Milano, 18 settembre 2013

Farmaci innovativi, prezzi e rimborsabilità

Sostenibilità del sistema e approcci alla valutazione (periodica) dei farmaci

Disclaimer

- Le opinioni riportate sono personali e non impegnano le istituzioni nelle quali lavoro (o sono coinvolto)

- Conflitti di interesse
  - Finanziari: no
  - Professionali/altri: nessuno (percepito)

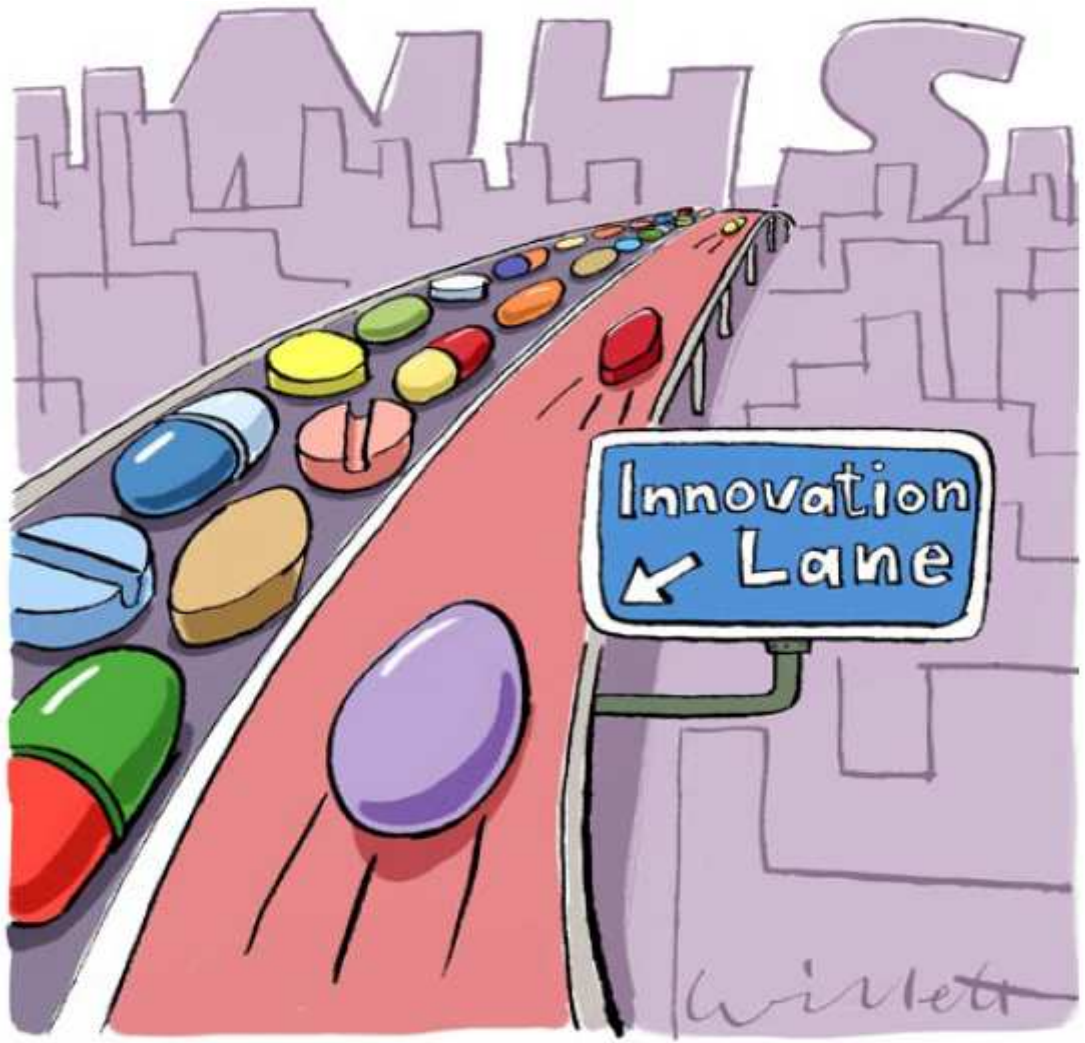
Gli argomenti

- Cosa intendiamo per innovatività?
- Quali esiti e quale entità delle differenze?
- Le difficoltà nell'accordo fra gli esperti: quanto sono riproducibili i giudizi sull'innovatività?
- Quali implicazioni per SSN e SSR?
  - Prezzi e rimborsi; nuovi studi; appropriatezza d'uso
- Conclusioni

