Workshop Grade

Napoli 2008

Contenuto di questa presentazione:

3 esempi di raccomandazioni in oncologia nell'ambito della fase di UPDATE del programma PRIER della regione Emilia Romagna.

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ORIGINAL REPORT

Developing Clinical Recommendations for Breast, Colorectal, and Lung Cancer Adjuvant Treatments Using the GRADE System: A Study From the Programma Ricerca e Innovazione Emilia Romagna Oncology Research Group

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Submitted April 19, 2007; accepted

ABSTRACT

Purpose
In the area of anticancer drugs, the legitimate search for effective interventions can be jeopardized by the strong pressure for accelerated approval, which may hinder the full assessment of their benefit-risk profile. We aimed to produce drug-specific recommendations using an explicit approach that separates the judgments on quality of evidence from the judgment about strength of recommendations.

Materials and Methods
We used the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system to develop recommendations for the use of specific anticancer drugs/regimens; 12 clinical

PANEL "TERAPIA ADIUVANTE MAMMELLA"

QUESITO: Nelle pazienti con tumore della mammella operato e linfonodi ascellari positivi deve essere raccomandato l'impiego dei taxani come terapia adiuvante?

MATERIALE DI BACKGROUND PER L'AGGIORNAMENTO DELLE RACCOMANDAZIONI

1. Elenco degli outcome considerati

Outcome	Valutazione	Referenza	Pagina
Sopravvivenza ad almeno 5 anni	Essenziale	ToE 4a	7
Intervallo libero da malattia ad almeno 5 anni	Essenziale	ToE 4b	8
Neurotossicità	Essenziale	ToE 4c	9
Neutropenia febbrile	Essenziale	ToE 4d	10
Cardiotossicità	Essenziale	ToE 4e	11
Qualità della vita	Importante	**Nessuno studio**	
Neoplasie iatrogene	Essenziale	**Nessuno studio**	

3a. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Ferguson CLib2007 (BCIRG001, BIG2-98, CALGB9344, E2197, ECTO, FinHer, HeCOG, GEICAM9906, PACS01, NSABP B-28, Taxit216, USOncology)	Systematic review and metanalysis of RCTs. **Search strategy:** The Cochrane Breast Cancer Group Specialised Register searched on the 9th January 2007. Handsearch for abstracts from 1995 to 2006. **Selection of studies:** independently performed by 2 reviewers. **Quality assessment:** each study was	**N:** 12 RCTs (7 publications, 5 abstracts), 21191 pts (11069 taxane arm, 10122 non-taxane arm). **Diagnosis:** early breast cancer. **Inclusion criteria:** both pre- and post-menopausal women. Varying risk profile: pts both with (node positive) and without (node negative) pathologically involved axillary lymph nodes (5	Taxanes containing adjuvant regimens vs adjuvant regimens not containing taxanes for operable early brest cancer.	**Primary:** overall survival. **Secondary:** disease free survival, toxicity, QoL.	**Weighted median FU:** 60,4 months (36-69 months). Toxicity data were extracted by a single reviewer. As definition of toxic events varied between trials, events were extracted and summated to best reflect the clinically important outcomes

3b. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Martin AnnOncol2007	**Accrual time:** July1999 – Dec.2001 **Generation of allocation sequence:** not reported. **Concealment of allocation:** not reported. **Baseline comparability:** study groups were homogeneous.	**N:** 1047 **Age:** 23-74. **Diagnosis:** women between 18 and 71 years who had undergone appropriate primary surgery for unilateral operable breast cancer. **Inclusion criteria:** without axillary involvement but with at least one high-risk criteria according to St Gallen 1998. **Exclusion criteria:** any T4 or M1 disease; previous history of cancer; abnormal renal, liver or medular function; abnormal cardiac ejection function; other serious illness or medical condition including cardiac disease and unstable diabetes mellitus.	**FAC** (N=519): 5-fluoroacil, doxorubicin, cyclophosphamide. **TAC-pre** (N=116): docetaxel, doxorubicin, cyclophosphamide. **TAC-post** (N=414): docetaxel, doxorubicin, cyclophosphamide + primary prophilactic G-CSF (PPG).	Toxicity, QoL.	**Median FU:** unclear. In July 2000, after 237 pts were enrolled the incidence of neutropenic fever events was reported to be nearly 25% in the TAC arm. Therefore, the protocol was amended to require PPG for the subsequent pts in the TAC arm. Pts included in the TAC arm prior to the amendement were defined as TAC-pre, while those enrolled after the amendement TAC-post.

4a. ToE per singolo outcome: sopravvivenza ad almeno 5 anni

Author(s):
Date: 2008-01-14
Question: Should taxanes be used in early brest cancer?
Settings: adjuvant treatent
Bibliography: Ferguson CLib2007, Martin AnnOncol2007

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	taxanes	control	Relative (95% CI)	Absolute		
Overall survival (Ferguson2007) (follow-up median 60.4 months[1])												
11	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1123/9150 (12.3%)	1360/9154 (14.9%)	HR 0.81 (0.75 to 0.88)	26 fewer per 1000 (from 17 fewer to 35 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Weighted

4b. ToE per singolo outcome: intervallo libero da malattia ad almeno 5 anni

Author(s):
Date: 2008-01-14
Question: Should taxanes be used in early brest cancer?
Settings: adjuvant treatent
Bibliography: Ferguson CLib2007, Martin AnnOncol2007

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	taxanes	control	Relative (95% CI)	Absolute		
Disease free survival (Ferguson2007) (follow-up median 60.4 months[1])												
11	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2312/10455 (22.1%)	2488/9488 (26.2%)	HR 0.81 (0.77 to 0.86)	44 fewer per 1000 (from 32 fewer to 53 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Weighted

