/16 **25%**
PORT	**9**	**14**	**0**	**10**	**33**
0.81 – 1.0	1/2	0/7	0	3/5	4/14 **28%**
0.61 – 0.8	1 (G4 1pt)/2	0/4			1/7 **14%**
≤ 0.60	0/5	1/3			2/12 **14%**
Tot.	**9/37 (24)**	**6/29 (21)**			**23/86**

Total G3-4 acute mucositis = 27%

No difference in acute mucositis according to CDDP schedule or Amifostine DI

Amifostine DI has been calculated as ratio of Amif umber of radiotherapy fractions ; CTX = Cetuximab

Mean definitive RT dose for G3/G4 acute mucositis (am) according to Amifostine administration and CT schedule

Definitive RT or RCT ± neoadjuv. CT		RTA group (53)	RT group (44)	Total 97 pts
RT ± CTX	**n. pts 4/10 + 13/29**	mean dose Gy (range)	mean dose Gy (range)	mean dose Gy (range)
Mean dose for G3 am	4 + 12	49 (46-56)	48 (46-56)	48.2 (46-56)
Mean dose for G4 am	0 + 1	===	50 (48-52)	50 (48-52)
RCT CDDP 100mg/m^2	**n. pts 7/28 +3/6**			
Mean dose for G3 am	5 + 3	46 (44-48)	46 (42-50)	46 (42-50)
Mean dose for G4 am	2 + 0	47 (44-50)	===	47 (44-50)
RCT CDDP 30mg/m^2	**n. pts 5/15 +2/9**			
Mean dose for G3 am	5 + 2	46 (44-50)	47 (42-50)	46.3 (42-50)
Mean dose for G4 am	0	===	===	===
Total	**n. pts 16/53 +18/44**	46.8 (44-56)	48 (42-56)	47.4 (42-56)

CTX = Cetuximab , 5 pts

G3-4 acute mucositis occurs at the same mean dose level in RTA *vs* RT pts

Mean Post-operative RT dose for G3/G4 acute mucositis (am) according to Amifostine administration and CT schedule

Definitive RT or RCT ± neoadjuv. CT		RTA group (33)	RT group (40)	Total 73 pts
RT ± CTX	**n. pts 4/10 + 4/21**	mean dose Gy (range)	mean dose Gy (range)	mean dose Gy (range)
Mean dose for G3 am	4 + 4	49 (46-52)	44.7 (44-46)	46.8 (44-52)
Mean dose for G4 am	0	===	===	===
RCT CDDP 100mg/m^2	**n. pts 2/9 + 2/10**			
Mean dose for G3 am	1 + 2	46	44 (42-46)	44.7 (44-46)
Mean dose for G4 am	1 + 0	50	===	50
RCT CDDP 30mg/m^2	**n. pts 1/14 + 3/9**			
Mean dose for G3 am	1 + 1	44	47	45.5 (44-47)
Mean dose for G4 am	0 + 2	===	49 (48-50)	49 (48-50)
Total	**n. pts 7/33 + 9/40**	48 (44-52)	45.7 (42-50)	46.7 (42-52)

G3-4 acute mucositis occurs at the same mean dose level in RTA *vs* RT pts

Follow-up procedures

- Pts were clinically evaluated for mucositis and xerostomia once a month for 3 months and every 3 months thereafter
- Chronic xerostomia was retrospectively evaluated and graduated according to CTCAE scale (ver 4.0)
- Local control (LC) was evaluated according to RECIST criteria (ver. 1.1)
- Chronic toxicity and LC were recordered in 145 pts with a longer than 6 months follow-up (25 pts lost at F-UP)

Amifostine administration and CT schedule

Definitive RT or RCT ± neoadjuvant CT		RTA group (81)	RT group (64)	Total 145 pts
RT ± CTX	**n. pts 4/16 + 18/40**	mean dose Gy (range)	mean dose Gy (range)	mean dose Gy (range)
Mean dose for G2 cx	4 + 15	53 (50-56)	52 (50-60)	52.4 (50-60)
Mean dose for G3 cx	0 + 3	0	53 (50-57)	53 (50-57)
RCT CDDP 100mg/m^2	**n. pts 15/36 + 7/14**			
Mean dose for G2 cx	11 + 3	58 (50-66)	55 (50-62)	57.3 (50-66)
Mean dose for G3 cx	4 + 4	54 (50-62)	56 (52-61)	55 (50-62)
RCT CDDP 30mg/m^2	**n. pts 12/29 + 7/10**			
Mean dose for G2 cx	9 + 2	53 (50-60)	50	52.4 (50-60)
Mean dose for G3 cx	3 + 5	50	53 (50-55)	52 (50-55)
Total	**n. pts 31/81 + 32/64**	54.6 (50-66)	53 (50-62)	53.8 (50-62)

No G4 cx toxicity ha
5/86 in RTA group a

G2-3 chronic xerostomia occurs at the same mean parotid dose level in RTA *vs* RT pts

Acute mucositis (am) and chronic xerostomia (cx) according to cancer site

Site	RTA pts	RT pts	RTA am	RT am	RTA cx	RT cx
Oral cavity	22	24	13%	33%	50% (2 pts G3)	44% (2 pts G3)
Nasopharynx	20	4	30% (2 pts G4)	50%	38% (1 pt G3)	33%
Oropharynx	21	13	33%	23%	38% (2 pts G3)	(5 pts G3)
Hypopharynx	6	8	16%	(1 pt G4)	16%	43%
Larynx	15	30	40% (1 pt G4)	(1 pt G4)	33% (2 pts G3)	(5 pts G3)
Miscellaneous	2	5				

pts =number of patients; only am

Chronic Xerostomia RTA (38%) n.s.
***vs* RT (50%) = n.s.**

Dose-Intensity (DI) and CDDP administration

Amifostine DI 81 pts*	100 mg/m2 3wks n. pts	30 mg/m2 weekly n. pts	CTX n. pts	RT only n. pts	Tot. %
Definitive RT/RCT	**25**	**15**	**1**	**7**	**48**
0.81 – 1.0	2/9	2/8	0/1	2/5	6/23 **26%**
0.61 – 0.80	2/4	3/6	0	0/1	5/11 **45%**
≤ 0.60	9/12	0/1	0	0/1	9/14 **64%**
PORT	**9**	**14**	**0**	**10**	**33**
0.81 – 1.0	1/2	1/6	0	1/4	3/12 **25%**
0.61 – 0.80	0/1	3/3	0	0/1	3/5 **60%**
≤ 0.60	2/6	2/5	0	1/5	5/16 **31%**

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χ 2 4.11 OR 2.65 (1.02-6.87)

“” “” **> 60% *vs* ≤ 60% : 30% *vs* 56% p 0.03** χ 2 4.81 OR 2.92 (1.10-7.73)

“” “” **> 60% *vs* no amifostine: 30% *vs* 50% p 0.03** χ 2 4.77 OR 0.47 (0.21-1.07)

XX

administration

Amifostine group: 68%

- Non Amifostine group: 48%

Conclusions

reduces CDDP compliance (100mg/m2) and *vice versa*

- Amifostine does not reduce acute mucositis
- Amifostine prevents chronic xerostomia significantly if given for more than 60% of RT fractions
- Amifostine does not decrease local control