WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

TOSSICITA' NELLE ASSOCIAZIONI CON LE TERAPIE SISTEMICHE

Icro Meattini

Radioterapia Oncologica
Azienda Ospedaliero - Universitaria
Careggi, Firenze

OVERVIEW

- Background
- Adjuvant chemotherapy
- Trastuzumab and biologic drugs
- Conclusions

OVERVIEW

- **Background**
- Adjuvant chemotherapy
- Trastuzumab and biologic drugs
- Conclusions

BACKGROUND

- In breast cancer, radiation therapy improves local control rate and survival.

- When chemotherapy and radiation are indicated the sequencing of the two treatments is still debated.

- The optimal sequencing of chemotherapy and radiotherapy after surgery was largely studied but remains controversial.

Calais G. Cancer Radiother. 2004;8:39-47

Available studies examining the effect of RT delivery delay after lumpectomy on local recurrence, when RT is administered as sole modality

Study	No of patients	Follow-up (m	RT timing (m)	LRR (%)	*p*-Value	OS	*p*-Value
Huang (4)							
Benk (3 (a							
Vujovic (2							
Nixon (24							
Whelan (2							
Bahena (2							
Slotman (							
Hebert-Cr							
Hershman							
Mikeljevi							

Available studies examining the sequence of CT-RT administration

Study	No of patients	Follow-up (m	RT timing (m)	LRR (%)	*p*-Value	OS	*p*-Value
Hartsel (38)	84	62	<4 >4	2 14	<0.05	–	>0.05
Buchholz (59)	105		>6 <6	2 24	<0.05	80 52	0.016
Recht (60)	295	78	<4 >4	5 35	<0.05	NP	NP
Leonard (61)	262	50?	<4 4–6 >6	5 3–5 2	>0.05	84 95 96	>0.05
Meek (62)	297			4 2	>0.05	91 83	NP
Yock (63)	279	84	<5 5–7 >7	5.5 4.8 7.4	>0.05	NP	NP
Dendale (64 (abstract)	283	83–136	NP CT first vs. RT first group	CT: 24.4 RT: 11	<0.03	9	-
Mc Cormick (65)	471	53–77		RT: 4 CT: 14 San: 4	>0.05		
Buzdar (66)	552	133			>0.05		
Recht, Bellon (67, 36)	244	135		38 (CT) 31 (RT)	>0.05	73 81	0.11 p: 0.41
Benchalal (68)	1831	102	After BCS After 3 CT After 6 CT	92 81.5 87.4 (L-DCIS)	<0.001 NS in multivariate analysis	48.4 76.9	<0.001
Metz (69)	221	50	<2 2–6 >6	13 4 12	>0.05	NP	NP
Hickey BE (70) Cochrane Collaboration Study (Review)	244 853 concurrent (2 trials)		7 m vs. >7 m		>0.5		

•
•Co
trea

63-70

2-116

39-47

BACKGROUND

•Fc al
rec nt
wit

Age
Surgical Margins
Lymph vascular invasion
Tumor size
Hormonal Status

•**Concomitant radio-chemotherapy** remains in principle an attractive treatment schedule to provide an additive interaction of tumor control and shortening the overall treatment time.

Bese NS. Clin Oncol (R Coll Radiol). 2009;21:532-5.
Ruo Redda MG, et al. Cancer Treat Rev. 2002;28:5-10.

OVERVIEW

- Background
- **Adjuvant chemotherapy**
- Trastuzumab and biologic drugs
- Conclusions

CMF

•156 patients underwent CMF chemotherapy and radiotherapy, either concurrently (CCRT group, 88 patients) or sequentially (SCRT group, 68 patients).

•The planned radiotherapy was completed in every patient.

•No grade 3 or 4 late treatment-related toxicity was observed in the CCRT or SCRT group. Compliance to the treatment as well as cosmetic outcome of the two groups were comparable.

•On multivariate analysis, concomitant administration of chemotherapy and radiotherapy was associated with improved local-regional control *(p = 0.0463)*.

Kim K, Chie EK, Han W, et al. Tumori. 2011;97:280-5.

CMF

•206 patients randomized to concurrent or sequential radiotherapy with CMF regimen *(Phase III trial)*.

•No differences in 5-year breast recurrence-free, metastasis-free, disease-free, and overall survival were observed in the two treatment groups.

•All patients completed the planned radiotherapy.

•No evidence of an increased risk of toxicity was observed between the two arms.

•No difference in radiotherapy and in the chemotherapy dose intensity was observed in the two groups.