NICE and new: appraising innovation

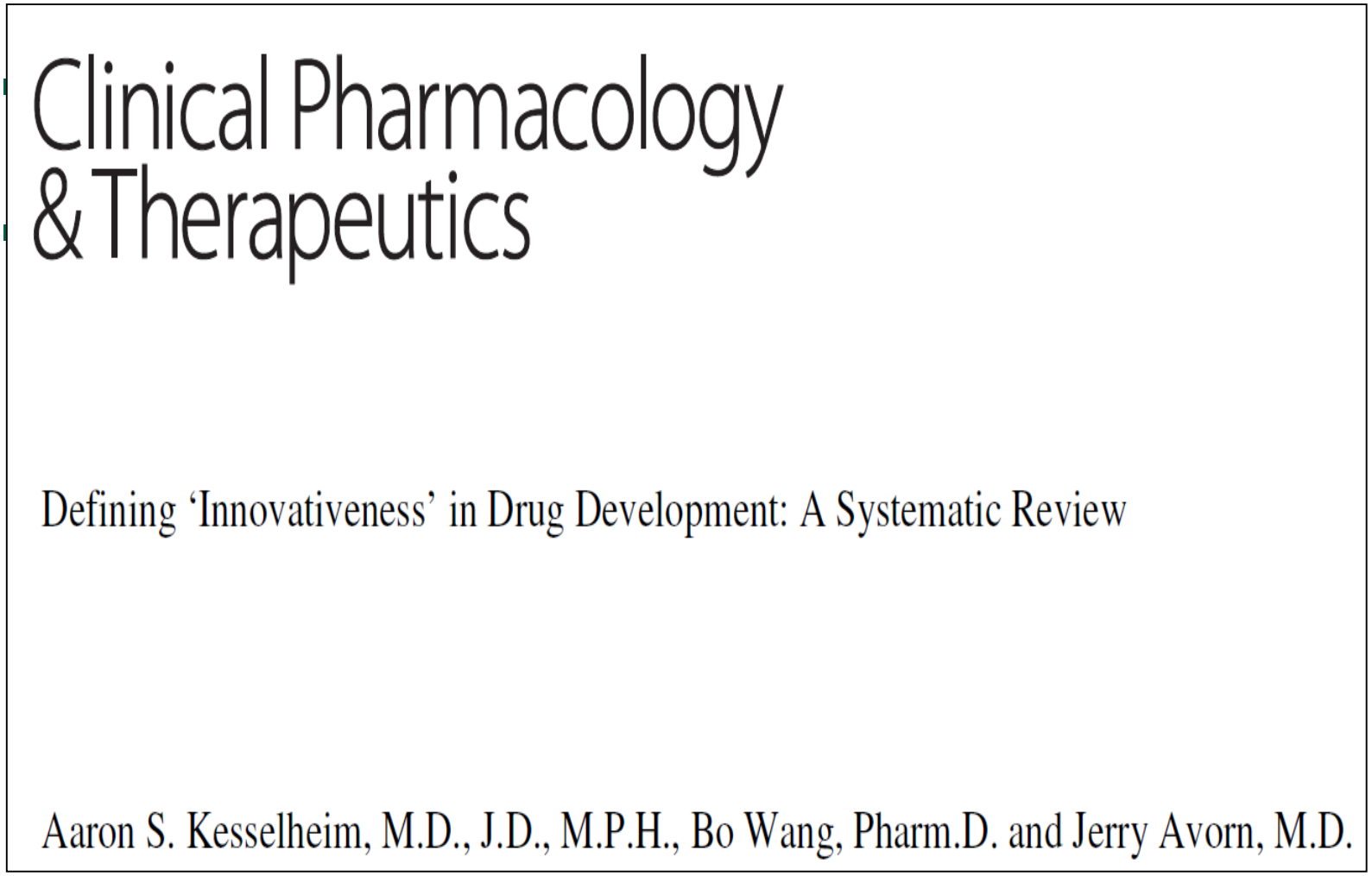
Innovation is essential in drug development but is not cheap. **Robin Ferner, Dyfrig Hughes, and Jeffrey Aronson** examine the challenges of encouraging innovation while ensuring clinical benefit

