Do PROs have incremental value in Oncology?

The case of QoL measures in breast cancer

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"Mario Negri", Milan - Italy

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Overview

- The speaker
- Use of PROs/QoL measures: Regulatory requirements and Agencies attitudes
- QoL in RCTs in breast cancer: a literature review
- QoL in RCTs in advanced breast cancer: is there added value?
- Conclusions

G. Apolone

- MD (1982), post doctoral degrees in internal medicine (1987) and clinical pharmacology (1992)
- At IRFMN since 1987
- Training period in U.S.A. (1989-1990)
- Head of Translational and Outcome Research Lab. (LaTOR)
- Expert at EMEA on anti-cancer drugs and HR-QoL (2000-)

My interests

- Methodological and ethics aspects of clinical research (on new drugs)
- Systematic reviews and meta-analysis (in collaboration with the Cochrane Center)
- Outcome Research projects (Anaemia in Elderly, Pain in Cancer, follow-up strategies in colo-rectal cancer)
- Educational, training and research activities with patients and advocacy associations (in Italy and in Europe)

My Conflicts of interests

Research support

- Italian and international Drugs Industries (from A to... Z)
- Public or non-profit organizations (60%)

Financial interests

- None

Individual interests

- Paid Consultant for GSK (post-marketing projects)
- Speaker fees from Amgen and NHS Health Authorities

Efficacy measures in CT (1)

- (Regular) Marketing approval requires substantial evidence about safety and efficay

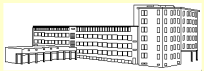
- Efficacy= Clinical benefit= Life prolongation or Life improvement

- The true/final endpoints are: Survival and/or better (quality of) life

Efficacy measures in oncology

- Biologic activity in Phase II CT (Response rate, quality and duration of response)
- Survival or improvement in patients' symptoms in Phase III RCT
- DFS in adjuvant setting
- In specific circumstances: impressive/outstanding tumor-related outcomes (complete response with reasonable duration)
- **(HR)-QoL to support tumor shrinking or toxicity or symptoms**
  (EMEA: either in Phase II/III as primary endpoint, but justified case per case)

Surrogate endpoints for efficacy in CT



- When the objective is "to cure": RR (CR), TTP

- When the objective is "to prevent": incidence, type of recurrence (site, symptomatic status), DFS

- When the objective is "palliation": survival benefit, ad-hoc (compound) Clinical Benefit Measure (CBM), tumor response

FDA and EMEA: an evaluation

- FDA: *JR Johnson et al*, JCO 2003; 7: 1404-1411

- EMEA: *S. Garattini, V. Bertelè*, BMJ 2002; 325:269-271

Approval of Oncology drugs: FDA

- Evaluation of endpoints used by FDA over the last 13 years
- 71 oncology drug applications (1990-2002)
- Tumor response endpoints in 26/57 (46%) RA applications
- Tumor response endpoints in 12/14 (86%) AA applications!

No approvals were based on HRQOL measures...!

Approval of Oncology drugs: EMEA

- Evaluation of endpoints used by EMEA over the last 6 years
- 14 "new" oncology drug applications (1995-2000)
- Most of the first applications in second/third lines
- Tumor response endpoints in 6/14 (43%) applications

No approvals were based on HRQOL measures...!

Reasons for NOT using HR-QoL

- Cumbersome and costly
- Complex methodological and statistical methods (compliance, missing, timing)
- Questionable "clinical" validity of questionnaires
- Difficult to "interpret" (meaning of findings)
- Lack of blinding/masking

PROBLEM: The alternatives are worse

Surrogates for QoL

- **Unrealistic survival benefits**: In most phase III CT in advanced disease, survival benefit (i.e., difference between arms) is about 7-9 weeks (median)

- **Biased tumor-based response**: most studies are SAT with no masking

- **Unvalidated CBM**: Composite endpoints to surrogate Quality of Life or "symptomatic" clinical benefit improvement

The questions about HR-QoL

Do the HR-QoL measures have a place in the list of potential endpoints to be used in the clinical research setting?

Do HR-QoL measures have an added value when used together with traditional clinical endpoints?

Examples

- **The contribution** of HR-QoL measures to select optimal treatment in breast cancer patients (PJ Goodwin et al, JCO 2003; 95: 263-)

- **The effects** of sytemic tharapy on health-related QoL in advanced breast cancer (A: Bottomley et al, Lancet Oncol 2003; 3: 260)

- **The added value of HR-QoL measures in advanced breast cancer patients (*Fossati* et al, Breast Cancer Res Treat, In Press)**

H-RQOL measurement in RCTs in breast cancer-taking stock

PJ Goodwin, JT Black, LJ Bordelau, PA Ganz
JCO 2003; 95: 263-

- Primary management (8): Qol provided added value,...
- Adjuvant setting (7): QoL did not influence...
- Metastatic disease (20): QoL provided little information,...
- Symptom control/supportive care (11): QoL guided treatment...
- Psychosocial interventions (20): QoL was essential,...