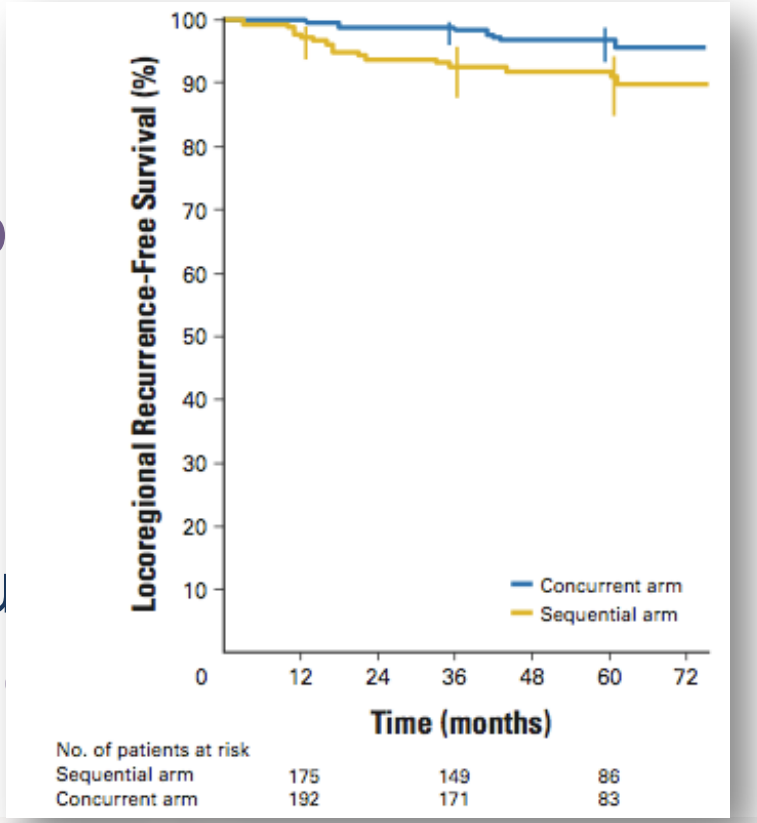
Arcangeli G, et al. IJROBP. 2006;64-161-7

	FNC + RT (n = 324)	FEC → RT (n = 314)	p
Type of toxicity			
Leukopenia, Grade 3–4	43 (14)	4 (<1)	$<10^{-4}$
Anemia, Grade 3	2 (<1)	0	0.49
Nausea–vomiting, Grade 3–4	39 (12)	54 (18)	0.065
Febrile neutropenia with hospitalization*	10 (1)	1 (<1)	0.007
Alopecia, Grade 2–3	27 (8)	154 (50)	$<10^{-4}$
Skin toxicity at RT end†			
Grade 0	23 (7)	37 (12)	0.03‡
Grade 1	206 (64)	208 (67)	
Grade 2	78 (24)	54 (18)	
Grade 3	16 (5)	10 (3)	
Cardiotoxicity			
No. of patients evaluated at 1 y	274	267	
Grade 1: LVEF decrease ≥15%§	7	2	
Grade 2: LVEF decrease ≥15%§ under normal range	10 (6)	4 (2)	0.02‖
Grade 3: Grade 2 + clinical symptoms	0	0	
3-y locoregional toxicity			
Lymphoedema (277/272)	50 (18)	42 (15)	0.41
Pigmentation (274/271)	72 (26)	58 (21)	0.18
Telangiectases (274/271)	55 (20)	36 (13)	0.034

Rouesse J, et al. IJROBP. 2006;64:1072-80

CNF – ARCOS

- Between February 1996 and Ap
- 716 patients
- Mitoxantrone *(12 mg/m²)*, fluorou cyclophosphamide *(500 mg/m²)* days for 6 courses.



- Node-positive subgroup, the 5-year LRFS was statistically better in the concurrent arm *(97% versus 91%; p=0.02)*, risk of locoregional recurrence decreased by 39% *(HR, 0.61; 95% CI 0.38-0.93)*.

Toledano A, et al. J Clin Oncol. 2007;25:405-10

CNF – ARCOSEIN trial

- Acute locoregional and systemic toxicity was mild in both arms.
- Esophagitis was more frequent in the concurrent arm *(p=0.04).*
- Nausea/vomiting was significantly higher in the sequential treatment arm *(p=0.008).*

- Subcutaneous fibrosis, telangectasia, pigmentation, and breast atrophy were significantly increased in the concurrent arm.
- No statistical difference was observed between the two arms concerning grade 2 or greater pain, breast edema, and lymphedema.

Toledano A, et al. J Clin Oncol. 2007;25:405-10

… beyond CMF/CNF

- Pilot studies showed the feasibility of simultaneous administration using CMF or CNF regimens.
- However, CNF is no longer considered as standard adjuvant chemotherapy because of secondary acute myeloid leukemia risk.

Chaplain G, et al. J Clin Oncol 2000;18:2836–2842
Crump M, et al. J Clin Oncol 2003;21:3066–3071

- CMF has been largely replaced by anthracyclines in high risk patients.

