Research Advocacy Network

Advancing Patient-Focused Research

Outcomes of Clinical Trials for Patients with Metastatic Breast Cancer

Summary of Qualitative Patient and Advocate Input

May 2017

Introduction

Both the metastatic breast cancer community and the research community have questioned if the use of traditional endpoints for clinical trials are optimal for providing results that are meaningful to patients. Recent trials in metastatic breast cancer have yielded statistically significant results, yet have not changed clinical practice. Our reliance on Progression Free Survival (PFS) as a surrogate for Overall Survival (OS) may have been incorrect. Patients with metastatic disease have told us that stable disease is a good outcome, yet stable disease is not included as an endpoint in clinical trials. Trials do not uniformly capture side effect burden and quality of life nor are they always reflected in clinical trial endpoints. A new initiative is trying to address these issues but has not had direct patient input from the metastatic community.

NCI's Breast Cancer Steering Committee (BCSC) formed a Working Group (WG) to re-review and prioritize the appropriate endpoints to include in metastatic breast cancer trials and bring those recommendations back to the BCSC. There are two advocate members of the WG: Jane Perlmutter and Mary Lou Smith. The WG is developing a manuscript covering the following topics:

- Consensus on Endpoint Definitions
- Critical Systematic Review of Literature
- Consideration of endpoints by biologic subtype (ER+/HER2+, ER+/HER2-, ER-/HER2+, ER-/HER2-)
- Endpoint choice by line of therapy, expected post-progression survival
- When is OS preferred as primary endpoint? When is PFS? Surrogacy or not?
- When PFS is preferred primary endpoint, WG consensus on meaningful relative/absolute gains
- PFS/toxicity-QoL burden balance and meaningful benefit

In looking at a variety of possible endpoints, including various measures of benefit, as well as toxicities and quality of life, the Working Group wants to know how patients value and balance these important endpoints. Input is needed from the patients who are living with metastatic breast cancer.

Improving the measurement of endpoints by increasing their relevance to patients, either by what is measured or by how it is described, may:

- Inform the design of trials
- Improve communications to boost accrual
- Help patients use clinical trial results to make treatment decisions

The Research Advocacy Network (RAN) is working to gather direct patient input regarding clinical trial endpoints. This report covers the first phase of our work, the qualitative input gathered via focus groups with patients and advocates with metastatic breast cancer. We hope to conduct a quantitative phase, a survey of patients, to measure the relative importance of endpoints from a larger sample.

Objectives

The objectives of the qualitative phase are relatively straightforward:

- Generate a list of patient-relevant endpoints
- Gather patient-friendly language regarding endpoints
- Create output that can inform current discussions (e.g., Endpoints Working Group of NCI Breast Cancer Steering Committee) and be used to develop a survey with patients to measure relative importance of endpoints

Methodology

The scope of the focus group work included:

- Two in-person focus groups with patients with metastatic breast cancer (MBC) at the Living Beyond Breast Cancer conference, "Thriving Together: 2017 Conference on Metastatic Breast Cancer"
- One web-based focus group with advocates, all who have MBC and either focus on or are involved in the needs of patients with MBC

To gather the groups, there was a screening instrument developed by RAN and distributed by LBBC to identify patients; also, this screener identified some candidates for "advocate" group based on their greater knowledge and involvement. Our goal was to keep patient groups to slightly more naïve participants so they would not defer to experts; we put experts in the advocate group.

The patient groups included 17 patients who attended 90-minute focus groups on April 28, 2017, just before the start of the LBBC conference. We had 10 people in one group and 7 in the other.

The advocate group included 5 advocates who attended a 90-minute web-based focus group on May 9, 2017. Some advocates came from LBBC screening (as noted above) and some came from RAN contacts.

All participants were promised that they would have confidentiality, so no results can be linked to names. Groups were recorded and notes were taken to assist in this reporting process. Each participant received a $50 Amazon.com gift card in appreciation for their time and thoughts.

This input is not intended to be a report on the state of patient and advocate preferences or priorities related to clinical trial endpoints. With a total of 22 participants, it is intended to enrich the understanding and contribute to the conversation regarding patient perspectives on clinical trial endpoints. We recommend quantifying preferences via a widely-distributed survey; the focus group input will allow us to create a survey that reflects patient language and leads to a true measure of priority.