4c. ToE per singolo outcome: neurotossicità

Author(s):
Date: 2008-01-14
Question: Should taxanes be used in early brest cancer?
Settings: adjuvant treatent
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	taxanes	control	Relative (95% CI)	Absolute		
Neurocostipation - TACpre (Martin2006)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/114	45/519	RR 1.21 (0.66 to 2.22)[3]	19 more per 1000 (from 43 fewer to 80 more)[3]	⊕⊕OO LOW	CRITICAL
Neurocostipation - TACpost (Martin2006)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	43/414	45/519	RR 1.20 (0.81 to 1.78)[3]	17 more per 1000 (from 21 fewer to 55 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Neuromood - TACpre (Martin2006)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/114	19/519	RR 0.96 (0.33 to 2.76)[3]	2 fewer per 1000 (from 39 fewer to 36 more)[3]	⊕⊕OO LOW	CRITICAL
Neuromood - TACpost (Martin2006)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	11/414	19/519	RR 0.73 (0.35 to 1.71)[3]	10 fewer per 1000 (from 32 fewer to 12 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] In July 2000, after 237 pts enrolled (121 FAC, 116 TAC), the incidence of neutropenic fever was nearly 25% in the TAC arm. Therefore the protocol was amended to require PPG for the subsequent pts in TAC arm to prevent neutropenic-related advers events.

[2] CI crossing no difference

[3] Calcolato con STATA

4d. ToE per singolo outcome: neutropenia febbrile

Author(s):
Date: 2008-01-14
Question: Should taxanes be used in early brest cancer?
Settings: adjuvant treatent
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	taxanes	control	Relative (95% CI)	Absolute	Quality	
Febrile neutropenia (Ferguson2007) (follow-up median 60.4 months[1])												
7[2]	randomised trial	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	752/5107	285/5117	RR 2.32 (1.11 to 4.49)	74 more per 1000 (from 6 more to 195 more)	⊖⊖⊖O MODERATE	CRITICAL
Febrile neutropenia - TACpre (Martin2006)												
1	randomised trial	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	32/114	16/519	RR 9.11 (5.18 to 16.02)[6]	250 more per 1000 (from 166 more to 334 more)[6]	⊖⊖OO LOW	CRITICAL
Febrile neutropenia - TACpost (Martin2006)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/414	16/519	RR 2.50 (1.39 to 4.49)[6]	46 more per 1000 (from 17 more to 76 more)[6]	⊖⊖⊖⊖ HIGH	CRITICAL

[1] Weighted

[2] Subgroup analysis:sequential anthracycline and taxane treatment (OR:1,57 - CI:0,48-5,17); concurrent anthracycline and taxane treatment (OR:6,80 - CI:1,91-24,15); taxane replacing antracicline (OR:1,99 - CI:1,00-3,93)

[3] Heterogeneity

4e. ToE per singolo outcome: cardiotossicità

Author(s):
Date: 2008-01-14
Question: Should taxanes be used in early brest cancer?
Settings: adjuvant treatent
Bibliography: Ferguson CLib2007, Martin AnnOncol2007

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	taxanes	control	Relative (95% CI)	Absolute	Quality	
Cardiotoxicity (Ferguson2007) (follow-up median 60.4 months[1])												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	67/5083 (1.3%)	68/5774 (1.2%)	RR 0.90 (0.53 to 1.54)	1 fewer per 1000 (from 6 fewer to 6 more)	⊖⊖⊖O MODERATE	CRITICAL

[1] Weighted

[2] CI crosses no difference and does not rule out a small increase.

Valutazione del profilo beneficio/rischio e formulazione iniziale della raccomandazione

QUESITO: Nelle pazienti con tumore della mammella operato e linfonodi ascellari positivi deve essere raccomandato l'impiego dei taxani come terapia adiuvante?

Nome componente panel:

_____

Quale è la Sua personale valutazione del bilancio tra i benefici e effetti indesiderati o effetti avversi ?

□ **Prevalgono** chiaramente **i benefici** sugli effetti indesiderati o effetti avversi

□ Il **bilancio** benefici/effetti indesiderati appare **incerto**

□ **Non** ci sono benefici

Quale delle seguenti raccomandazioni è, secondo Lei, appropriata per questa specifica decisione clinica:

Nelle pazienti con tumore della mammella operato e linfonodi ascellari positivi, i taxani come terapia adiuvante

Devono essere utilizzati

□ **Potrebbero** essere utilizzati

□ **NON dovrebbero** essere utilizzati

□ **NON devono** essere utilizzati

Taxani

Panelist	Data voto	bilancio	forza r
1	04/09/2008	0	1
2	04/09/2008	1	1
3	04/09/2008	1	1
4			
5	04/09/2008	1	1
6	04/09/2008	1	2
7			
8			
9	04/09/2008	1	1
10	04/09/2008	1	2
11	25/09/2008	1	2
12			
13	22/09/2008	0	1
14	04/09/2008	0	1
15	04/09/2008	1	1
16	04/09/2008	1	2
17			
18	04/09/2008	1	1
19			
20			
21	04/09/2008	1	1
22			
23	04/09/2008	1	1
n. votanti e mediane:	**15**	**1**	**1**

bilancio	-1	nessun beneficio
	0	incerto
	1	prevalgono i benefici
forza racc	-2	negativa forte
	-1	negativa debole
	1	positiva debole
	2	positiva forte

Risultati bilancio	
0	nessun beneficio
3	incerto
12	prevalgono i benefici

Risultati forza	
0	negativa forte
0	negativa debole
11	positiva debole
4	positiva forte

1. Racc. valida per donne con buona riserva midollare, non anziane e per cui è indicato tratt. chemioterapico.

PANEL "TERAPIA ADIUVANTE MAMMELLA"

QUESITO: Nelle pazienti con tumore della mammella HER-2 positivo (HER-2 con positività 3+ in immunoistochimica o con positività al test FISH), in assenza di cardiopatia, è raccomandato l'impiego del Trastuzumab in terapia adiuvante?