Early Breast Cancer Trialists' Collaborative Group. Lancet. 2005;365:1687-1717
Bese NS. Clin Oncol (R Coll Radiol). 2009;21:532-5

Toxicity	Group A No (%)	Group B No (%)	p value
Anemia			
Grade I	35 (32.4%)	25 (19.2%)	0.009
Grade II	13 (12%)	7 (5.4%)	
Grade III	2 (1.9%)	1 (1.3%)	
Grade IV	0		
Neutropenia			
Grade I	13 (12%)	15 (11.5%)	0.4
Grade II	27 (25%)	26 (20%)	
Grade III	8 (7.4%)	8 (6.2%)	
Grade IV	2 (1.9%)	0	
Thrombopenia			
Grade I	2 (1.9%)	2 (1.5%)	0.341
Grade II	2 (1.9%)	0	
Grade III	1 (0.9%)	0	
Grade IV	0	1 (0.8%)	

CMF.

effect of

=0.062), EFS

e 2/3/4 skin

5%; p=0.013).

Ismaili N, et al. Radiation Oncology. 2009;4:12

Anthracyclines

- 60 patients *(2002-2007)*
- Anthracyclines-based regimens *(doxorubicin plus cyclophosphamide or epirubicin followed by CMF)*

- Acute skin G3 (8.9%) and G4 (1.7%) toxicity
- 10.7% LVEF decline >10% and <20%
- Radiotherapy stopped in 21.3% and chemotherapy in 57.1%

Livi L, et al. Radiol Med. 2011;116:1050-8

Anthracyclines

- Concomitant administration of anthracyclines *(e.g. doxorubicin, epirubicin)* is associated with and increased risk of serious skin toxicity.

Fiets WE, et al. Eur J Cancer. 2003;39:1081-1088
Ismaili N, et al. Radiation Oncology. 2009;4:12

- Concerning concomitant treatment, limited data are available but it should be avoided due to the potential risk of augmented cardiac toxicity.

Valagussa P, et al. Ann Oncol. 1994;5:209-216
Shapiro CL, et al. N Engl J Med. 2001;344:1997-2008

- Avoiding concomitant use of RT and anthracylines-based chemotherapy remains the standard of care

J Natl Cancer Inst. 2001;30:S5-11

Taxanes

•20 patients *(1998-1999)* received concurrent adjuvant RT and paclitaxel after doxorubicin-based CT.

- 65% developed > G2 cutaneous toxicity
- (33% G3)

- High incidence pulmonary toxicity (20%)

•Concurrent radiation and paclitaxel should be approached cautiously.

Hanna YM, et al. The Breast Journal. 2002;8:149-153

Taxanes

- RT plus paclitaxel after AC regimen.
- 24 patients *(1999-2001)*. Follow-up 11.5 months
- 33.3% patients had RT stops *(median 3.5 days)*
- None had a chemotherapy dose reduction.
- No cases of pneumonitis.
- Concurrent treatment was well tolerated.

Ellerbroek N, et al. The Breast Journal. 2003;9:74-78

	NCI toxicity grade			
	1	2	3	4
Hematologic				
Absolute neutrophil count	5	13	10	33
Hemoglobin	20	5		
Platelets	5	0		
Febrile neutropenia	0	0		
Nonhematologic				
Hypersensitivity reaction	5	0		
Fatigue	48	15		
Deep vein thrombosis/ pulmonary embolism	0	0		
SGOT/SGPT	8	8		
Arthralgia	28	18		
Myalgia	43	10		
Nausea	20	3		
Vomiting	10	0		
Stomatitis	8	0		
Diarrhea	10	5		
Dyspepsia	10	0		
Sensory neuropathy	50	5		
Hypertension	3	0		
Hyperglycemia	8	3		

		Pneumonitis (any grade)	
Patient subset	No.	No.	Percent
All patients	40	7	18%
Nodal irradiation	27	6	22%
Tangents, only	13	1	8%
Weekly paclitaxel	16	3	19%
Nodal irradiation	10	2	20%
Tangents, only	6	1	14%
Every-3-week paclitaxel	24	4	17%
Nodal irradiation	17	4	24%
Tangents, only	7	0	0%
IMN radiotherapy			
Yes	8	1	13%
No	32	6	19%
Radiation dermatitis			
Grade 0–1	32	6	19%
Grade 2	8	1	13%

among patients rece

•Weekly concurrent
feasible.

Burstein HJ, et al. IJROBP. 2006;64:496-504

Taxanes

- Potent radiosensitizing effect through cell cycle arrest at the G2-M junction.

Hennequin C, et al. Cancer Res. 1996;56:1842-50
Milas L, et al. Semin Radiat Oncol. 1999;9:12-26

- Potential increase in therapeutic ratio for concurrent chemo-radiotherapy.

