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Clinical report

Survival in patients with metastatic breast cancer: analysis of randomized studies comparing oral aromatase inhibitors versus megestrol

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In patients with metastatic breast cancer, second-line therapy with aromatase inhibitors can improve survival in comparison with megestrol. We conducted a meta-analysis to assess the effectiveness of aromatase inhibitors versus megestrol. After a *Medline* search, three trials (evaluating letrozole, anastrozole or exemestane versus megestrol) were included in the survival meta-analysis. Our methodology retrieved patient-level information on survival. In comparison with megestrol, aromatase inhibitors prolonged survival at levels of statistical significance (relative death risk for oral aromatase inhibitors=0.79, 95% confidence interval 0.69–0.91; *p*=0.0011). A lifetime analysis of the pooled survival curves of aromatase inhibitors versus megestrol found a mean survival gain of 4.1 months per patient. Aromatase inhibitors confer a significant survival benefit to patients with metastatic breast cancer as compared with megestrol. A preliminary calculation of the cost per life year gained shows that the pharmacoeconomic profile of these drugs is favorable. [© 2000 Lippincott Williams & Wilkins.]

Key words: Aromatase inhibitors, breast cancer, survival.

Introduction

In patients with metastatic breast cancer who have not responded to tamoxifen, the optimal second-line hormonal therapy remains undefined. Megestrol is considered to be the standard treatment, but in recent times several aromatase inhibitors (given orally, e.g. exemestane, letrozole and anastrozole, or parenterally, e.g. formestan) have been developed and tested both in controlled and in uncontrolled clinical studies. Phase II studies[1–3] do not permit us to define the therapeutic role of these new agents in comparison with megestrol. On the other hand, the results of phase III randomized controlled trials (RCTs) evaluating aromatase inhibitors versus megestrol[4–8] have been conflicting[9,10] and have never been included in a systematic overview or in a meta-analysis.

In the present study, we conducted a meta-analysis of the survival data obtained in RCTs comparing aromatase inhibitors with megestrol.

Methods

Study design

Our study was aimed at evaluating survival for the two following therapeutic options in patients with metastatic breast cancer: (i) aromatase inhibitors and (ii) megestrol. Our analysis consisted of two sequential phases: (i) a literature search of the RCTs that evaluated survival for these two treatment options, and (ii) survival analysis with meta-analytic pooling of the results from the pertinent trials and with statistical testing.

Literature search

Eligible studies were identified through a *Medline* search on the Internet (*PubMed Medline*, 2000 version; address http://www4.ncbi.nlm.nih.gov/PubMed/). This search covered the period from 1 January 1966 to 10 May 2000, and was based on two key words ('aromatase', 'survival') and two search limits ('randomized controlled trials', 'English language').

Our *Medline* search was supplemented by two additional searches on the *Iowa-IDIS* database (Iowa Drug Information Service, University of Iowa, IA) from 1966 to February 2000 and on the *Drugdex* databank (*Drugdex*, volume 103; Micromedex, Englewood, CO). In addition, we reviewed all the references listed in the trials we found.

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Selection

Our literature search identified the RCTs that evaluated survival in patients with metastatic breast cancer treated with aromatase inhibitors. Among these, only the studies that met the following criteria were included in our meta-analysis: (i) enrolment of patients with metastatic breast cancer not responsive to tamoxifen; (ii) randomized assignment to either an aromatase inhibitor or megestrol; (iii) survival assessment (with presentation of the survival graph); and (iv) the aromatase inhibitor is approved for this clinical indication by either FDA or EMEA or both. This fourth criterion was adopted to ensure the practical transferability of the results of our meta-analysis, and to frame our findings as a practical guide for drug selection and prescription in the every-day practice.

Meta-analysis of survival data

Survival meta-analysis of individual patient data. This analysis was carried out using individual patient information,[11–14] i.e. survival length and status at the last contact. In particular, the data of individual survival (with slight approximations; see Appendix 1) were derived from the information reported in the figures of the original survival graphs. After obtaining these survival data for all subjects enrolled in the pertinent studies, our analysis generated a pooled survival curve for aromatase inhibitors and a pooled survival curve for megestrol. In the survival comparison between the two treatments, standard life-table methods (Kaplan–Meier analysis) and standard techniques for univariate or multivariate testing (i.e. log-rank test and Cox model for multivariate relative risk estimation, respectively) were used. When possible, the survival data were analyzed using an intention-to-treat approach. The assessment of inter-trial heterogeneity was based on Cox model.

Meta-analysis of aggregate survival data. The meta-analytic comparison between aromatase inhibitors and megestrol was re-assessed using trial-specific aggregate survival data, and so without using patient-level information. The statistical method utilized for this analysis has been described previously[15] and reflects a traditional approach for conducting a survival meta-analysis. Its application produced a meta-analytic odds-ratio of death for aromatase inhibitors versus megestrol and an assessment of the inter-trial heterogeneity.