MATERIALE DI BACKGROUND PER L'AGGIORNAMENTO DELLE RACCOMANDAZIONI

1. Premessa

In fase di aggiornamento il Panel ha ritenuto opportuno differenziare la raccomandazione a seconda del rischio di recidiva, ammettendo la possibilità di raccomandazioni con forza diversa, in funzione del diverso bilancio rischio/ beneficio, nelle diverse categorie di rischio. Partendo dal presupposto che un rischio di recidiva più elevato sia passibile di maggiori benefici in termini assoluti, e che il livello di rischio associato alla terapia sia lo stesso a prescindere dalla probabilità di recidiva, si è quindi deciso di **organizzare i dati in funzione della dimensione del tumore e del coinvolgimento linfonodale come fattori per stratificare il rischio di recidiva.**

Pertanto il quesito originale *"Nelle pazienti con tumore della mammella HER-2 positivo (HER-2 con positività 3+ in immunoistochimica o con positività al test FISH), in assenza di cardiopatia, è raccomandato l'impiego del Trastuzumab in terapia adiuvante?"* viene riproposto sotto forma dei tre seguenti sottoquesiti:

QUESITO 1. Nelle pazienti con tumore della mammella HER-2 positivo (HER-2 con positività 3+ in immunoistochimica o con positività al test FISH) e linfonodi ascellari positivi, in assenza di cardiopatia, è raccomandato l'impiego del Trastuzumab in terapia adiuvante?

QUESITO 2. Nelle pazienti con tumore della mammella HER-2 positivo (HER-2 con positività 3+ in immunoistochimica o con positività al test FISH) in assenza di linfonodi ascellari positivi, con T > 1 cm, in assenza di cardiopatia, è raccomandato l'impiego del Trastuzumab in terapia adiuvante?

QUESITO 3. Nelle pazienti con tumore della mammella HER-2 positivo (HER-2 con positività 3+ in immunoistochimica o con positività al test FISH) in assenza di linfonodi ascellari positivi, con T ≤ 1 cm, in assenza di cardiopatia, è raccomandato l'impiego del trastuzumab in terapia adiuvante?

2. Elenco degli outcome considerati

Outcome	Valutazione	Referenza	Pagine
Sopravvivenza ad almeno 5 anni	Essenziale	**Nessuno studio**	-
Sopravvivenza ad almeno 3 anni	Essenziale	ToE 5a, 6a, 6b, 7a	13,17,18,19
Intervallo libero da malattia ad almeno 5 anni	Essenziale	**Nessuno studio**	-
Intervallo libero da malattia ad almeno 2 anni	Essenziale	ToE 5b, 7b	14,20
Cardiotossicità	Essenziale	ToE 5c,7c	15,21
Qualità della vita	Importante	**Nessuno studio**	-

3. Tabella riassuntiva referenze bibliografiche

Referenza	Table of Evidence (ToE)
Piccart-Gebhart (HERA) NEJM2005	Già incluso nella precedente raccomandazione. Nelle ToE sono presenti i dati riportati nell'aggiornamento (Smith2007)
Smith (HERA) Lancet2007	Follow up a 2 anni di HERA. Nelle ToE sono presenti i dati di Overall Survival (OS), Disease Free Survival (DFS) e tossicità.
Suter (HERA) JCO2007	Dati non presentati nelle ToE perché sono gli stessi di Smith.
Untch (HERA) Ann Onc 2008	Dati per alcuni sottogruppi.
Romond (B-31 + N9831) NEJM2005	Già incluso nella precedente raccomandazione. Nelle ToE sono presenti solo i dati relativi alla tossicità, per OS e DFS vedi Perez2007.
Perez (B-31 + N9831) ASCO2007	Aggiornamento di Romond. Nelle ToE sono presenti i dati relativi a OS e DFS.
Tan-Chiu (B-31) JCO2005	Non presente nelle ToE perché stessi dati di cardiotossicità del B-31 trial (Romond2005).
Joensuu (FinHer) NEJM2006	Short term. Nelle ToE sono presenti i dati relativi a OS, DFS e tossicità.
Raganathan (BCIRG006) ClinBreastCancer2007	II interim analysis presentata da Slamon al 29° ASCO. Nelle ToE sono presenti i dati relativi a OS, DFS e tossicità.
Jones (BCIRG006) CancerEpidBiomarkPrev2007	No ToE perché non randomizzato, solo dati di cardiotossicità su 36 pts.

4a. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Piccart-Gebhart NEJM2005 (HERA trial)	**Accrual time:** Dec.2001-June2005 Multicenter, international. **Generation of allocation sequence:** not reported. **Concealment of allocation:** not reported. **Baseline**	**N:** 5081 female. **Median age:** 49 **Diagnosis:** HER2 positive (immunohistochemistry score 3 or fluorescence in-situ hybridisation positive) early invasive breast cancer who had completed local regional therapy and a minimum of 4 courses of predefined std adjuvant or neo adjuvant chemotherapy. **Inclusion criteria:** node-positive disease or node-negative disease if the pathological tumor size was larger than 1 cm. **Exclusion criteria:** distant metastases; previous invasive breast carcinoma; neoplasm not involving	**ArmA** (N=1694): trastuzumab, initial dose 8mg/kg, mantainace dose 6mg/kg every 3 weeks for 2 years. **ArmB** (N=1694): trastuzumab, initial dose 8 mg/kg, mantainance dose 6 mg/kg every 3 weeks for 1 year. **ArmC** (N=1693):	**Primary:** disease free survival. **Secondary:** cardiac safety, overall survival, site of first disease free survival event, time to distant recurrence.	Evaluation of ArmB vs ArmC only. First planned INTERIM ANALYSIS. **Median FU:** 1 year (0 - 36 months). Major eligibility violation in 11 pts (8 in ArmB and 3 in ArmC): LVEF<55 in 4 pts, HER2+ not centrally

