Original article

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Does a drug do better when it is new?

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Background: When assessing a new, promising therapeutic approach, a clinician's perception of a drug's effectiveness may be shaped by different kinds of phenomena, and among them, a favorable attitude towards new treatments, and as a result a tendency to overestimate their efficacy (wish bias).

Materials and methods: A retrospective study of published randomized clinical trials of doxorubicin-based chemotherapy for advanced breast cancer was carried out. Global (complete plus partial) response rate over time with allowance for type of drug regimen (mono- or polychemotherapy) and prior adjuvant therapies was assessed in the doxorubicin-containing arm using multivariate logistic regression analysis.

Results: Twenty-nine studies published from 1975 to 1999 were retrieved for a total of 2234 women with advanced breast cancer enrolled in the doxorubicin-containing arms. There was a significant decrease in response rate to doxorubicin as first-line treatment over time that resisted adjustment for important differences in therapeutic management [odds ratio for global response = 0.89, 95% confidence interval (CI) 0.81 to 0.99].

Conclusions: Although only one drug (doxorubicin) in one clinical context (advanced breast cancer) has been analyzed, our findings support the use of double blind methodology whenever possible when assessing subjective endpoints and encourage further studies aimed at defining the clinical relevance of a wish bias in medicine.

Key words: advanced breast cancer, chemotherapy, wish bias

Introduction

Although response criteria of neoplastic diseases to anticancer drugs have been strictly codified for a long time to ensure objectivity, this endpoint still requires subjective assessment by investigators. In the context of randomized clinical trials, withholding information about treatment allocation from the evaluating clinician, i.e. masking, is feasible, but often cumbersome and in oncology such practice is rather uncommon. In a meta-analysis of metastatic breast cancer medical treatment from 189 randomized trials [1], blind evaluation of response was reported in six trials while responses were simply reviewed by independent or extramural assessors in 23 trials. In these situations a bias due to financial and academic conflicts of interest or more subtle forms of 'wish bias' [2] could easily arise and account for the impression that when a drug is new it does better.

To explore and support this hypothesis we updated and extended data gathered for the above-mentioned meta-analysis and we chose to evaluate doxorubicin performance. Doxorubicin was deemed particularly apt to our aims, since this drug, alone or in combination, has been used since the early seventies and it is still widely used as a comparator for the evaluation of new drugs in breast cancer treatment [3]. Under the effect of the biases described we would expect to observe a declining response rate to doxorubicin, still detectable after taking into account changes in disease management over time.

Materials and methods

Combing through the studies used for the meta-analysis and retrieved according to the search strategy reported in the original paper [1], we collected randomized trials comparing chemotherapic regimens containing doxorubicin with doxorubicin-free regimens. Trials enrolling patients pre-treated with chemotherapy for metastatic disease were excluded.

For each study we considered only the doxorubicin-containing arm and extracted global (complete plus partial) response rate. Performance of doxorubicin over time (using randomization starting year as time variable) was evaluated using first a univariate and then a multiple logistic regression model containing those variables that were statistically significant (P <0.05) in univariate analysis [4].

Results

Twenty-nine trials [5–33], published from 1975 to 1999, were used in this study. The characteristics of the studies and

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Table 1. Description of trials

No. of trials	No. of patients	No. of patients for response	Adjuvant chemotherapy (% patients)	Palliative hormonal therapy (% patients)	Chemotherapy regimen (% patients)			Doxorubicin mean dose (mg/m^2)
					Doxorubicin as single agent	Doxorubicin plus one drug (C or V)	Doxorubicin plus two or more drugs (C, F, M or V)	
29	2234	2196	28	100[a]	13	19	68	43 (range 20–75)

[a]Total number of patients for whom information was available = 1994.
C, cyclophosphamide; F, 5-fluorouracil; M, methotrexate; V, vincristine.

Table 2. Details of the multivariate model

Variables	Odds ratio of global response	95% CI	*P* value
Time[a]	0.89	0.81–0.99	0.025
Polychemotherapy with 2 drugs versus monochemotherapy	1.41	1.03–1.94	0.031
Polychemotherapy with >2 drugs versus monochemotherapy	1.69	1.30–2.19	0.0001
Adjuvant chemotherapy: no versus yes	1.24	1.00–1.53	0.049

[a]Randomization starting year, 5 year interval.
CI, confidence interval.

patients are listed in Table 1. A total of 2234 women with advanced breast cancer were enrolled in arms that included doxorubicin. Global response rates over time are illustrated in Figure 1, where the area of each circle has been made proportional to the trial's sample size. Median response rate was 53%, range 36% to 82%.

While searching for relevant information to be used in multivariate analysis, we noticed no clear trend over time in planned dose of doxorubicin, inside either mono- or polychemotherapy categories. On the other hand, the proportion of patients treated with adjuvant chemotherapies and the proportion of patients undergoing single-agent chemotherapy regimens for advanced disease increased over time and therefore these variables were included in the multivariate model. Odds ratios (OR) for global response rate and their confidence intervals (CI) of a multivariate logistic regression model are reported in Table 2. The 11% relative decrease in the odds of a global response to doxorubicin every 5 years (OR 0.89, 95% CI 0.81 to 0.99) seems difficult to explain from a clinical point of view and might suggest the influence of other confounders. This is compatible with the result of the test of the model adequacy (analysis based on residuals) whose statistical significance ($P = 0.0001$) shows that other unknown explanatory variables should be added to improve the data fitting.

