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Does biomarker information impact breast cancer patients' preferences and physician recommendation for adjuvant chemotherapy?

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Abstract

Purpose—This study aimed to examine how biomarker information would impact patients' preferences and physicians' recommendations for adjuvant breast cancer therapy.

Methods—At the 18-month follow-up, participants in a large, double blind randomized controlled trial of adjuvant chemotherapy with bevacizumab or placebo (E5103) were surveyed about their preferred treatment (either chemotherapy A alone or chemotherapy A+B) in two hypothetical scenarios: 1) without biomarker information; and 2) after learning that they tested positive for a “B-receptor” which modestly increased both the benefit and toxicity expected with chemotherapy A+B. We performed a cross-sectional analysis of the prospectively collected survey data and used the McNemar's test to examine changes in treatment preferences. A one-time survey of clinical investigators who enrolled patients on the trial evaluated physician recommendations in response to the same biomarker information.

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Compliance with Ethical Standards: Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Results—439 patients completed both scenarios on 18-month survey. Most participants preferred A + B in both scenario 1 and 2 (77% and 76% respectively). The increase in benefit and toxicity associated with the positive biomarker information in scenario 2 led 60/439 (14%) of patients to switch their treatment preference. The corresponding physician survey revealed that most physicians chose regimen A+B in scenario 1 (77%), and more so after the biomarker information was available in scenario 2 (84%).

Conclusions—Information about a positive biomarker indicating increased benefit and toxicity from additional chemotherapy did not change many participants' preferred treatment. The majority preferred the most effective course in both scenarios. Similarly, most investigators discounted increased toxicity and valued increased benefit.

Parent Trial Registration—NCT00433511

Keywords

breast cancer; biomarkers; patient preferences; adjuvant therapy; risk; toxicity

Introduction

Biomarkers are used widely in medicine to risk stratify patients for the development of disease and disease outcomes. In cancer care, biomarkers of the disease and patient are routinely employed to help to identify patients who may be at increased risk for disease recurrence (e.g. genomic risk tests such as Mammprint) and/or to identify those who may benefit from a particular therapy (e.g. hormone receptors and tamoxifen, HER2 expression and trastuzumab), or those who may experience greater toxicity from therapy (e.g., *DPYD* deficiency and 5-fluorouracil therapy). Ideally, a treatment biomarker will identify those who benefit with limited or no toxicity. However, for some medicines, such as bevacizumab, early retrospective biomarker studies have suggested that patients who may benefit also experience increased toxicity.[1,2]

As we continually move toward personalized, precision medicine, biomarkers are becoming increasingly utilized, particularly in cancer.[3] Biomarker information can have a significant impact on clinical decision-making. Studies suggest that the introduction of well-tested biomarkers may alter the course of treatment, and are important to help inform clinicians' recommendations. In breast cancer, the use of OncotypeDx as a marker of potential benefit of chemotherapy (or lack thereof) and use of HER2 testing are recent examples.[4] In several other malignancies, they are also a mainstay for selection for assessing risk and selecting therapy.

The necessity of rigorous assessment of the value of biomarkers in clinical practice is clearly recognized.[5] However, most biomarkers are not absolute with regard to their potential prognostic and predictive impact for either benefit or toxicity. Not all patients who receive treatment directed at least in part by a biomarker will experience a good outcome and some will have toxicity from treatment even if a biomarker indicated they were not likely to. Given this uncertainty, it is important to understand how patients view potential benefits and risks with and without a biomarker, especially given that many of the new biomarker assays

are costly and may not actually affect treatment recommendations or decisions in some settings. The purpose of this study was to examine how biomarker information would impact patients' preferences for therapy in the setting of a moderate benefit, modest increased risk scenario. To complement the patient perspective, we also evaluated physician perspectives and recommendations.