4b. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Smith Lancet2007 (2 years FU HERA trial)	**Accrual time:** Dec.2001-June2005 Multicenter, international. **Generation of allocation sequence:** not reported **Concealment of allocation:** not reported. **Baseline comparability:** balanced.	**N:** 5102 female. **Median age:** 49 **Diagnosis:** HER2 positive (immunohistochemistry score 3 or fluorescence in-situ hybridisation positive) early invasive breast cancer who hadb completed local regional therapy and a minimum of 4 courses of predefined std adjuvant or neo adjuvant chemotherapy. **Inclusion criteria:** node-positive disease or node-negative disease if the pathological tumor size was larger than 1 cm. **Exclusion criteria:** locally	**ArmA** (N=1701): trastuzumab, initial dose 8mg/kg, mantainace dose 6mg/kg every 3 weeks for 2 years. **ArmB** (N=1703): trastuzumab, initial dose 8 mg/kg, mantainance dose 6 mg/kg every 3 weeks for 1 year. **ArmC** (N=1698): observation alone.	**Primary:** disease free survival. **Secondary:** overall survival, grade 3 or 4 AE.	Evaluation of ArmB vs ArmC only. Second INTERIM ANALYSIS. **Median FU:** 23,5 months. 97 (5,7%) pts assigned to ArmC and 58 (3,4%) assigned to ArmB were lost to FU. As of May 2006, 861 pts in the observation group had switched to

5. Nota sulle Tabelle dei risultati della metanalisi per singolo outcome

Le seguenti meta-analisi sono state sviluppate seguendo la metodologia Cochrane. Per approfondire i metodi si rimanda al protocollo dello studio: Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. (Protocol) Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006243. DOI: 10.1002/14651858.CD006243.

Poiché si tratta di dati non pubblicati, le informazioni qui contenute sono fornite ad USO INTERNO del Panel e non devono essere DIFFUSE o RIPRODOTTE senza l'autorizzazione scritta degli Autori.

Per l'outcome Cardiotossicità il metodo statistico utilizzato è Mantel-Haenszel OR
Per un approfondimento sulle proprietà del metodo di Mantel-Haenszel nelle meta-analisi di eventi rari si veda:
Higgins J PT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008].
The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Piccart-Gebhart NEJM2005 (HERA trial)	**Accrual time:** Dec.2001-June2005 Multicenter, international. **Generation of allocation sequence:** not reported. **Concealment of allocation:** not reported. **Baseline comparability:** balanced.	**N:** 5081 female. **Median age:** 49 **Diagnosis:** HER2 positive (immunohistochemistry score 3 or fluorescence in-situ hybridisation positive) early invasive breast cancer who had completed local regional therapy and a minimum of 4 courses of predefined std adjuvant or neo adjuvant chemotherapy. **Inclusion criteria:** node-positive disease or node-negative disease if the pathological tumor size was larger than 1 cm. **Exclusion criteria:** distant metastases; previous invasive breast carcinoma; neoplasm not involving the breast (except for curatively treated basal-cell or squamous-cell carcinoma of the skin or in situ of the cervix); clinical stage T4 tumors including inflammatory breast cancer or involvement of supraventricular nodes; suspicious internal mammary nodes (unless subjected to radiotherapy); prior mediastinal irradiation (except for internal mammary node irradiation for the present breast cancer); cumulative doses of anthracycline exceeding 360 mg per square meter of body surface area for doxorubicin or 720 for epirubicin; stem-cell support for	**ArmA** (N=1694): trastuzumab, initial dose 8mg/kg, mantainace dose 6mg/kg every 3 weeks for 2 years. **ArmB** (N=1694): trastuzumab, initial dose 8 mg/kg, mantainance dose 6 mg/kg every 3 weeks for 1 year. **ArmC** (N=1693): observation alone.	**Primary:** disease free survival. **Secondary:** cardiac safety, overall survival, site of first disease free survival event, time to distant recurrence.	Evaluation of ArmB vs ArmC only. First planned INTERIM ANALYSIS. **Median FU:** 1 year (0 - 36 months). Major eligibility violation in 11 pts (8 in ArmB and 3 in ArmC): LVEF<55 in 4 pts, HER2+ not centrally confirmed in 3 pts, microinvasive breast cancer in 3 pts, metastatic disease in 1 pt. 39 pts in ArmB and 52 pts in Armc had node-negative disease with tumors 1 cm in diameter or less. 20 pts assigned to ArmB didn't receive treatment and 3 pts assigned to ArmC received trastuzumab: these 23 pts are included in the alternative group for the safety analysis Trastuzumab was

Author(s):
Date: 2008-02-19
Question: Should trastuzumab be used in HER2 positive early breast cancer?
Settings: adjuvant treatment
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	trastuzumab	control	Relative (95% CI)	Absolute		
Overall survival (Smith2007) (follow-up median 23.5 months)												
1[1]	randomised trial	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	59/1703	90/1698	HR 0.66 (0.47 to 0.91)	18 fewer per 1000 (from 5 fewer to 28 fewer)	⊖⊖⊖O MODERATE	CRITICAL
Overall survival (Perez2007) (follow-up median 2.9 years[3])												
1[4]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	124/1672	195/1679	HR 0.63 (0.49 to 0.81)	41 fewer per 1000 (from 21 fewer to 57 fewer)	⊖⊖⊖⊖ HIGH	CRITICAL
Overall survival (Joensuu2006) (follow-up median 37 months[5])												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[6]	none	6/116	14/116	HR 0.41 (0.16 to 1.08)	69 fewer per 1000 (from 101 fewer to 9 more)	⊖⊖⊖O MODERATE	CRITICAL
Overall survival (Ranganathan2007) (follow-up median 36 months)												
1	randomised trial[7]	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/1074	150/1073	HR 0.59 (0.42 to 0.85)	55 fewer per 1000 (from 20 fewer to 79 fewer)	⊖⊖⊖O MODERATE	CRITICAL

[1] 2 years FU of HERA2005
[2] Highly selected population.
[3] Range up to 6,4 years.
[4] Aggiornamento di Romond2005 presentato all'ASCO 2007
[5] median FU time in trastuzumab group=37 months, in control group=35 months
[6] Few pts, few events, CI crossing no difference
[7] Second interim analysis
[8] The full paper has not been yet published. We lack basic information about design and population.