Under the hypothesis of observing a more extreme result when partial response instead of global response is considered, the same multivariate model was used to separately evaluate complete and partial response rates in all but two trials [5, 6] where this information was available. While complete response remained constant over time (OR 0.99, 95% CI 0.85 to 1.15) the partial response trend (OR 0.91, 95% CI 0.82 to 1.00) in this subset of studies mirrored the results for global response.

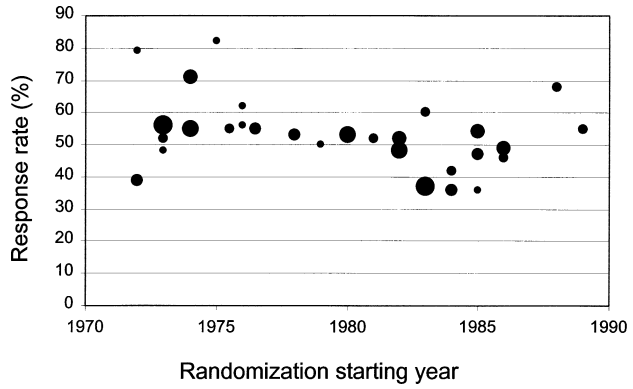

Figure 1. Global response rate by year.

Discussion

Bias in the evaluation of the efficacy of a new drug may be the consequence of a complex situation due to the influence of many factors, such as economic or academic conflicts of interest, or just the expression of an inherent aspect of medical practice that tends to overestimate a new, promising therapeutic approach (wish bias). Although empirical evidence of the existence of a wish bias are minimal, even recent official guidelines [34] for clinical trial evaluation underline the need for minimizing the effect of 'investigator expectations'. Obviously, the best way to circumvent this bias is to rely on double blind methodology; whose first use in oncology dated back to 1960 by Gehan and Schneiderman [35]. However, of the 29

studies included in our review, this approach was only used in one study [23], and in another two [24, 29] patients records were externally audited.

In this retrospective analysis of heterogeneous studies collected over more than two decades, we detected a negative trend in response rate over time and our hypothesis is that such a trend might represent indirect evidence of the effect of different kinds of phenomena and, among them, a wish bias. Moreover, it seems reasonable that this negative trend was mainly due to a decrease in the rate of partial response since evaluation of partial response involves more subjective judgment than complete response. It is reassuring that, in order to verify the correctness of our methodologic approach, the multivariate model also captured the greater efficacy of polychemotherapy versus single-agent chemotherapy and the negative influence of adjuvant chemotherapy to further chemotherapic treatment performed in a metastatic setting, effects which have already been well documented by clinical oncologists [3, 36–38].

Another way to study the phenomenon of wish bias would be to compare doxorubicin response rate in trials where this agent was considered a new drug (i.e. doxorubicin compared with regimens containing cyclophosphamide, methotrexate, fluorouracil and vincristine in different combinations) [5–21] with trials where doxorubicin was itself a comparator to newer drugs like epirubicin, mitoxantrone, vinorelbine or taxanes [22–33]. When we followed this approach doxorubicin showed greater activity in trials where this agent was considered a new drug. This result, however, did not reach statistical significance in a multivariate model including all variables (Table 2) except for the variable time, which was substituted by the dichotomous predictor 'doxorubicin new' versus 'doxorubicin as a comparator' (OR 1.25, 95% CI 0.98 to 1.58; $P = 0.072$).

Therefore, the results of this review are to be interpreted within the context of its limitations: (i) we analyzed only one drug and one endpoint in one specific clinical context; (ii) we did not use individual patient data and therefore our capacity to investigate sources of clinical heterogeneity was limited; (iii) our analytical approach did not entail comparison of patients within trials (i.e. like with like) and we could not rule out potential confounding effects of unmeasured characteristics of patients which can be balanced by the randomization process only; (iv) we did not consider as a possible heterogeneity factor the presence of sponsorship by pharmaceutical companies or any other financial links; (v) we could not consider the substantial changes in disease management, for example evolution of imaging techniques, in the long period covered by these trials.

Great concern has been expressed in the literature about possible systematic distortion in cost-effectiveness analysis [39], clinical efficacy [40] and drug safety profile [41], specifically due to financial conflicts of interest [42]. Our study was not designed to capture the effects of conflicts of interest but the possible peculiar effect of an attitude favoring new promising drugs. Regarding the sources of sponsorship for the trials considered in this study, it is remarkable that almost half of the patients were enrolled in trials that did not report any source of funding.

Since indirect evidence for the existence of a wish bias emerged from our analysis, we believe that blinding should be strongly recommended for any subjective endpoint assessment (response, time to progression, etc.) and the search for this kind of bias should be unremitting in order to encourage the medical research community into adopting a more objective approach and also to maintain public confidence.

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