Methods

We surveyed participants in a large, double blind randomized controlled trial, ECOG-ACRIN Cancer Research Group Protocol 5103 (E5103), a phase III adjuvant breast cancer trial that randomized 4994 patients to doxorubicin (60 mg/m²) and cyclophosphamide (AC) for four cycles, followed by 12 weeks of weekly paclitaxel with placebo (Arm A) or to the same chemotherapy with either concurrent bevacizumab (Arm B) or concurrent plus sequential bevacizumab (Arm C). Treatment assignment was unblinded with the last placebo/bevacizumab infusion (week 18-22), after which, only Arm C participants continued on open label bevacizumab for an additional 30 weeks. Patients enrolling on E5103 between 1/5/2010-6/8/2010 participated in the Decision-Making/Quality of Life component (DM/QOL) longitudinal survey study. Patients were assessed at 5 timepoints including baseline (pretreatment) and at 18 months post-baseline, to examine potential long-term effects of the treatments on patients' quality of life. Telephone interviewing was used to collect data at each of these assessment points. Analyses presented here focus on participants' responses to the 18-month assessment which included an expanded set of items about the impact of a theoretical biomarker on preferences for therapy.

For the parallel physician survey, we sent an email with link to the brief survey to all physicians who could register patients to E5103. The physician survey was conducted between 1/14/2013-4/1/2013.

Measures

We developed two scenarios to examine how biomarker information might impact preferred treatment. The scenarios were pilot tested with 15 breast cancer patients undergoing chemotherapy and 5 providers. Based on feedback we made edits to improve comprehension and acceptability. The survey asked respondents for their preferred treatment (either chemotherapy A alone or chemotherapy A+B) in two hypothetical scenarios: 1) without predictive biomarker information; and 2) after learning that they tested positive for a "B-receptor" which modestly increased both the benefit and toxicity of chemotherapy A+B. The *risk* information was given in both numerical (table) and graphical (100-person pictograph) format. See Figure 1 for scenarios. The scenarios generally reflected the potential anticipated benefits and risks with and without treatment B for patients with average risk level of *recurrence or toxicity* similar to those enrolled on the trial. Respondents indicated their preferred treatment, the strength of preference on a 6-point scale (from 0-not sure to 5-strongly prefer it), and the main reason for their choice (e.g., greater benefit, less toxicity, presence of positive biomarker). For these scenarios, we focused on the impact of testing positive for the biomarker because we assumed that if the biomarker was negative, that all participants would not take chemotherapy A+B.

The parallel physician survey contained similar biomarker questions as the patient survey but focused on treatment recommendation for a theoretical patient.

Statistical Methods

The study had 86% power to detect a change in preferred treatment from scenario 1 to scenario 2 of 20% with 400 respondents assuming a 7% difference between the discordant cell rates of those who would no longer use the chemotherapy A+B regimen and those who now would (two-sided 0.05 level McNemar's test). Testing between groups was performed by the Fisher's exact test for categorical variables and by the Wilcoxon rank sum test for continuous or ordinal level data. Two sided p-values <0.05 were considered statistically significant.

Results

During the DM/QOL enrollment period, 571 participants started protocol therapy and 519 participants who had not withdrawn prior to 18 months were contacted. Eighty-five percent (439/519) responded to both hypothetical scenarios. Please see Figure 2 for flow diagram for this analytic sample. Response at 18 months did not vary by whether a participant had been randomized to placebo or one of the experimental therapy arms: Arm A 89/106 (84%), Arm B 175/210(83%), Arm C 175/203 (86%) (p=0.49).

Arms were well balanced with respect to patient demographics and disease characteristics (Table 1). There were also no differences with respect to these same characteristics between participants in this DM/QOL substudy and those from the parent E5103 trial not in this substudy.

Table 2 presents the participants' treatment preferences in scenarios 1 and 2. In response to scenario 1, without biomarker information, the majority (77%) of patients preferred chemotherapy A+B (338/439) with 23% (101/439) preferring chemotherapy A alone. Ninety-one percent of individuals who chose A+B (309/338) indicated that the fact that most women were alive and cancer free with that therapy was the most important reason for their preference. Among patients who chose chemotherapy A alone, 89% (90/101) indicated fewer patients having serious problems with A as the most important reason for their treatment preference.