QoL in patients undergoing systemic therapy for advanced breast cancer

A Bottomley and P. Therasse
Lancet Oncol 2003; 3:620-

- In 19 RCTs,...most (12) on chemotherapy,.... and as secondary endpoint (15),...
- Only 7 reportes significant differences in HRQOL,...
- Several limitations were identified with methods,...
- Findings provide some information BUT limitations limit value,..

Some approaches are proposed to improve design

HR-QoL in RCTs on ABC

- **TITLE**: QoL in RCTs of cytotoxic or hormonal treatment of advanced breast cancer patients. Is there added value?

- **AUTHORS**: Fossati R, Confalonieri C, Mosconi P, Pistotti V, Apolone G

- **OBJECTIVE**: to verify if the provision of HR-QoL data (in addition to the more traditional clinical endpoints) might allow to better select treatment regimen (evaluation of the added value of HR-QoL in RCTs)

HR-QoL in RCTs (2)

- **METHODS**:
  - Identification and retrieval of RCTs on advanced breast cancer with HR-QoL assessment
  - Double, independent evaluation of contents
  - Description of methods, tools, Authors' conclusions
  - Evaluation of clinical added value

- **DATA**: 252 papers identified, 33 RCTs eligible (10.791 pts)

- **RESULTS**: Descriptive (how QoL was assessed) and evaluative (whether QoL had an effect on treatments selection)

Clinical added value

PRIMARY INDICATORS:

- Proportion of studies (or patients) where the results from the HR-QoL evaluation help take a final decision about the treatments value/efficacy (in addition to the findings from clinical endpoints)

SECONDARY INDICATORS:

- Original statements (in the paper) by Authors expliciting their decision making process for choosing the best treatment opinion (whether they chose treatment because of HR-QoL data)

OPERATIONALLY:

- A matrix formed by clinical (efficacy and safety) and HR-QoL (questionnaires scores) findings

Descriptive results

Type of study

- 13 hormonal/20 chemotherapy
- 19 first/14 second line
- 26 different/7 same drugs

Type of HR-QoL questionnaires

17 different tools used in 33 papers (11 only once)

- LASA (Priestman and Baum) questionnaires: 10
- EORTC:10
- RSCL:6
- Spitzer:4
- FACT: 3
- FLIC:3
- Others:10

Descriptive results (2)

End-points

- In all RCTs at least one clinical outcomes (RR,TTP/TTF,OS)
- In 7/33 RCTs QoL as primary endpoint
- In 7/33 a-priori identification of target domains

Results: clinical and QoL measures

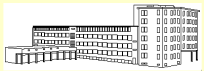
		Statistical significant (<0.05%)
At least one Clinical (RR,TTP,TTF,OS)	18/33	54%
QOL measures (selected)	8/33	24%
QOL measures in primary	2/7	29%

Results: Authors point-of-view

In 12 RCTs Authors used QoL findings in the Abstract to summarize conclusions

12/33 36%

Results: Clinical added value



CLINICAL EFFICACY AND TOXICITY	HR-QoL DIFFERENCE		TOTAL
	Yes	**No**	
Better clinical efficacy **and** better toxicity	1	2	3
Better clinical efficacy **but** worse toxicity	0	9	9
Better clinical efficacy **and** same toxicity	1	4	5
Same clinical efficacy **but** different toxicity	4	4	8
Same clinical efficacy **and** same toxicity	2	5	7
TOTAL	8 (2828)	24 (7507)	32 (10355)

Results: a synthesis

DESCRIPTIVE PART:

- very few information in papers about relevant methodological aspects (analysis plan, sample size, statistical methods, compliance)
- tools and methods etherogeneity
- poor strategies to minimize and "treat" missing data

SECONDARY INDICATORS: in 12/33 papers, in the Abstract Authors used HR-QoL data as part of their decision making process for recommending the best regimen

PRIMARY INDICATORS: possible alternative interpretations

Added value results (to be discussed)

- **Half empty:** Added value of HR-QoL in this set of data: rather unsatisfactory
  - only 8/33 positive QoL results
  - when significant differences in toxicity only 4/17 positive results, and only 1/5 when equivalence

- **Half full** Added value of HR-QoL in this set of data: rather satisfactory
  - 8/33 positive results! (with very obsolete questionnaires!)
  - good capability to identify regimens in uncertain situation (6/15)

More common limitations in the 3 reviews

- (A priori) hypothesis tested
- Rationale of measures choice
- Measures properties
- CT design (randomization, sample size, masking)
- Study implementation (mode, timing, compliance)
- (Statistical) data analysis (missing, multiple testings)
- Results presentation and reporting

Conclusions (1)

- HR-QoL has a potential role but the field is still plagued by conceptual, methodological and logistic problems

- Simpler alternatives (TRB, CBM, etc) are worse (in terms of methodology, validity, interpretability) but are more accepted by clinicians, researchers and regulators

Conclusions (2)

- EMEA and FDA are "skeptical" about the value of PROs and HR-QoL as a potential efficacy ("symptomatic" clinical benefit) endpoint in anti-cancer-drugs

- In the past, both Agencies have chosen the approach of not publishing general recommendations that would *prescribe* methodological standards (now, in preparation)