Results

For the most part, we have organized the synthesized input using the questions from the discussion guide. Our format is as follows:

Questions we posed are in underlined.
Patient input is in regular font.
Advocate input is in italics.

Topic One: How to talk about "endpoints" and gather useful information

To introduce the topic to patients, we thought quite a bit about how to ask what they would want a clinical trial to measure. Initially, we framed the question as shown below. Note that we used the word "outcome" more than "endpoint" as it seemed more patient-friendly.

In the first patient group:
Researchers who design clinical trials have to state the outcome they will measure… what the trial is designed to measure. There are some common outcomes they have used. There is also a Working Group that is trying to broaden what is measured.

We would like to inform the researchers with **your** input about what types of outcomes are meaningful. Note that a clinical trial outcome can be meaningful or important to you because (1) it would make the trial appealing to you as a potential participant OR (2) because it is the outcome of a completed trial you are using to make a treatment decision (so it's important to you as information).

Our first discovery was that discussing outcomes with the two contexts in mind (trial accrual and trial results use) led to a great deal of input that was "off topic" from our standpoint. Many participants discussed the pros and cons, as well as considerations, related to entering a trial (e.g., IV versus oral, randomization). While this is interesting, it does not relate directly to endpoints and was using too much of the focus group time on topics unrelated to endpoints.

Based on the discussion in the first focus group, we made a real-time decision to modify the context for the second focus group. We set up the discussion using a focus on the **second** of the two contexts, using the trial information. This seemed to greatly improve the relevance of the conversation when considering our objectives.

For the advocate group (third group), we continued to use the context of "using trial results" for most of the discussion. Then, after all the benefit endpoints had been discussed, we attempted to ask if their thoughts would be different if we had asked for meaningful endpoints using the other context - when one is deciding whether to enter a trial. With several attempts to clarify our question (do your thoughts about what is meaningful differ when considering entering a trial versus when considering a trial's results), including a good attempt by the one participant who understood the distinction, we left the topic.

Even so, in all the groups, we have results that are directly related to endpoints.

- Finding: While outcomes and endpoints may seem like a clear focus to those involved in research, it does not come naturally to patients and advocates to consider just "outcomes". Other trial issues immediately enter the conversation.
- Finding: Attempting to distinguish between importance of endpoints for the decision to enter a trial versus using a trial's results may be too complicated to explore. If future work, such as a survey, had a large enough sample size, half the respondents could be asked to answer in the context of trial entry and half in the context of trial results usage.

➢ Implication: When gathering patient input regarding endpoints, it is essential to dedicate time and effort to explaining the context and clarifying the goal/focus (or, accept and embrace that some input will be off topic).

Topic Two: Reactions to outcomes on the benefit side

We began the focus groups by showing the list below, comprised of currently used and proposed benefit-related outcomes. We referred to these as measures of whether the treatment is working.

- Overall survival (length of life, measured from the start of a particular treatment)
- Progression-free survival (length of time, measured from the start of a particular treatment, that one lives with the disease but it does not get worse)
- Time to treatment failure (length of time from entry into trial to discontinuation of treatment for any reason)
- Disease response (cancer shrinks or disappears)
- Stable disease (cancer is neither decreasing nor increasing in extent or severity)
- No evidence of disease [*not shown in advocate group*]

First, we asked for reactions to these in terms of meaningfulness and importance.
<u>What is your reaction to these? Which are meaningful to you and why? Which are not meaningful and why not?</u>

- Overall survival. Some said it is desired, but most patient responses were negative:
    - It takes too long; would mean getting drugs later
    - Meaningless because of mindset (common mindset: is take a treatment until it fails, start another treatment until it fails, etc.)
    - It is meaningless at this stage because there are so many drugs
    - Chance of it being your last drug is low
    - *It's the 'bottom line' for patients, but relatively unimportant to this advocate [NOTE: interesting response from an advocate given that the patients in the focus groups did not rate OS as highly meaningful. That said, they were conference attendees.]*
    - *Interestingly, advocates put higher weight on Overall Survival, particularly in a more "poll-oriented" question we asked at the end of the group.*
- Progression-free survival had mixed reviews:
    - It's important because it can be measured quickly
    - Doesn't account for the burden of treatment (i.e., maybe it's better to do nothing for 3 months rather than take a treatment and have side effect(s) for 3 months)
    - Seems like it can cover so many things and seems same as "stable disease"
    - Seem same as Time to Treatment Failure -- time until disease comes back
    - *Important… bottom line*
    - *Has become surrogate for Overall Survival, measured in months*
- Time to Treatment Failure also had mixed reviews:
    - Can also be measured quickly
    - Once one has been on several treatments, TTF becomes critical
    - Sounds good; means it is working for other people