BMJ | 30 JANUARY 2010 | VOLUME 340



Defining ‘Innovativeness’ in Drug Development: A Systematic Review

(Kesselheim et al, Clin Pharmacol Therap 2013)



Su quali esiti valutare l’innovatività

J Ambulatory Care Manage
Vol. 31, No. 1, pp. 65–68

Something New Every Day

Defining Innovation and Innovativeness in Drug Therapy

Jeffrey K. Aronson, MA, MBChB, DPhil, FRCP, FBPharmacolS, FFPM

Abstract: The word "innovation" comes from the Latin noun *innovatio*, derived from the verb *innovare*, to introduce [something] new. It can refer either to the act of introducing something new or to the thing itself that is introduced. In terms of commerce, it is defined in the *Oxford English Dictionary* as "the action of introducing a new product into the market; a product newly brought on to the market," a definition that illustrates both aspects of the word's meaning. "Innovativeness" is the property of being an innovation. Here I identify several different types of innovativeness in drug therapy, including structural, pharmacological or pharmacodynamic, pharmaceutical, and pharmacokinetic innovativeness, and I stress the over-riding importance of clinical innovativeness, which should result in a better benefit to harm balance at an affordable cost. **Key words:** *benefit to harm balance, drug therapy, innovation, innovativeness*

Cosa si può intendere per innovatività

(da Aronson, J Ambulatory Care Manage 2008)

- *Structural innovativeness:* ad es., nuova struttura chimica
- *Pharmaceutical innovativeness:* ad es., modalità di rilascio
- *Pharmacokinetic/pharmacodynamic:* ad es., numero somministrazioni giornaliere, nuovo meccanismo d'azione; meno interazioni
- *Clinical innovativeness:* is possessed by a medicinal product that produces significantly more benefit than its predecessors and/or significantly fewer adverse effects … resulting in a better benefit to harm balance …

Quando una differenza è sufficientemente rilevante?

VOLUME 25 · NUMBER 15 · MAY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, Arie Figer, Joel R. Hecht, Steven Gallinger, Heather J. Au, Pawel Murawa, David Walde, Robert A. Wolff, Daniel Campos, Robert Lim, Keyue Ding, Gary Clark, Theodora Voskoglou-Nomikos, Mieke Ptasynski, and Wendy Parulekar

From the Divisions of Medical Oncology, Hematology, and Surgical Oncology, Princess Margaret Hospital, Toronto; National Cancer Institute of Canada Clinical Trials Group, Kingston; Algoma District Cancer Program, Sault Ste Marie, Ontario; Cross Cancer Institute, Edmonton, Alberta, Canada; the Australasian Gastrointestinal Tumor Group, Sydney, Australia; Norton Healthcare Pavilion, Louisville, KY; UCLA Medical Center, Los Angeles, CA; M. D. Anderson Cancer Centre, Houston, TX; OSI Pharmaceuticals, Boulder, CO; Sourasky Medical Centre, Tel Aviv, Israel; Great Poland Centre for Oncology, Poznan, Poland; Confidence Medical Centre, San Isidro, Argentina; and the National University Hospital, Singapore, Singapore.

Submitted June 26, 2006; accepted November 8, 2006; published online ahead of print at www.jco.org on April 23, 2007.

Supported in part by OSI Pharmaceuticals, Melville, NY.

Presented in part at the American Society of Clinical Oncology Gastrointestinal Symposium, Hollywood, FL, January 27-29 2005; and the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, FL,

ABSTRACT

Purpose
Patients with advanced pancreatic cancer have a poor prognosis and there have been no improvements in survival since the introduction of gemcitabine in 1996. Pancreatic tumors often overexpress human epidermal growth factor receptor type 1 (HER1/EGFR) and this is associated with a worse prognosis. We studied the effects of adding the HER1/EGFR-targeted agent erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer.

