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Institut de recherche en santé d'Ottawa

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Cumulative meta-analysis to determine key milestones in the Life Cycle of Evidence in Cancer Care (LIFE CYCLE Project)

Presenter: Lorenzo Moja

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THE OTTAWA HOSPITAL L'HÔPITAL D'OTTAWA

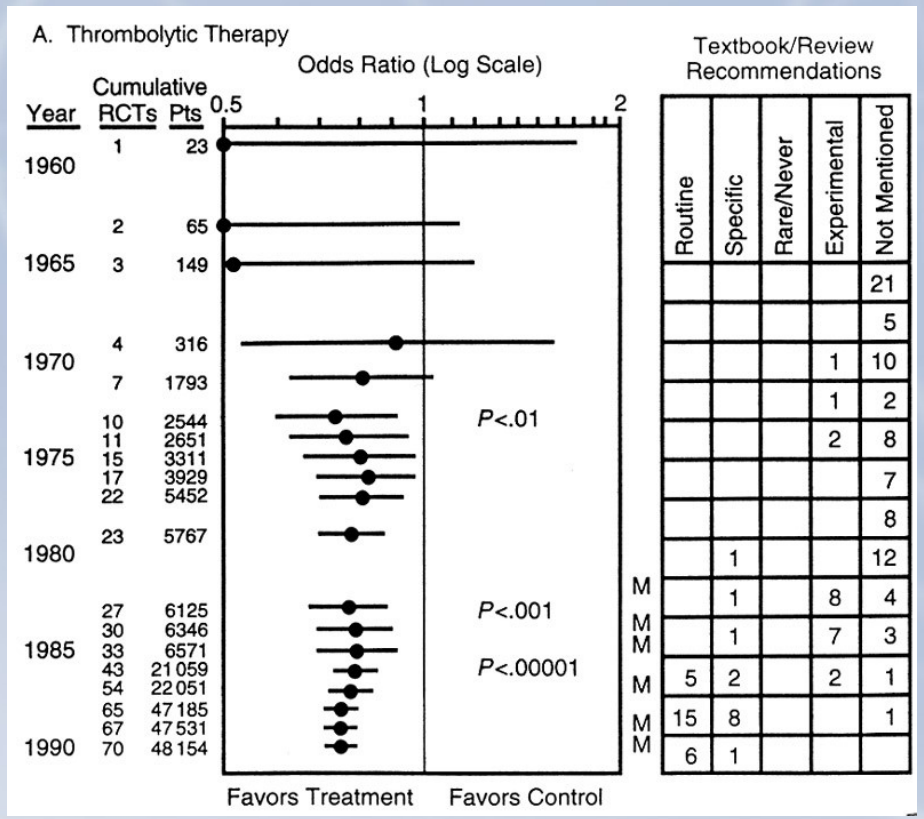
Université d'Ottawa • University of Ottawa

XIII Cochrane Colloquium - Melbourne

A Comparison of Results of Meta-analyses of Randomized Control Trials and Recommendations of Clinical Experts

Treatments for Myocardial Infarction

Elliott M. Antman, MD; Joseph Lau, MD; Bruce Kupelnick; Frederick Mosteller, PhD; Thomas C. Chalmers, MD



In 1992, Antman performed a cumulative meta-analysis of randomized controlled trials (RCTs) for treatments of acute myocardial infarction.

- **Findings suggested that there was clear evidence of benefit from thrombolysis by 1973.**
- **However, textbooks and review papers did not routinely recommend thrombolysis until 1986.**

This landmark study has been widely cited as evidence of the research-clinical recommendation gap.

Antman, JAMA 1992

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Overall Objectives

1. To identify the natural history (“life cycle”) of evidence concerning novel chemotherapy agents (NCA) for
    - non-small cell lung cancer (NSCLC) and
    - metastatic breast cancer (MBC)
2. To determine the research-clinical recommendation gap
3. To determine the recommendation-clinical practice gap

Methods

Cumulative meta-analyses of NCAs approved in Canada between 1992 – 2002

- The primary outcome of interest was overall survival (phase II/III RCTs were eligible).
- Many trials poorly reported (no hazard ratios or no stratified survival curves).

  Method by Follman: t-tests on the difference in median survivals/progression free survivals between comparison arms, which approximates a random effects model (Follman & Proschan, 1999).