    - Problematic because there are so many reasons for "failure" and, in fact, the definition does not match the name. People may discontinue the trial for many reasons that are not "treatment failure", such as not liking oncologist or because of side effects [Note: we understand that leaving due to toxicity is a 'failure' but participants did not seem to view it that way; for them, failure seemed to mean treatment was not working on disease.]
    - *Definition does not fit title; discontinuation for any reason, but patient may stop for reasons other than treatment failure. Need to know how many people started, how many withdrew, and the reasons they withdrew.*
    - Feels too "general"; may be more acceptable if "failure" reasons are classified into disease-related and not disease-related
    - The "for any reason" part of the definition seems too broad
    - *Don't care about this measure; PFS more important*
    - *Only useful if broken down by people with degree of prior treatment*
- Disease response
    - Patients didn't speak about this item, except one person said, "not so great"
    - *For patients with bone metastasis, disease response does not give good information (bone mets take awhile to see; scars look like metastatic lesions)*
    - *If one metastasis is being followed, but there are a number of lesions, this measure doesn't accurately reflect overall condition of patient.*
    - *With "mixed response" understood as a complexity, advocates understand disease response and stable disease as good measures*
- Stable disease
    - *Explored with advocates, but still got into complexities of what trial is measuring since metastatic disease often involves more than one tumor or more than one site*
- NED did not seem meaningful to those who understand metastatic disease:
    - Sounds good, but still waiting for other shoe to drop
    - Family hears NED and thinks patient is cured (patient knows otherwise)
    - Better phrasing for metastatic would be "no evidence of active disease" or "no measurement of disease"

Sometimes in reaction to a new question and sometimes woven into the discussion above, we learned about the language. We asked this directly:
<u>Are they being expressed or measured in a way that works for you? Would you want to change how the actual outcome is measured? How so? Or, would you want to improve how it is described? How so?</u>

- A key reaction: These terms are hard for a nonmedical person to read.
    - Put in layperson's terms.
    - More simply put: How long will this drug work? How much longer can I live to get to the next drug? (Another example related to side effects: "What is grade 3? Tell me what it is going to do to me.")
- Other suggestions:
    - Progression-free duration
    - Time of treatment duration
    - *Mixed response*
    - *Durable response*
- Other language and "benefit" reactions:
    - Some like the word "survival" and some do not; some find it hopeful and others find it seemingly dismal (as in, "so weak but hope I can survive")
    - Several noted that they do not want to hear how long they have to live
    - Some want to see the range/distribution of results, not just the average, in terms of response and dose
        - *Shortest and longest response or survival*
        - *Effective dose vs highest tolerated*
    - Some wondered how mixed results are classified, such as response in one area of metastasis but progression in another
    - *Researchers and patients have different objectives. Researchers want to know how well drug works; patients want to extend own life. Trialists need to think about what patient wants as well as what they want.*

Summary on the Benefit Side:

- Finding: Some are familiar with terms such as Overall Survival and Progression-Free Survival and have learned the related nuances and challenges (note that the composition of groups tended to more educated/involved patients). But, overall, the language used and the definitions can be misunderstood and the relevance to patients is questionable.
- Finding: Patients feel they understand the researcher mindset but that it does not match the patient objectives. These patients with MBC not only think about the impact of the treatment in an isolated sense, as if it were their last treatment, but think about it as getting them to the next treatment.
- Finding: Patients look at trial results with perhaps more emphasis than we may have realized in terms of trial composition. This should not be surprising; in fact, it's easy to relate to. But, it needs to be considered in communication of results. Each person may decide whether the results apply to their situation.

- Implication: Just focusing on debate regarding the currently considered list of endpoints seems insufficient. Patients raised a variety of questions and suggested improvements in language that need consideration. We could use these results to craft more patient-friendly expression of measures and test them with a larger sample.