Author(s):
Date: 2008-02-19
Question: Should trastuzumab be used in HER2 positive early breast cancer?
Settings: adjuvant treatment
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	trastuzumab	control	Relative (95% CI)	Absolute		
Overall survival (Moja-Parmelli2008) (follow-up 23.5 - 37 months[1])												
5[2]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	275/4565	449/4566	HR 0.62 (0.52 to 0.74)	36 fewer per 1000 (from 25 fewer to 46 fewer)	⊖⊖⊖⊖ HIGH	CRITICAL
Disease free survival (Moja-Parmelli2008) (follow-up 23.5-37 months[1])												
5[2]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	649/4565	1046/4566	HR 0.57 (0.51 to 0.63)	91 fewer per 1000 (from 78 fewer to 105 fewer)	⊖⊖⊖⊖ HIGH	CRITICAL
Cardiotoxicity (Moja-Parmelli2008) (follow-up 23.5-36 months[1])												
4[3]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/4418	11/4437	OR 5.25 (3.66 to 7.54)[4]	8 more per 1000 (from 5 more to 13 more)	⊖⊖⊖⊖ HIGH	CRITICAL

[1] Mediane

[2] Perez2007 (B-31, N9831), Smith2007 (HERA), Raganathan2007 (BCIRG006), Joensuu2006 (FinHer)

[3] Romond2005 (B-31, N9831), Smith2007 (HERA), Raganathan2007 (BCIRG006)

[4] Peto OR

1. Trastuzumab N+

Panelist	Data voto	bilancio	forza r
1	04/09/2008	1	2
2	04/09/2008	1	2
3	04/09/2008	1	1
4			
5	04/09/2008	1	2
6	04/09/2008	1	2
7			
8			
9	04/09/2008	1	2
10	04/09/2008	1	2
11	25/09/2008	1	
12			
13	22/09/2008	0	
14	04/09/2008	1	
15	04/09/2008	1	
16	04/09/2008	0	
17			
18	04/09/2008	1	
19			
20			
21	04/09/2008	1	
22			
23	04/09/2008	1	
n. votanti e mediane:		15	1

bilancio	-1	nessun beneficio
	0	incerto
	1	prevalgono i benefici
forza racc	-2	negativa forte
	-1	negativa debole
	1	positiva debole
	2	positiva forte

2. Trastuzumab T>1cm N-

Panelist	Data voto	bilancio	forza r
1	04/09/2008	1	2
2	04/09/2008	1	2
3	04/09/2008	0	1
4			
5	04/09/2008	1	2
6	04/09/2008	1	2
7			
8			
9	04/09/2008	1	1
10	04/09/2008	1	2
11	25/09/2008	1	2
12			
13	22/09/2008		
14	04/09/2008		
15	04/09/2008		
16	04/09/2008		
17			
18	04/09/2008		
19			
20			
21	04/09/2008		
22			
23	04/09/2008		
n. votanti e mediane:		15	

bilancio	-1	nessun beneficio
	0	incerto
	1	prevalgono i benefici
forza racc	-2	negativa forte
	-1	negativa debole
	1	positiva debole
	2	positiva forte

Trastuzumab T<1 cm N-

Panelist	Data voto	bilancio	forza r
1	04/09/2008	0	1
2	04/09/2008	0	1
3	04/09/2008	0	1
4			
5	04/09/2008	0	1
6	04/09/2008	0	1
7			
8			
9	04/09/2008	0	1
10	04/09/2008	0	1
11	25/09/2008	0	1
12			
13	22/09/2008	0	-1
14	04/09/2008	0	-1
15	04/09/2008	0	1
16	04/09/2008	-1	-2
17			
18	04/09/2008	0	1
19			
20			
21	04/09/2008	0	1
22			
23	04/09/2008	0	1
n. votanti e mediane:		15	0 1

bilancio	-1	nessun beneficio
	0	incerto
	1	prevalgono i benefici
forza racc	-2	negativa forte
	-1	negativa debole
	1	positiva debole
	2	positiva forte

Risultati bilancio	
1	nessun beneficio
14	incerto
0	prevalgono i benefici

Risultati forza	
1	negativa forte
2	negativa debole
12	positiva debole
0	positiva forte

PANEL "TERAPIA COLON RETTO E FARMACI INNOVATIVI"

QUESITO: Nei pazienti con tumore del colon retto metastatico EGFR positivo deve essere raccomandata la combinazione Irinotecan e Cetuximab dopo il fallimento della terapia citotossica contenente Irinotecan?

MATERIALE DI BACKGROUND PER L'AGGIORNAMENTO DELLE RACCOMANDAZIONI

1. PREMESSA

Nell'ambito delle attività di aggiornamento delle raccomandazioni sull'uso appropriato dei farmaci oncologici il gruppo di coordinamento metodologico si è concentrato su due tipi di attività:

a) aggiornamento della letteratura scientifica relativamente a quanto pubblicato dopo il 2005;

b) rivalutazione dell'appropriatezza e pertinenza dei dati provenienti dagli studi eleggibili rispetto al quesito oggetto della raccomandazione.