Secondary analyses of the survival data. These secondary analyses included: (i) a repetition of the randomized survival comparisons of anastrozole versus megestrol, letrozole versus megestrol and exemestane versus megestrol, which had the purpose to confirm the agreement between our re-constructed survival data and the original survival data of the trials; (ii) a retrospective survival comparison of anastrozole versus letrozole versus exemestane; and (iii) a retrospective survival comparison between the control groups (treated with megestrol). In cases (ii) and (iii), the secondary analyses lacked the randomized design and suffered from the potentially different selection criteria of the different studies; hence, these analyses were not aimed at providing conclusions about these comparisons, but had the purpose to suggest hypotheses for interpreting the results of our analysis.

Lifetime survival gain estimation. The two pooled survival curves for aromatase inhibitors and megestrol were subjected to a lifetime analysis (Gompertz model[16,17]) in order to estimate the mean lifetime survival gain per patient.[18] According to current guidelines on cost-effectiveness studies[19] and considering the potential economic implications of our study, the calculations of this analysis were based both on an undiscounted approach and on a discounted approach (annual discount rate=3%).

Results

Literature search

The literature search identified a total of 19 studies, five of which were eligible for our analysis.[4–8] On the basis of our selection criteria, the studies by Buzdar *et al.*[7] and by Goss *et al.*[8] were excluded because the aromatase inhibitors of these two trials (fadrozole and vorozole, respectively) have not been approved by FDA or EMEA. Other 14 studies were excluded because they were not RCTs comparing the two treatment options considered by the meta-analysis. Hence, only three clinical trials evaluating three oral aromatase inhibitors (i.e. exemestane,[6] letrozole[4] and anastrozole[5] met the inclusion criteria of our analysis (Table 1).

Survival meta-analysis of individual patient data

The total number of patients was 803 for oral aromatase inhibitors and 845 for megestrol. The survival information for these patients was derived from: (i) Figure 1 for the study by Kaufman *et al.*,[6] (ii) Figure 1 for the study by Dombernowsky *et al.*[4] and (iii) Figure 1 for the study by Buzdar *et al.*[5] In all three

Table 1. Characteristics of three RCTs included in the meta-analysis

Study[a]	Follow-up length (months)	Aromatase inhibitor group		Megestrol group		Survival comparison between aromatase inhibitor versus megestrol	Statistical level for the survival comparison
		No. of patients	Type of hormone therapy	No. of patients	Type of hormone therapy		
Kaufmann *et al.*[6]	38	366	exemestane 25 mg/day	403	megestrol 160 mg/day	2-year rate of 66% for exemestane versus 57% for controls	$p=0.039$ or $p=0.046$[b]
Dombernowsky *et al.*[4] [c]	31	174	letrozole 2.5 mg/day	189	megestrol 160 mg/day	2-year rate of 53% for letrozole versus 44% for controls	$p=0.15$
Buzdar *et al.*[5]	40	263	anastrozole 1 mg/day	253	megestrol 160 mg/day	2-year rate of 58% for anastrozole versus 43% for controls	$p<0.025$

[a]For all of these studies, the inclusion criterion was metastatic breast cancer after tamoxifen failure.
[b]By log-rank test and by Cox analysis, respectively.
[c]This study included also a low-dose letrozole group (0.5 mg/day) which was not considered by our analysis.

cases, the graphs were constructed using the intention-to-treat approach.

In the trial by Dombernowsky *et al.*[4] the legends to the survival graphs provided complete information on the time distribution of deaths and on the time distribution of right-censored patients. In the remaining two trials, the survival information was estimated by the approximate procedure described in Appendix 1. The individual survival times of the 1648 patients are not presented herein, but have been published on the Internet site http://members.xoom.com/sifotpn/supplements/aromat.htm.

Our survival meta-analysis yielded the two survival curves shown in Figure 1. The log-rank test showed a significantly better survival for oral aromatase inhibitors versus megestrol (χ^2=11.6; $p<0.001$). The Cox analysis (that considered the effect on survival of two variables: 'study', introduced as a categorical variable stratified on three levels, and 'treatment', introduced as a categorical variable stratified on two levels) calculated a relative death risk of 0.79 for oral aromatase inhibitors versus megestrol [95% confidence interval (CI) 0.69–0.91; p=0.0011]. In the comparison across the three trials (which evaluated inter-trial heterogeneity), the study-specific values of relative death risk (Cox model) were the following: 1.14 (95% CI 1.04–1.26; p=0.0056) for Buzdar's study[5] and 0.74 (95% CI 0.66–0.82; $p<0.001$) for Kaufmann's study[6] (values calculated in comparison with Dombernowsky's study[4] which was assumed to have death risk=1); these data show that there was some inter-trial heterogeneity in the clinical material namely because the overall survival pattern was significantly worse in Buzdar's study as compared with the other two studies.