Research-clinical recommendation gap

- All relevant textbooks and clinical practice guidelines were reviewed and recommendations documented.

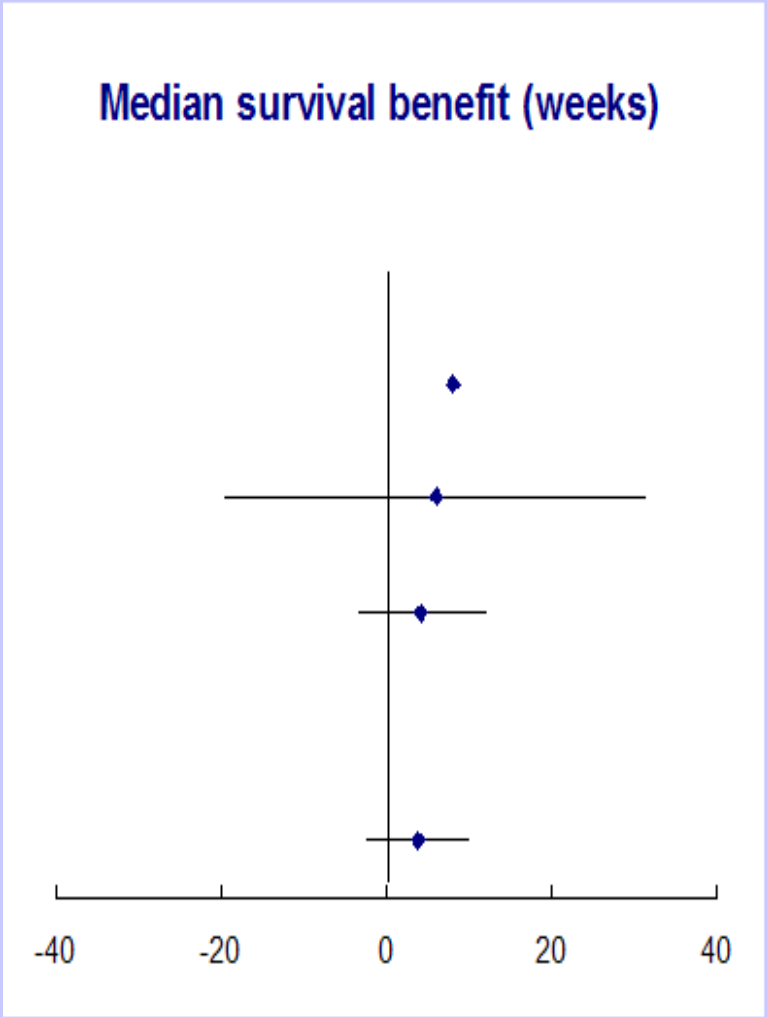
Clinical recommendation–practice gap

- Administrative data (Cancer Care Ontario Oncology Patient Information System 'OPIS' database) to explore physician uptake and utilization patterns for each NCA at Ontario regional cancer centers.