Mason KA, et al. Clin Cancer Res. 1999;5:4191-8

- Increase the risk of pneumonitis and dermatitis.

Taghian AG, et al. J Natl Cancer Inst. 2001;93:1806-11
Bellon JR, et al. IJROBP. 2000;48:393-7

- Longer follow up needed, no definitive conclusions about safety.

OVERVIEW

- Background
- Adjuvant chemotherapy
- **Trastuzumab and biologic drugs**
- Conclusions

Trastuzumab and RT

- In pivotal trials *(B-31, N-9831, BCIRG 006)*, RT was always administered **concurrently** with trastuzumab.

- Limited RT information was available from the joint analysis of the B-31 and N-9831 trials.

- Interim subgroup analysis of patients stratified by surgery type/RT revealed improved DFS in the trastuzumab with paclitaxel arm.

Romond EH, et al. N Engl J Med. 2005;353:1673-1684
Halyard MY, et al. J Clin Oncol 2009;27:2638-2644

Trastuzumab and RT

- Higher incidence of leukopenia occurred in patients who received *AC→T→H* compared with those who received *AC→T* *(odds ratio=1.89; 95% CI, 1.25 to 2.88)*.

- In the group treated with *AC→T→H*, the 3-year cumulative incidence of cardiac events was **2.7%** with or without RT.

- In the group treated with *AC→TH→H*, the 3-year cumulative incidence of cardiac events was **1.7%** and **5.9%** with or without RT, respectively.

Halyard MY, et al. J Clin Oncol 2009;27:2638-2644

Large Investigational Studies

- Grade 3 acute skin toxicity *(3.9%)* and esophagitis *(0.3%)*
- Grade 2 late telangiectasia *(3.5%)*, local pain *(2.8%)*, and fibrosis *(7%)*
- Asymptomatic LVEF alteration *(50%)*, thromboembolic event *(18.2%)*, ischemic cardiomyopathy *(6.8%)*, pericarditis *(4.5%)*, hypertrophic cardiomyopathy *(2.3%)*, and arterial hypertension *(2.3%)*
- Cumulative incidence of cardiac events was 13.3%
- No cardiac-related deaths occurred

Jacob J, et al. Cancer Res 2012;72(suppl 3):485s

Large Investigational Studies

	n	%
Skin toxicity (CTC v3.0)		
Early dermatitis (during RT; *n* = 143)		
Grade 0	32	22
Grade 1	53	37
Grade 2	50	35
Grade 3	8	6
Skin toxicity at any time (during or following RT; *n* = 135)		
≥Grade 2	66	51
<Grade 2	69	48
Esophagus toxicity (CTC v3.0)		
Early esophagitis (during RT) (*n* = 136)		
Grade 0	86	64
Grade 1	32	24
Grade 2	15	11
Grade 3	1	1
Esophagus toxicity at any time (during or after RT; *n* = 136)		
≥Grade 2	16	12
<Grade 2	120	88
RT suspended because of dermatitis or esophagitis		
RT suspended during 5–10 days		
Yes	3	2
No	88	60
NA	55	38
LVEF decrease after RT		
Decrease of LVEF (number of points)		
Median	5	
Mean (SD)	6 (5)	
Range	0–24	
Decrease of LVEF		
Defined by CTC v3.0 scale[a] (*n* = 92)	9	10
Defined following HERA trial criteria[b] (*n* = 111)	6	5

Grade ≥2 dermatitis: 51%

Grade ≥2 esophagitis: 12%

Grade ≥2 LVEF decreases: 6-10%

Concomitant treatment is feasible in clinical practice

Patient selections for IMC irradiation are highly recommended

Belkacémi Y, et al. Ann Oncol. 2008;19:1110-1116

OVERVIEW

- Background
- Adjuvant chemotherapy
- Trastuzumab and biologic drugs
- **Conclusions**

Conclusions

•It remains **controversial** whether **delaying radiotherapy** in order to deliver chemotherapy compromises local disease control and survival.

•Any benefit in local control must be **balanced** against a **potential increase in toxicity**.

Clin Oncol (R Coll Radiol). 2006;18:247-56

Conclusions

- **Increased cardiotoxicity** and **skin reactions** preclude the **concomitant radiotherapy** and **anthracycline-based** chemotherapy.

- Further investigations are warranted to determine the **safety of taxane-based schedules** used concomitantly with radiotherapy *(pneumotoxicity)*.

- Concurrent administration of **targeted treatment** with radiotherapy is considered a **safe** and valid option.

Cancer Treat Rev. 2009;35:409-16

Conclusions

•A **"tailored"** approach on sequencing of chemotherapy and radiation is recommended.

-histological and biological features
-patient status
-treatment modality

→in order to **optimize** the delivery of adjuvant treatments.

Cancer Treat Rev. 2010;36:443-50

Grazie per l'attenzione ...