Nel caso specifico di questa raccomandazione il quesito riguardava l'appropriatezza d'uso del Cetuximab in associazione ad Irinotecan, dopo fallimento del trattamento con solo Irinotecan.

Il gruppo di coordinamento metodologico ha condiviso con i Panel le decisioni di:

a) non modificare la formulazione del quesito alla base della raccomandazione

b) approfondire la valutazione dei dati di letteratura rispetto al quesito clinico

c) evitare la categoria della "non raccomandazione" a favore delle due categorie di "forza della raccomandazione "positiva" o "negativa", a loro volta articolate nelle due sottocategorie (a loro di "debole" o "forte").

1. Elenco degli outcome considerati

Outcome	Valutazione	Referenza	Pagina
Sopravvivenza mediana	Essenziale	ToE 4a	10
Sopravvivenza libera da progressione	Essenziale	ToE 4b	11
Risposta globale	Importante	ToE 4c	12
Qualità della vita	Importante	Nessuno studio	
Neutropenia di grado IV	Essenziale	ToE 4d	13
Mortalità correlabile al trattamento	Essenziale	Nessuno studio	
Altre tossicità di grado III e IV	Essenziale	ToE 4e	14
Tossicità a carico di cute e mucose di grado III e IV	Essenziale	Nessuno studio	
Interruzione in assenza di progressione di malattia	Essenziale	Nessuno studio	

2. Tabella riassuntiva referenze bibliografiche

Referenza	Table of Evidence (ToE)
Cunningham NEJM2004	**Incluso.** Lo studio è tuttavia **poco pertinente** ai fini della raccomandazione in quanto valuta in realtà l'efficacia dell'Irinotecan in aggiunta al Cetuximab.
Jonker NEJM2007	**Incluso** Lo studio è tuttavia **poco pertinente** della raccomandazione in quanto valuta l'efficacia del Cetuximab + terapia di supporto vs sola terapia di supporto.
Sobrero JCO2008	**Incluso**: valuta l'efficacia di Cetuximab + Irinotecan vs Irinotecan da solo. **La trasferibilità alla raccomandazione è limitata** dal fatto che la valutazione è effettuata per pazienti che hanno fallito la terapia con Oxaliplatino e non Irinotecan.

Nota: non esiste alcuno studio strettamente pertinente la raccomandazione, per come è attualmente formulata.

REFERENZE

1. Cunningham d, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, VanCutsem E (2004)

3a. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Cunningham NEJM2004 **Full text**	**Accrual time:** July2001-May2002 Multicenter, European trial. **Randomization:** adequate. **Concealment of allocation:** not reported. **Baseline**	**N:** 329 randomized. **Median age:** 59 **Diagnosis:** stage IV, histologically confirmed colorectal adenocarcinoma. **Inclusion criteria:** more than 18 years of age; Karnofsky performance status score of 60 or more; adequate hematologic, renal and liver functions.	**ArmA** (N=111): Cetuximab monotherapy. Cetuximab given at an initial dose of 400 mg per square meter followed by weekly infusions of 250 mg per square meter. A histamine receptor	**Primary:** rate of confirmed radiologic tumor response. **Secondary:** time to progression, duration of response, overall survival time, incidence of AE.	Intention to treat analysis. **Median FU:** not reported. The independent review committee, which was blinded to the treatment assignement assessed disease progression during irinotecan regimen given

3b. Tabelle descrittive studi selezionati

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Jonker NEJM2007 **Full Text**	**Accrual time:** Dec.2003-Aug.2005 **Randomization:** adequate. **Concealment of allocation:** not reported. **Baseline comparability:** balanced.	**N:** 572 randomized. **Median age:** ArmA=63,0; ArmB=63,6 **Diagnosis:** advanced colorectal cancer expressing EGFR that was detectable by immunohistochemical methods in a central reference laboratory. **Inclusion criteria:** pts treated with	**ArmA** (N=287): Cetuximab plus best supportive care. Cetuximab given intravenously as an initial dose of 400 mg per square meter, administered over a period of 120 min, followed by weekly maintenance infusions of 250 mg per square meter, administered over a period	**Primary:** overall survival. **Secondary:** progression free survival, response rate, QoL, safety.	Intention to treat analysis. Safety analysis was conducted on an on-treatment basis. **Median FU:** 14,6 months. 4 pts assigned to the cetuximab group never received the treatment and 5 pts assigned to supportive care alone received cetuximab off protocol. 6 pts assigned to supportive care

4a. ToE per singolo outcome: sopravvivenza mediana

Author(s):
Date: 2008-04-14
Question: Should Cetuximab with Irinotecan be used in patients with metastatic colorectal cancer?
Settings:
Bibliography: Cunningham NEJM2004, Jonker NEJM2007, Sobrero JCO2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cetuximab with Irinotecan	control	Relative (95% CI)	Absolute		
Overall survival (Cunningham2004) (Median survival 8,6 vs 6,9 months)												
1	randomised trial	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	140/218 (64.2%)	75/111 (67.6%)	HR 0.91 (0.68 to 1.21)	35 fewer per 1000 (from 141 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Overall survival (Jonker2007) (follow-up median 14.6 months; Median survival 6,1 vs 4,6 months)												
1	randomised trial	no serious limitations	no serious inconsistency	serious[4]	no serious imprecision	none	222/287 (77.4%)	234/285 (82.1%)	HR 0.77 (0.64 to 0.92)	87 fewer per 1000 (from 26 fewer to 154 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Overall survival (Sobrero2008) (Median survival 10,7 vs 10,0 months)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	serious[6]	serious[7]	none	445/648 (68.7%)	429/650 (66%)	HR 0.975 (0.854 to 1.114)	9 fewer per 1000 (from 58 fewer to 39 more)	⊕⊕OO LOW	CRITICAL

[1] Data were collected and analysed by medical and statical investigators from Merck.
[2] The study evaluates the efficacy of the Irinotecan: Cetuximab + Irinotecan vs Cetuximab alone
[3] Intervention contamination: 56 pts in monotherapy group received irinotecan after progression.
[4] The study evaluate the efficacy of Cetuximab alone: Cetuximab + best supportive care vs best supportive care alone
[5] Median follow up not reported
[6] The study evaluate the efficacy of Cetuximab + Irinotecan after Fluoropyrimidine and Oxaliplatin failure
[7] Intervention contamination: 46.9% of pts assigned to Irinotecan received Cetuximab during the follow up period. This lowers substantially the sample size.