Health Canada Approval of NCAs

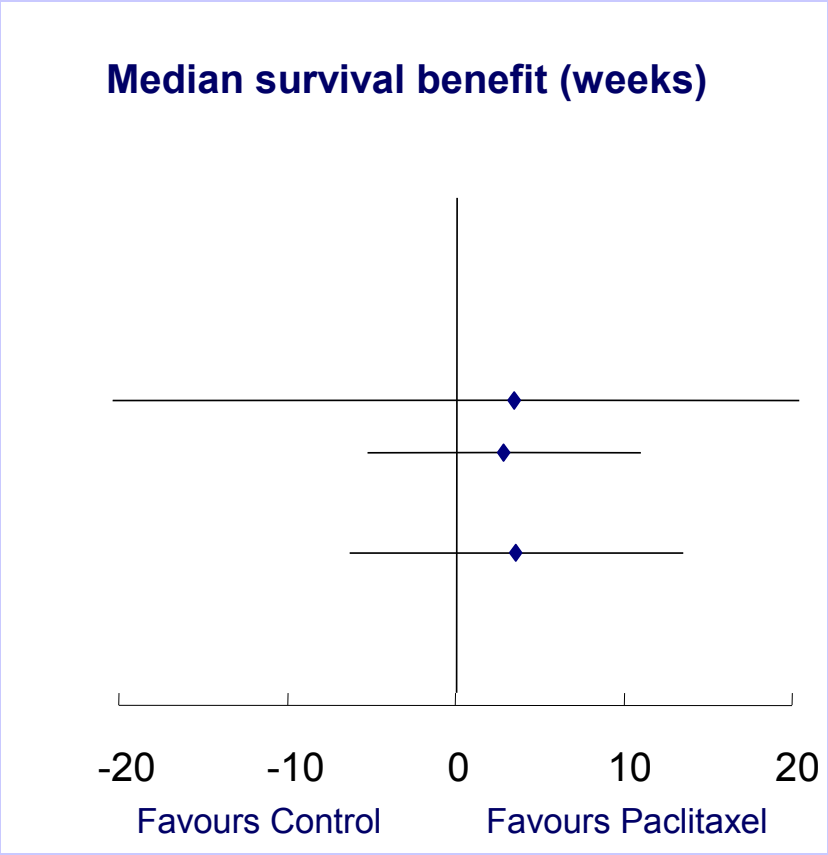
NCA	BRAND NAME	NOC DATE	MANUFACTURER
Capecitabine	Xeloda	31 Aug 1998	Hoffman-La Roche Ltd
Docetaxel MBC	Taxotere	21 Jul 1995	Rhone-Poulenc Rorer Canada Inc.
Doxorubicin Hydrochloride	Caelyx	20 Jul 1998	Schering Canada Inc.
Fludarabine	Fludara	16 Jun 1992	Berlex Canada Inc.
Gemcitabine Hydrochloride	Gemzar	23 Dec 1996	Eli Lilly Canada Inc.
Irinotecan Hydrochloride	Camptosar	4 Jul 1997	Pharmacia & Upjohn Inc.
Paclitaxel NSCLC MBC	Taxol	29 Dec 1992	Bristol-Myers Squibb Canada Inc.
Raltitrexed Disodium	Tomudex	12 Sep 1996	Zeneca Pharma Inc.
Topotecan Hydrochloride	Hycamtin	15 Apr 1997	SmithKline Beecham Pharma
Vinorelbine NSCLC	Navelbine	10 May 1994	Burroughs Wellcome

Vinorelbine for NSCLC: cumulative meta-analysis, summary of recommendations and key milestones.



Year	RCTs		Textbook & CPG recommendations				Key Milestones
	Cum. Patients	Cum. RCTs	NM	E	I	S	
1992			1				
1993			1	2			
1994	406	1	1	2		1	1st FDA approval NOC (NSCLC)
1995							
1996	838	3	2			2	CCO CPG (S)
1997				1		3	ASCO CPG (S) CCO funding
1998	1153	4	1	1		1	
1999						1	
2000						2	
2001			1			4	
2002	1524	6	3			1	

Paclitaxel for NSCLC: cumulative meta-analysis, summary of recommendations and key milestones.



Year	Studies		Textbook & CPG recommendations				Key Milestones
	Cum. Patients	Cum. RCTs	NM	E	I	S	
1992			2				1st FDA & 1st NOC (ovarian)
1993			1	2			
1994				1			
1995				2			
1996			2	1		2	CCO guideline (NM)
1997	817	2		2	1	1	ASCO guideline (S)
1998	1379	4		2		1	FDA approval NSCLC
1999						1	
2000	1379	4	1		1	1	
2001					1	1	
2002			2			1	NOC NSCLC

Recommendation-Clinical Practice Gap

- Over 50% of CPGs recommended vinorelbine by 1996

  (approved in 1994 – CCO guidelines in 1996)

- Practice date available from 1997

- 80% physicians had used vinorelbine by 1997

- 100% had used vinorelbine by 1998

- Over 50% of CPGs recommended paclitaxel use by 2002

  (approved in 2002 – no CCO guidelines)