Meta-analysis of aggregate survival data

In this analysis, the pooled odds-ratio of death for oral aromatase inhibitors was 0.73 (95% CI 0.62–0.86; $p<0.001$) at 24 months, which was very close to the relative risk obtained from the meta-analysis of individual patient data. The level of inter-trial heterogeneity was significant (χ^2=14.8, d.f.=2, $p<0.01$).

Secondary analyses of the survival data

Our first secondary analysis repeated the survival comparison reported in three studies by Kaufmann,[6] Dombernowsky[4] and Buzdar,[5] the results (Table 2) showed a very close agreement between our reconstructed survival data and the original results reported in the three trials. Regardless of the methodological

approach adopted, both of our meta-analyses found a significant inter-trial heterogeneity. To understand the sources of this heterogeneity, our second secondary analysis explored the retrospective survival comparison of anastrozole versus letrozole versus exemestane (without including any of the control groups). Its results (Table 3) indicated that all of the pairwise comparisons between these three agents reached the level of statistical significance. In this analysis exemestane ranked first, letrozole second and anastrozole third.

Our third secondary analysis explored the retrospective survival comparison of the three megestrol groups of the three trials (without including any of the aromatase groups). Its results (Table 3) indicate that the megestrol group of Kaufmann's study[6] had a significantly better survival pattern than the other two control groups.

Lifetime survival gain estimation

After application of the Gompertz model to the two pooled curves of Figure 1, the mean lifetime survival was 33.0 months per patient in the aromatase group and 28.9 months per patient in the megestrol group (undiscounted analysis). Using 3% annual discount rate, these two figures were 31.6 and 27.7 months, respectively. The undiscounted survival gain was 4.1 undiscounted per patient (3.9 months in the discounted analysis).

Discussion

Our study tried to summarize the current information on the effectiveness of aromatase inhibitors through a survival meta-analysis of individual patient data. Our overall results show that aromatase inhibitors improve survival at levels of statistical significance. There are, however, several points of controversy.

First, our meta-analysis was negatively affected by the presence of a significant heterogeneity. Pooling together the survival data of exemestane, anastrozole and letrozole into a single patient group was helpful to define the overall effectiveness of this new class of anti-cancer hormonal agents, to quantify the magnitude of their clinical benefit and to form the basis of a simplified cost-effectiveness evaluation (see below). On the other hand, the presence of this heterogeneity supports the hypothesis of some differences among these three aromatase inhibitors.

Table 2. Repetition of the survival comparison reported in the three trials by Buzdar *et al.*, [5] Dombernowsky *et al.* [4] and Kaufmann *et al.*[6]

Clinical material	Statistical comparison	Death risk (95% CI, *p* value) by Cox analysis		Results of log-rank analysis	
		From our reconstructed data	From the original data	From our reconstructed data	From the original data
Buzdar's study[5]	anastrozole ($n=263$) versus megestrol ($n=253$)	0.82 (0.66–1.02, $p=0.07$)	0.78 (0.60–<1.0, $p<0.025$)	$p=0.055$	not reported
Kaufmann's study[6]	exemestane ($n=366$) versus megestrol ($n=403$)	0.73 (0.56–0.95, $p=0.02$)	0.77 (0.59–0.99, p0.046)	$p=0.016$	$p=0.039$
Dombernosky's study[4]	letrozole ($n=174$) versus megestrol ($n=189$)	0.81 (0.62–1.05, $p=0.11$)	0.82 (0.63–1.08, $p=0.15$)	$p=0.093$	not reported

Table 3. Retrospective non-randomized comparison between the three aromatase inhibitors (secondary analysis no. 2) and between the three control groups (secondary analysis no. 3)

Statistical comparison	Death risk (95% CI, *p* value) by Cox analysis
Anastrozole ($n=263$) versus letrozole ($n=174$)	1.17 (1.02–1.35, $p=0.023$)
Exemestane ($n=366$) versus letrozole ($n=174$)	0.70 (0.60–0.82, $p<0.001$
Buzdar's control group ($n=253$) versus Dombernowsky's control group ($n=189$)	1.11 (0.98–1.27, $p=0.09$)
Kaufmann's control group ($n=403$) versus Dombernowsky's control group ($n=189$)	0.76 (0.66–0.87, $p<0.001$)