When biomarker information was introduced, 76% (334/439) of patients preferred regimen A+B and 24% (105/439) preferred A alone. The modest increase in benefit and toxicity associated with the positive biomarker information in scenario 2 led 60/439 (14%) of participants to switch their preference, with 28 people changing from preferring A alone to preferring A+B and 32 people switching preferences from A+B to A after introduction of the new biomarker information (p=0.69). Among all participants, the main reasons reported for their treatment preference in scenario 2 were more women alive and cancer free with chemotherapy A+B (64% [281/439]), the lower risks with chemotherapy A (20% [88/439]), and positive biomarker result (10% [43/439]).

Participants were also asked the strength of their preferences, and those who preferred chemotherapy A+B felt more strongly about their preference for both scenario 1 and scenario 2 ($p<0.01$). (see Table 3) On a likert scale of 0-5 (not sure to strongly prefer), 92% of patients preferring chemotherapy A+B in scenario 1 answered 3 regarding the strength of their preference in contrast to 81% preferring chemotherapy A. In scenario 2, 91% of those preferring chemotherapy A+B answered 3 compared to 75% who preferred chemotherapy A.

In exploratory analyses, no significant differences were observed in preferences, strength of preferences, or proportion of participants switching preferences from scenario 1 to scenario 2 between respondents who had been randomized to receive bevacizumab or not in the parent treatment study.

For the physician survey, 15% (166/1123) of physicians who were the registering investigator for a patient on the parent study and had an active email on file responded to both hypothetical scenarios. Without biomarker information (Scenario 1), 77% (127/166) of physicians recommended chemotherapy A+B. With biomarker information (Scenario 2), 16% (27/166) switched their treatment preference with a significant number switching to chemotherapy A+B ($p=0.02$) with 84% (140/166) of physicians overall recommending chemotherapy A+B. Of those preferring chemotherapy A+B in scenario 2, 82% indicated the fact that most women were alive and cancer free as the most important reason for this selection and 16% indicated positive biomarker (B-receptor test result) as the second most important reason.

Discussion

Precision medicine represents an emerging approach for disease treatment and prevention that takes into account each individual's heterogeneity in genes, environment, and lifestyle. [6] Many precision medicine initiatives are underway that have the potential to vastly improve how we deliver care for patients with cancer, in particular. Well-tested and validated predictive biomarkers offer the promise of the ability to target treatment more appropriately to those who will benefit or benefit most, while sparing those who might be least likely to benefit or have the greatest risks of toxicity.[7] This has important implications for both individual patients as well as society including potential cost savings.

There has been little prior research assessing patient reactions to a biomarker and how it might influence their preferences for treatment. Our findings from participants in a large adjuvant breast cancer chemotherapy trial suggest that a biomarker which predicts modest increased benefits and risks for patients would have only limited impact on patient preference for therapy. The fact that the majority of both patients and providers seem to discount increased risk of toxicity in the face of potentially increased benefit suggests that such information will likely only be helpful for the majority if associated risks and benefits are more than modest. Nearly a quarter of patients (23% in scenario 1 and 24% in scenario 2) were focused on the toxicity and would not choose to take the additional treatment (treatment B), with or without a positive biomarker.

Although some patient (11%) and physician (16%) respondents indicated that the positive biomarker was the main reason for their choice of preferred treatment, overall, introduction of the biomarker information did little to change the participants' preferred treatment.