4b. ToE per singolo outcome: sopravvivenza libera da progressione

Author(s):
Date: 2008-04-14
Question: Should Cetuximab with Irinotecan be used in patients with metastatic colorectal cancer?
Settings:
Bibliography: Cunningham NEJM2004, Jonker NEJM2007, Sobrero JCO2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cetuximab with Irinotecan	control	Relative (95% CI)	Absolute		
Progression free survival (Cunningham2004) (Median PFS 4,1 vs 1,5 months[1])												
1	randomised trial	serious[2]	no serious inconsistency	very serious[3]	no serious imprecision	none	153/218 (70.2%)	102/111 (91.9%)	HR 0.54 (0.42 to 0.71)	176 fewer per 1000 (from 87 fewer to 267 fewer)	⊕OOO VERY LOW	CRITICAL
Progression free survival (Jonker2007) (follow-up median 14.6 months)												
1	randomised trial	no serious limitations	no serious inconsistency	serious[4]	no serious imprecision	none	273/287 (95.1%)	269/285 (94.4%)	HR 0.68 (0.59 to 0.85)	85 fewer per 1000 (from 30 fewer to 127 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Progression free survival (Sobrero2008) (Median PFS 4,0 vs 2,6 months)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	serious[6]	no serious imprecision	none	610/648 (94.1%)	598/650 (92%)	HR 0.692 (0.617 to 0.776)	94 fewer per 1000 (from 61 fewer to 130 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Percentage of pts who progressed at 6 months

[2] Data were collected and analysed by medical and statical investigators from Merck.

[3] The study evaluates the efficacy of the Irinotecan: Cetuximab + Irinotecan vs Cetuximab alone

[4] The study evaluate the efficacy of Cetuximab alone: Cetuximab + best supportive care vs best supportive care alone

[5] Median follow up not reported

[6] The study evaluate the efficacy of Cetuximab + Irinotecan after Fluoropyrimidine and Oxaliplatin failure

4c. ToE per singolo outcome: risposta globale

Author(s):
Date: 2008-04-14
Question: Should Cetuximab with Irinotecan be used in patients with metastatic colorectal cancer?
Settings:
Bibliography: Cunningham NEJM2004, Jonker NEJM2007, Sobrero JCO2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cetuximab with Irinotecan	control	Relative (95% CI)	Absolute		
Response rate (Cunningham2004)												
1	randomised trial	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	50/218 (22.9%)	12/111 (10.8%)	RR 2.12 (1.18 to 3.82)[3]	121 more per 1000 (from 41 more to 202 more)[3]	⊕OOO VERY LOW	CRITICAL
Response rate (Jonker2007) (follow-up median 14.6 months)												
1	randomised trial	no serious limitations	no serious inconsistency	serious[4]	serious[5]	none	23/287 (8%)	0/285 (0%)	RR 46.67 (2.85 to 764.74)[3]	80 more per 1000 (from 48 more to 112 more)[3]	⊕⊕OO LOW	CRITICAL
Response rate (Sobrero2008)												
1[6]	randomised trial	no serious limitations	no serious inconsistency	serious[7]	no serious imprecision	none	106/648 (16.4%)	27/650 (4.2%)	RR 3.94 (2.62 to 5.92)[3]	122 more per 1000 (from 90 more to 154 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] Data were collected and analysed by medical and statical investigators from Merck.
[2] The study evaluates the efficacy of the Irinotecan: Cetuximab + Irinotecan vs Cetuximab alone
[3] Calcolato con STATA
[4] The study evaluate the efficacy of Cetuximab alone: Cetuximab + best supportive care vs best supportive care alone
[5] Wide confidence interval
[6] Median follow up not reported
[7] The study evaluate the efficacy of Cetuximab + Irinotecan after Fluoropyrimidine and Oxaliplatin failure

4d. ToE per singolo outcome: neutropenia di grado IV

Author(s):
Date: 2008-04-14
Question: Should Cetuximab with Irinotecan be used in patients with metastatic colorectal cancer?
Settings:
Bibliography: Cunningham NEJM2004, Jonker NEJM2007, Sobrero JCO2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cetuximab with Irinotecan	control	Relative (95% CI)	Absolute		
Neutropenia (Cunningham2004)												
1	randomised trial	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	20/212 (9.4%)	0/115 (0%)	RR 22.33 (1.36 to 365.82)[4]	94 more per 1000 (from 53 more to 136 more)[4]	⊖OOO VERY LOW	CRITICAL
Neutropenia (Sobrero2008)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	196/638 (30.7%)	151/629 (24%)	RR 1.28 (1.07 to 1.53)[4]	67 more per 1000 (from 18 more to 116 more)[4]	⊖⊖⊖O MODERATE	CRITICAL

[1] Data were collected and analysed by medical and statical investigators from Merck.