Patients and Methods
Patients were randomly assigned 1:1 to receive standard gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo in a double-blind, international phase III trial. The primary end point was overall survival.

Results
A total of 569 patients were randomly assigned. Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/gemcitabine arm with a hazard ratio (HR) of 0.82 (95% CI, 0.69 to 0.99; $P = .038$, adjusted for stratification factors; median 6.24 months *v* 5.91 months). One-year survival was also greater with erlotinib plus gemcitabine (23% *v* 17%; $P = .023$). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; $P = .004$). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization. There was a higher incidence of some adverse events with erlotinib plus gemcitabine, but most were grade 1 or 2.

Conclusion
To our knowledge, this randomized phase III trial is the first to demonstrate statistically significantly improved survival in advanced pancreatic cancer by adding any agent to gemcitabine. The recommended dose of erlotinib with gemcitabine for this indication is 100 mg/d.

Quando una differenza è sufficientemente rilevante?

VOLUME 27 · NUMBER 35 · DECEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval

Alberto Sobrero, *Ospedale San Martino, Genova, Italy*
Paolo Bruzzi, *Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*

Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval *(Sobrero & Bruzzi, JCO 2009)*

Premessa

- Differenze statisticamente significative ma non sempre clinicamente rilevanti
- Molti farmaci approvati in base a miglioramenti di indicatori surrogati
- Costi rilevanti anche a fronte di benefici non chiari

Proposta alternativa

- Alzare l’asticella

Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval *(Sobrero & Bruzzi, JCO 2009)*

Vantaggi

- Stimolo all'innovazione
- Immissione in commercio solo di farmaci più rilevanti
- I costi dei nuovi farmaci diventano più 'ragionevoli'
- Necessari meno pazienti nelle sperimentazioni cliniche

Svantaggi

- Rischio di non riconoscere piccoli incrementi che sommati ne danno uno grande

Riproducibilità nella valutazione delle evidenze da parte di esperti

- Esperti diversi, posti di fronte agli stessi dati, danno spesso valutazioni differenti
- Come gestire le situazioni di incertezza

Health Policy 105 (2012) 221–225

Contents lists available at SciVerse ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

International comparison of assessments of pharmaceutical innovation

Joel Lexchin[a,b,c,*]

[a] School of Health Policy and Management, York University, Toronto, Ontario, Canada
[b] University Health Network, Toronto, Ontario, Canada
[c] Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 20 October 2011
Received in revised form 6 February 2012
Accepted 8 February 2012

Keywords:
Canada
Drug regulation
Review status
Therapeutic innovation

ABSTRACT

Introduction: This study was undertaken to compare decisions about medicines innovation made by two Canadian organizations, the Therapeutic Products Directorate (TPD) and the Human Drug Advisory Panel (HDAP), with those made by similar organizations in other countries.

Methods: Assessments by TPD and HDAP were compared to those made by the Food and Drug Administration (FDA) and the drug bulletin Prescrire International, respectively.

Results: Between 2004 and 2009 the TPD gave priority reviews to 46 of 137 (34%) products compared to 71 of 145 drugs (49%) by the FDA ($p = 0.011$). Of 109 drugs in common the two agreed on the review status in 88 (weighted Kappa = 0.606). In the same time period HDAP categorized 12 of 120 (10%) drugs as innovative while Prescrire did the same for 49 of 624 (8%) new drugs and new indications for older drugs ($p = 0.4664$). Of 84 drugs in common the two agreed on the evaluation for 70 (weighted Kappa = 0.319).

Discussion: Differences between the different organizations may be due to a variety of factors. These differences have significant policy implications.