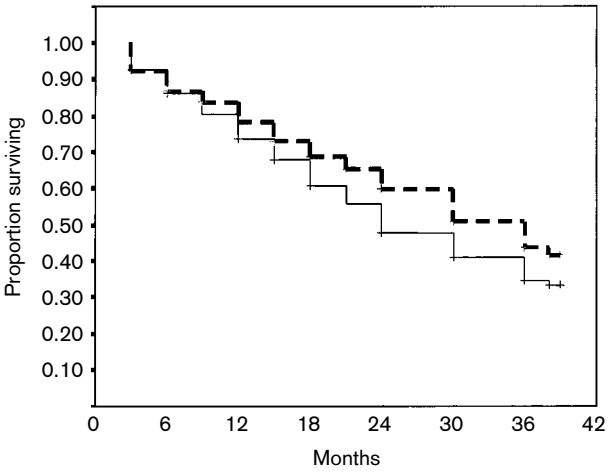

Figure 1. Survival in patients with metastatic breast cancer: the upper curve (dashed line) shows the survival pattern for patients treated with an aromatase inhibitor (n=803), while the lower curve (solid line) refers to patients with megestrol (n=845). Both curves were calculated by standard actuarial methods using individual patient data. See text for details.

Two secondary analyses (nos 2 and 3) were specifically aimed at exploring the sources of this inter-trial heterogeneity. The analysis no. 2 found that, in terms of survival, exemestane was superior to anastrozole and letrozole was superior to anastrozole (with a statistical significance for both differences). Did this finding depend on a real difference between these agents or on different selection criteria of the respective patient cohorts?

To explore this question, our secondary analysis no. 3 compared the three megestrol groups with one another and found a significantly better survival pattern for Kaufmann's megestrol group in comparison with the other two control groups. In general, the characteristics of Kaufmann's patient cohort seemed to be prognostically more favorable than those of the other two studies; as a result, the superiority of exemestane over the other two agents might simply be related to the selection of patients with a better prognosis. In brief, our results suggest the hypothesis of potentially relevant differences among these three aromatase inhibitors, but no definite conclusion can at present be offered on this point.

The values of survival gain estimated for the aromatase inhibitors versus megestrol can be interpreted in the context of a simplified cost-effectiveness analysis. A preliminary evaluation must first consider that the price of these agents is very homogenous across the European countries. For example, the price of exemestane, expressed in Euros/day of treatment at the dose of 25 mg, is 7.54 in Germany, 8.03 in the UK, 7.49 in Holland, 7.37 in Denmark, 7.85 in Sweden and 6.81 in Italy, i.e. about 7.5 Euros/patient/day. In addition, regardless of the country, the three aromatase inhibitors show very small price differences from one another (considering the Italian prices, letrozole costs 6.63 Euros at the dose of 2.5 mg/day, anastrozole 6.49 Euros at the dose of 1 mg/day and exemestane 7.54 Euros as previously pointed out). Also the price of megestrol (e.g. 3.25 Euros/day at the dose of 160 mg according to the Italian price) does not show any important variations between countries.

With an approximate calculation, the choice of using an aromatase inhibitor instead of megestrol implies an increase in cost of about 4.25 Euros/patient/day or 127.5 Euros/patient/month. Because the life expectancy of these patients is around 30 months/patient according to our lifetime analysis, the lifetime increase in cost can be estimated as $127.5 \times 30 = 3825$ Euros/patient. On the other hand, the order of magnitude of the survival gain is around 4 months/patient (in comparison with megestrol), i.e. approximately 0.333 years/patient. The cost per life year gained is the ratio between the lifetime incremental cost and the lifetime incremental effectiveness (or lifetime survival gain). In this case, this pharmacoeconomic parameter is 3825/0.33=11 486 Euros per life year gained, which more or less correspond to US$12 000 per life year gained.

Current standards in the area of cost-effectiveness analysis tend to assign a favorable cost/effectiveness profile to values around 10 000 or 20 000 Euros per year of life gained even though values around 50 000 Euros (or around US$50 000) per year gained have previously been accepted for many types of therapeutic intervention. Hence, on the basis of our preliminary evaluation, the cost-effectiveness ratio for aromatase inhibitors in comparison with megestrol seems to be favorable.

We conclude that in patients with metastatic breast cancer not responsive to tamoxifen, aromatase inhibitors can improve survival in comparison with megestrol at an acceptable cost.

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Appendix 1: approximations introduced in our survival analysis

In our analysis, each of the two survival curves (aromatase inhibitor group and megestrol group) was analyzed by the approximate method described by Fine *et al*.[20] in order to convert the aggregate survival data originally published in graphical form into values of individual survival. This method determines the distribution over time of deaths and of terminations of follow-up (i.e. 'cases of right censored patients') using a graphical analysis of the published curves. The calculation requires also the knowledge of the total number of patients and of the total number of deaths (reported separately for the two arms of the study under examination). This approximated method for constructing individual survival times has previously been used in numerous retrospective overviews and in meta-analyses of survival data.[20–25]