[2] The study evaluates the efficacy of the Irinotecan: Cetuximab + Irinotecan vs Cetuximab alone

[3] Wide confidence interval

[4] Calcolato con STATA

[5] Median follow up not reported

4e. ToE per singolo outcome: altre tossicità di grado III e IV

Author(s):
Date: 2008-04-14
Question: Should Cetuximab with Irinotecan be used in patients with metastatic colorectal cancer?
Settings:
Bibliography: Cunningham NEJM2004, Jonker NEJM2007, Sobrero JCO2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cetuximab with Irinotecan	control	Relative (95% CI)	Absolute	Quality	
Grade III & IV AE (Cunningham2004)												
1	randomised trial	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	138/212 (65.1%)	50/115 (43.5%)	RR 1.50 (1.19 to 1.89)[4]	218 more per 1000 (from 83 more to 387 more)[4]	⊖OOO VERY LOW	CRITICAL
Grade III & IV AE (Jonker2007) (follow-up median 14.6 months)												
1	randomised trial	no serious limitations	no serious inconsistency	serious[5]	serious[3]	none	226/288 (78.5%)	162/274 (59.1%)	RR 1.33 (1.18 to 1.49)[4]	193 more per 1000 (from 118 more to 269 more)[4]	⊖⊖OO LOW	CRITICAL
Grade III & IV AE (Sobrero2008)												
1[6]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	369/638 (57.8%)	274/629 (43.6%)	RR 1.06 (0.96 to 1.16)[4]	31 more per 1000 (from 23 fewer to 85 more)[4]	⊖⊖⊖⊖ HIGH	CRITICAL

[1] Data were collected and analysed by medical and statical investigators from Merck.
[2] The study evaluates the efficacy of the Irinotecan: Cetuximab + Irinotecan vs Cetuximab alone
[3] Wide confidence interval
[4] Calcolato con STATA
[5] The study evaluate the efficacy of Cetuximab alone: Cetuximab + best supportive care vs best supportive care alone
[6] Median follow up not reported

Cetuximab

Panelist	Data voto	bilancio	forza r
1			
2	11/07/2008	0	1
3			
4	07/07/2008	0	1
5	05/06/2008	0	1
6	18/07/2008	0	1
7	09/07/2008	-1	-2
8	05/06/2008	-1	-1
9			
10	08/07/2008	0	1
11			
12			
13	05/06/2008	0	1
14	05/06/2008	0	1
15	05/06/2008	0	1
16	05/06/2008	0	1
17	14/07/2008	0	1
18			
19	05/06/2008	0	-1
20	21/07/2008	-1	-1
21	08/06/2008	0	-1
22			
23	05/06/2008	0	-1
n. votanti e mediane:	**16**	**0**	**1**

bilancio	-1	nessun beneficio
	0	incerto
	1	prevalgono i benefici
forza racc	-2	negativa forte
	-1	negativa debole
	1	positiva debole
	2	positiva forte

Risultati bilancio	
3	nessun beneficio
13	incerto
0	prevalgono i benefici

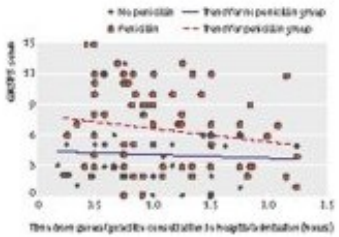
Risultati forza	
1	negativa forte
5	negativa debole
10	positiva debole
0	positiva forte

BMJ helping doctors make better decisions

Comment

Preventing child deaths

Reviews of timely standardised precise data, combined with epidemiological research, could reduce child deaths, says an editorial about the recently-published UK Confidential Enquiry into Maternal and Child Health by Professor Jane Freemantle, of Melbourne University, and research fellow Anne Read, of the University of Western Australia.



Student BMJ: Paper+

Penicillin and meningococcal disease: case-control study

Amy Davis takes you through an observational study that looked at whether penicillin prescribed by a general practitioner before admission to hospital improved children's outcomes.

Observations

The soap opera that saves lives

A soap opera on South African television that is run by public health activists is now to be screened across eight neighbouring countries, with the help of a grant from the UK government. *Soul City* is watched by more than 34 million people in South Africa, over 70% of the population, and tackles a range of gritty health and social issues.

This week's print issue

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Conclusioni

Non esistono interventi “magici”

Due fasi temporali: ricerca-raccomandazione e raccomandazione-pratica clinica

Percorso tecnico (tempi 1-2 anni, richiede investimento di risorse, giovani su cui investire)

Percorso culturale (tempi >2 anni, importante pay-back per l’azienda e il sistema sanitario)

Processo già avviato (non pienamente manifesto)

Conclusioni

Benefici se ricerca e pratica clinica si avvicinano:

- Risorse destinate al trasferimento di conoscenze
- Impatto (leadership culturale)
- Grant
- Pubblicazioni
- SSN e pazienti

Centro Cochrane Italiano

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Centro Cochrane Italiano (CCI)

E' la branca italiana della **Cochrane Collaboration**. Si occupa di **ricerca, formazione** **iniziative editoriali**. Le principali aree di ricerca del CCI riguardano la **metodo** **revisioni sistematiche e il trasferimento dei risultati della ricerca** **clinica**.

Chi siamo

La Cochrane Collaboration

E' una iniziativa internazionale no-profit [illegible] lo scopo di raccogliere, valutare criticamente e diffondere le info[illegible]azioni relative all'efficacia degli interventi sanitari. Produce sintesi rigorose della lett[illegible]ratura [illegible]edica, denominate **revisioni sistematiche**, raccolte all'interno della **Cochrane Library**.

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Sao Paulo, Brazil, 23-27 Oct. 2007

News dal CCI

Convegni e workshop:
XII Riunione annuale "Qualità del reporting dei trial e delle revisioni sistematiche" 29-30 Novembre, Milano.

I master:
VI Edizione del Master in " Evidence based medicine e metodologia della ricerca sanitaria", Febbraio-Ottobre 2007, Modena.

II Edizione del Master "Orientarsi in salute e società per fare scelte consapevoli" Marzo-Maggio 2007, Milano.

Current news at The Cochrane Collaboration