International comparison of assessments of pharmaceutical innovation

(Lexchin J, Health Policy 2012)

		Human Drug Advisory Panel		
		Innovativo	**Non innovativo**	
Prescrire	**Innovativo**	5	7	
	Non innovativo	7	65	
				84

Accordo oltre il caso:
Indice Kappa = 0,32

Kappa	Riproducibilità
> 0,75	Eccellente
0,40-0,75	Adeguata
< 0,40	Bassa

Fleiss L., 1981

VOLUME 29 · NUMBER 16 · JUNE 1 2011

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice

Francesco Trotta, Hubert G.M. Leufkens, Jan H.M. Schellens, Richard Laing, and Giovanni Tafuri

Franceso Trotta, Giovanni Tafuri, Italian Medicines Agency, Rome, Italy; Hubert G.M. Leufkens, Jan H.M. Schellens, Giovanni Tafuri, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht; Hubert G.M. Leufkens, Jan H.M. Schellens, Medicines Evaluation Board, The Hague; Jan H.M. Schellens, The Netherlands Cancer Institute, Amsterdam, the Netherlands; and Richard Laing, WHO, Geneva, Switzerland.

Submitted January 5, 2011; accepted March 14, 2011; published online ahead of print at www.jco.org on May 2, 2011.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Italian Medicines Agency, the Medicines Evaluation Board, or the World Health Organization.

Authors' disclosures of potential conflicts of interest and author contribu-

ABSTRACT

Purpose
The aims of this study were to compare the approaches of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in the evaluation and approval of new anticancer indications and to identify possible clinical implications associated with these differences.

Methods
Information on the European Union therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Reports and from the FDA review reports.

Results
Overall, 42 anticancer drugs were approved by EMA between 1995 and 2008, corresponding to a total of 100 indications. In 47 of 100 indications, a difference was found. For 19 of these 47 indications, the difference was that one agency approved an indication, whereas the other agency did not. For the remaining 28 indications, the same indication was approved by both of the agencies and differences were evaluated through an algorithm; in 10 cases, discrepancies in therapeutic indications between EMA and FDA were considered clinically relevant. We found an overall trend that the agency that was second to give a positive approval was usually more restrictive in terms of wording of the indication compared with the agency that provided approval first. Regarding the use and robustness of available clinical data for evaluation, no clear associations could be found.

Le ragioni dei disaccordi

Alcune possibili differenze di giudizio:

- Selezione della popolazione in studio (trasferibilità dei risultati)
- Scelta del/i trattamenti di confronto
- Valore da attribuire agli esiti (ad es., surrogati, compositi)
- Validità dei dati raccolti (ad es., randomizzazione, mascheramento)
- Validità delle analisi
- Studi inclusi nel confronto

Implicazioni derivanti dalla valutazione di innovatività

Cosa può significare premiare l'innovatività?

- Estensione brevetto (ad es., malattie rare)
- Inserimento o meno all'interno dei farmaci rimborsabili dal SSN (e/o la rapidità della decisione di inserimento)
- Riconoscimento, almeno in Italia, dell'esclusione dai vincoli dei tetti di spesa
- Prezzo del farmaco

I farmaci del SSN: fra innovatività e sostenibilità

- Non è plausibile pagare prezzi differenti per ‘prestazioni’ sovrapponibili
- L’innovatività di un farmaco è indicazione-specifica
- Anche per i farmaci innovativi è necessario verificare l’uso appropriato

Valutazione di innovatività e implicazioni per i prezzi

Quali sono i possibili margini di manovra?

- Farmaci (clinicamente) innovativi: accettare un prezzo maggiore rispetto all'esistente
- Altri farmaci: prezzo di rimborso non superiore alle terapie di confronto

Rimane da definire un comportamento coerente per:

- Livello max che l'SSN può pagare (es., per QALY)
- Miglioramenti che non modificano esiti clinici

In conclusione

- Avere chiaro su quale indicatore si valuta l'innovatività
- Definire cosa il SSN si considera clinicamente innovativo
  - Condivisione con i cittadini
  - Comprensibilità per le aziende farmaceutiche
- Prezzi simili per profili B/R simili
- Abituarsi a convivere con margini di incertezza: ci vuole tempo per produrre risposte a quesiti aggiuntivi
  - Necessità di studi post autorizzativi
- Importanza uso appropriato