- 100% had used paclitaxel by 2001

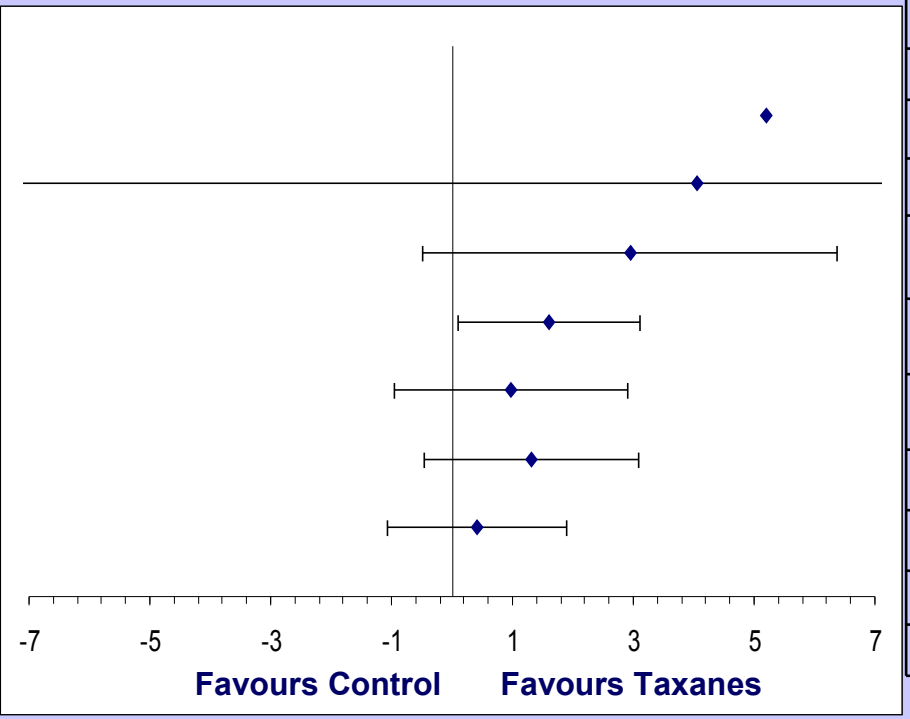
Vinorelbine and Paclitaxel for NSCLC

- The cumulative meta-analysis failed to demonstrate with statistical significance any point in time where evidence favoured vinorelbine or paclitaxel combinations over platinum control regimens.

- All summary pooled points trended towards favouring both vinorelbine and paclitaxel combinations.
  The final pooled median survival advantage for
  Vinorelbine was 3.9 weeks (95% CI -2.29, 10.09).
  Paclitaxel was 3.6 weeks (95% CI -6.25, 13.51).

Taxanes for MBC: cumulative meta-analysis of median overall survival with summary of recommendations and key milestones.

Median survival benefit (months)



Taxanes

Year	Cum. Patients	Cum. RCTs	NM	E	I	S	Key Milestones
1991			4				
1992			2				1st FDA & NOC (ovarian)
1993			2	4			NOC P new indication
1994							FDA P 2nd line +
1995			1	3			1st NOC D
1996	100	1		4			FDA D 2nd line +
1997	553	2		4	2		
1998	1120	4		2	4		
1999	1838	6			2	2	NOC D post failure of CT
2000	2169	7			4	2	
2001	3141	9			3	5	NOC D 1st line
2002	4190	13			6	2	NOC D 2nd line combo
2003					2	4	CCO CPG (S)
2004						4	

Data from 9 textbooks and 8 CPGs all available editions

Taxanes for MBC

- Similar to NSCLC, the cumulative meta-analysis failed to demonstrate with statistical significance any point in time where evidence favoured taxanes combination over control regimens.

- All summary pooled points trended towards favouring the taxanes, the final pooled median survival advantage for taxanes was 0.42 months (95% CI -1.06, 1.89), approximately two weeks.

Our study in the context (I)

In contrast to the findings of Antman study

- For two metastatic conditions there was no research-clinical recommendation gap
- Instead there was a premature generation of recommendations based on limited evidence

Our study in the context (II)

Antman and Life Cycle are two case studies

Several differences

- Cardiology / Oncology
- Evidence generated between the late 1950s and 1990 / evidence in the 1990s
- Different emphasis on better knowledge management during the last fifteen years
- Oncologists may prefer to adopt novel chemotherapy agents for patients with extremely poor prognosis also in condition of important uncertainty about benefits

Our case study in the context (III)

In agreement to the findings of Ioannidis study

- For two metastatic conditions the cumulative evidence showed that results of early trials are commonly over-estimations of true effect

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context: Controversy and uncertainty ensue when the results of clinical research on

- This can be true not in only highly cited clinical research but also throughout abstracts of meetings

In Life Cycle for one condition the generation of recommendations determined high rates of adoption within two years in clinical practice settings

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