Topic Three: Input on other outcomes that would be meaningful

While quite a bit of input was not related to endpoints and is not included in this summary, we thought the input that related to how patients read clinical trial results was sufficiently related to the topic and SO important to participants that it must be reported. The main topic that was not surprising, really, was that people seek to determine if the trial is relevant to them. Patients *and advocates* talked a lot about their desire to know as much as possible about the characteristics of the people in a trial, such as age, race and ethnicity, gender, how far in treatment, how far in progression, tumor markers, genetic status, aggressiveness of disease, and ER/PR/HER2 status. They said they feel they only hear about those who stay in a trial, but want to know about those who do **not** stay in it. Finally, some said they want to know if it was 'fast-track' and want to know how much experience there is with the drug.

When it came to other possible measures or outcomes, we chose to let the participants generate ideas before showing them a list. We asked: <u>We have talked about how to measure whether a treatment is working. What other outcomes would be meaningful to you?</u>

- Quality of life was mentioned, as a general statement. More specific items related to quality of life included:
    - Continue with normal life; *live their life*
    - *Impact on lifestyle*
    - Close to normal; 25% of normal; 50% of normal; etc.
    - Change in physical capabilities; incapacitated
    - Intimacy
    - Weight change
    - Depression, mental health, emotional effects
    - *A wrap-up statement: Is it worth taking/staying on the drug (researchers, even clinicians, don't understand this)?*
- Side effects are also a concern (some of the quality of life measure are intertwined with side effects). Some mentioned included:
    - Appetite
    - Energy
    - Potential for infection

    - Cognitive effects, memory problems, and chemo brain
    - Pain
    - "Too sick to get out of the house" (is treatment worse than disease?)
    - Shake, drop things, trip
- Also, related to side effects:
    - Can side effects be managed?
    - *How many other therapies are needed to tolerate side effects of treatment?*
    - Short-term, long-term, permanent
    - How bothersome?
- *Financial toxicity*

Summary on the "Other" Measures

- Quality of Life – particularly the effect on living their everyday life in a way that is some percent of "normal" and is worth being on treatment – is an important measure.

➢ Implication: Based on these groups, trial outcome measurements need to include quality of life to be meaningful to patients in decision-making. It is also worth exploring what quality of life measures would be most useful, as the general scale may not capture the aspect of "everyday life" that these patients seemed to care most about.

Topic Four: Voting

While the total number of participants causes us to hesitate about even sharing these results, we did ask participants to indicate which of the outcomes shown and generated in their particular focus group were most meaningful to them; they were allowed to select more than one. Each group was a little different as each had its own list. The summary of this input is as follows:

- There was a heavy concentration of votes on Quality of Life, adverse events, and effects on everyday life
- On the benefit side, the votes were spread around a bit:
    - Considering the conversation, it was somewhat surprising to see that many chose Overall Survival, especially in the advocate group
    - Progression-free survival was next most commonly chosen
    - No Evidence of **Active** Disease was chosen by quite a few people in one of the patient groups that had discussed its distinction from NED
    - No other benefit was chosen by more than two people across all groups

Summary on the Voting

- The votes, again, showed the importance of Quality of Life measures.
- The votes for Overall Survival were a bit of surprise, as the conversations seemed less positive on this front. This may demonstrate the known downside of focus groups: that the loudest voices can influence what is expressed aloud and groupthink may exist. A survey may provide more reliable insights on patient priorities.

Considerations for Next Steps

We understand the Endpoints Working Group needs to work with this input. For the near-term conversations, these focus groups support the following ideas:

- Patient input is useful and important*
- The current language used in endpoint measurement is not patient-friendly
- Patients with MBC have a mindset on treatment that is "getting to the next treatment"
- Patients with MBC do care about how they are living their everyday lives and consider measures that relate to qualify of life and how they are living their lives as important in their treatment decisions
- On the benefit side, more work is needed to define and express patient-relevant endpoints. Seemingly, from this small group, Overall Survival and Progression-Free Survival were most interesting, but the discussion suggests there is significant room for further exploration and improvement

*Research Advocacy Network hopes to conduct a patient survey, using these focus groups as input, to gather a larger set of patient input.

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