These findings from patients and oncologists from a large randomized trial utilizing a double-blinded placebo control to evaluate the role of a promising novel cancer therapy should help to inform further research in this area regarding the utility of biomarker information. There have been prior studies examining patients' attitudes toward molecular testing which are generally positive, and some literature examining how biomarkers impact physician decisions and adherence to guidelines.[8,9] However, there is a paucity of research examining how biomarker information impacts or influences patients' treatment preferences. [10] A few studies examining patient's reactions to OncotypeDX results suggest that genomic information may have more influence than standard information on preferences for chemotherapy.[11,12] In our study, 10% of women reported the theoretical positive biomarker test result itself was more important than the associated benefits or toxicities in determining their preferred treatment.

These results should be interpreted in the context of a number of limitations. First, study participants may be different than the general public and our findings, in particular, do not tell us anything about patients who were not offered or refused participation in this trial. We have no information on non-trial participants but other research suggests that patients who are offered and participate in clinical trials often represent select populations with regard to medical and sociodemographic factors.[13] Further, we did not evaluate more than modest benefit or risk scenarios given we wanted to most emulate realistic potential findings from the parent clinical trial and thus our results may not reflect patient or provider preferences in other scenarios. It would be particularly interesting to assess the threshold of toxicity beyond which any incremental benefit, regardless of scale, would not be chosen. Finally, while the patient participant survey responses were high and thus findings are likely representative of trial participants, the assessment of physicians' preferences was limited by a low response rate and thus should be interpreted with caution.

Nevertheless, this is one of the few studies that we are aware of that has attempted to understand the impact of a potential biomarker on treatment decisions and preferences among patients who have participated in a clinical trial and thus have had experience with weighing the potential benefits and risks of the cancer treatment. In light of the important impact of patient and provider views and preferences on interpretation of findings from biomarker validation studies and treatment decisions, we believe it is critical that as biomarkers are developed and tested, consideration of whether and how they might affect decisions and care should be studied prospectively. We should continue to improve our understanding of patient perspectives on novel biomarkers and their potential impact on patient decisions and physician recommendations, particularly in settings where the biomarker leads to modest discriminatory effects. Precision medicine relies on the identification of biomarkers to predict response to treatment and prognosis. These biomarkers will refine estimates, but they will not remove all uncertainty. The value of information provided by these biomarkers can be evaluated by their ability to change decisions and improve health outcomes. Thus, future research will be needed to determine

thresholds for the value of any given biomarker as this field continues to grow and enhance understanding of how to incorporate these potentially costly tests into clinical decisions, recognizing that the value of information for some patients might be negligible.

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Table 1: Comparing Chemotherapy A and A&B

	Benefits: The number of women out of 100 who will be alive and cancer free in 5 years:	Serious Problems: The number of women out of 100 who will have a stroke or heart problem:
Chemotherapy A	80 women	1 woman
Chemotherapy A & B	85 women	3 women

Figure 1. Comparing Chemotherapy A and A&B

Table 2. Comparing A and A&B for 100 women who have positive B-receptor

	Benefits: The number of women out of 100 who will be alive and cancer free in 5 years:	Serious Problems: The number of women out of 100 who will have a stroke or heart problem
Chemotherapy A	80 women	1 woman
Chemotherapy A&B	90 women	6 women

Figure 2: Comparing Chemotherapy A and A&B for women with positive B-receptor

Figure 1. Two hypothetical scenarios presented to survey participants depicting average anticipated risk of recurrence and serious toxicity:
A) Scenario 1: without predictive biomarker information
B) Scenario 2: after learning that they tested positive for a “B-receptor” which modestly increased both the benefit and toxicity of chemotherapy A+B.

Figure 2. Flow Diagram of Participants*

*Respondents at 18 months may or may not have responded at baseline.

Table 1
Patient Demographics and Disease Characteristics

	Placebo Arm: A (n=89 [*])	Experimental Treatment: Arms B/C (n=350 [*])	Total n=439	p-value ^{**}
Age				
Median (range)	52(26 – 75)	51(25 – 76)	51(25 – 76)	0.87
Gender				
Female	87 (98)	348(99.7)	436(99.3)	0.11
Male	2(2)	1(<1)	3 (<1)	
Race				
White	79(89)	299(85)	378(86)	0.52
Black	9(10)	38(11)	47(11)	
Other	1(1)	13(4)	14(3)	
Ethnicity				
Hispanic	4(5)	17(5)	21(5)	1.00
Non-Hispanic	80(95)	310(95)	390(95)	
Unknown/missing	5	23	28	
Marital Status				
Single	4(5)	33(10)	37(9)	0.19
Married/Partner	68(80)	232(71)	300(73)	
Separated/Divorced/Widowed	13(15)	62(19)	75(18)	
Unknown/missing	4	23	27	
Education				
Less than High School	1(1)	22(7)	23(6)	0.98
High School, Technical School, Some College	48(57)	156(48)	204(49)	
College	36(42)	150(45)	186(45)	
Unknown/missing	4	22	26	
Menopausal Status				
Premenopausal	36(40)	137(39.6)	173(39.7)	0.18
Perimenopausal	6(7)	16(5)	22(5)	
Postmenopausal	45(51)	192(55)	237(55)	
Male	2(2)	1(<1)	3(<1)	
Unknown/missing	-	4	4	
Hormone Receptor Status				
ER – and PR –	30(34)	123(35)	153(35)	0.90
ER + and/or PR +	59(66)	227(65)	286(65)	
Grade				
1	9(10)	27(9)	36(8)	0.99
2	29(33)	125(37)	154(36)	
3	49(56)	189(55)	238(56)	

	Placebo Arm: A (n=89 [*])	Experimental Treatment: Arms B/C (n=350 [*])	Total n=439	p-value ^{**}
Unknown/missing	2	9	11	
Tumor Size				
2 cm	35(39)	126(36)	161(37)	0.63
> 2 – 5 cm	44(49)	184(53)	228(52)	
> 5 cm	10(11)	40(11)	50(11)	
Node Category				
Negative	22(25)	99(28)	121(28)	0.65
1 – 3	36(40)	132(38)	168(38)	
4	31(35)	119(34)	150(34)	
Surgery				
Breast Conserving Surgery	41(46)	150(43)	191(44)	0.63
Mastectomy	48(54)	200(57)	248(56)	

^{*} In E5103, patients were randomized in a 1:2:2 ratio across the placebo and 2 bevacizumab arms.

^{**} based on Fisher's exact test for categorical variable and Wilcoxon test for ordered or continuous variables.

Table 2
Participants' treatment preferences in scenarios 1 and 2

		Scenario 2: With “positive B-receptor”		Total
		Preferred chemotherapy A	Preferred chemotherapy A+B	
Scenario 1: Without biomarker information	Preferred chemotherapy A	73	28	101
	Preferred chemotherapy A+B	32	306	338
	Total	105	334	439

Shaded cells indicated number of individuals who changed their preferences between Scenario 1 and Scenario 2

Table 3
Strength of participant preferences in Scenarios 1 and 2

Scenario 1 Strength of Preference	Chemotherapy A	Chemotherapy A+B	Total	p-value *
Unknown	0	1(<1)	1(<1)	
0 not sure	3(3)	5(1)	8(2)	<0.01
1	4(4)	6(2)	10(2)	
2	13(13)	16(5)	29(7)	
3	34(34)	70(21)	104(24)	
4	16(16)	106(31)	122(28)	
5 strongly prefer it	31(31)	134(40)	165(37)	
Total	101	338	439	
Scenario 2 Strength of Preference	Chemotherapy A	Chemotherapy A+B	Total	p-value *
Unknown	0	2(<1)	2(<1)	
0 not sure	3(3)	8(2)	11(3)	<0.01
1	7(7)	3(1)	10(2)	
2	16(15)	17(5)	33(8)	
3	31(30)	87(26)	118(27)	
4	15(14)	102(31)	117(27)	
5 strongly prefer it	33(31)	115(34)	148(34)	
Total	105	334	439	

* based on Wilcoxon rank sum test.