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Meaningful engagement of the patient in rare cancer research: sarcoma as an exemplar

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A B S T R A C T

Patient advocates who understand scientific methods and proper research processes can bring valuable perspectives to modern research. This is particularly important in rare cancers like sarcoma as each patient becomes a precious source of information to better diagnose, understand the biology and the effect of treatment. Reviewing approaches used by other cancer patient advocates can provide valuable insights to develop effective research advocates in rare cancers such as sarcoma.

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A R T I C L E I N F O

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Introduction

Sarcoma as a group of cancers is rare and presents an opportunity to illustrate the importance of including the patient perspective when planning research especially in rare cancers. In the late 1980s, it was noted that patients should be involved in the development of cancer research.[1,2] The specific insights that are most valuable as well as how to best gain these insights continue to evolve over time.[3-6] This review will highlight the engagement of patients in cancer research and describe the opportunity to engage patient advocates in the development of research in rare cancers using sarcoma as an exemplar.

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Rare cancers collectively account for 13% (220,000 new cases) of all cancers diagnosed annually in adults age 20 and above in the United States.[7] The United States Rare Diseases Act of 2002 defines a rare disease as one that affects fewer than 200,000 persons.[8] Individual subtypes of rare cancers often account for a few hundred of new cases annually, thus making rigorous statistically significant research a challenge.[9] In children, sarcomas represent 15% of all cancer cases or approximately 1200 new cases per year.[10] In adults, sarcomas comprise 1% of all new adult cancers cases.[10]

Sarcomas are a cancer of the bony skeleton and its connective tissues. There are more than 80 distinct histotypes of sarcoma that arise in the bone or soft tissue.[11,12] Each subgroup represents a rare cancer. In rare cancers such as sarcoma, each patient becomes a precious source of information to better diagnose, understand the biology and the effect of treatment.

To engage patients most effectively, education on scientific method and the research process is needed. Tailoring education will help patient advocates understand the most important points in the research process to incorporate their perspective. Patient advocates can become research advocates, effectively bringing the patient voice to research.

The SARC Sarcoma Research Advocacy Council is an example of a program focused on teaching the principles of research and the research process to sarcoma patient advocates, providing them guidance on effectively communicating their perspective to strengthen sarcoma research. The goal is to effectively leverage the patient voice to develop strong, rigorous research aimed at improving outcomes for patients facing rare cancers like sarcoma.

Discussion

Engaging the patient voice

Early initiatives to engage the voice of cancer patients can be traced to breast cancer advocacy.[1] Four key factors were identified as instrumental to their success in bringing their voice to the forefront: (1) Discussing breast cancer openly and publicly, (2) Engaging public health advocates to establish guidelines and then educating the broader population on the importance of screening, (3) Leading legislative initiatives to secure funding for early detection and research and (4) Collaborating with the scientific community, government agencies and business as partners to make progress.[1] By 2002 they were participating in the design of research protocols, collaborating in grant reviews, and providing guidance on funding decisions.[1,5] The National Breast Cancer Coalition conducted a course to educate breast cancer advocates in scientific methods so they could more knowledgably engage and share their perspective.[1] Clearly, this community of advocates were able to secure a strong position for the patient voice at the research table through drive, perseverance, and education.

The National Organization of Rare Diseases (NORD) brought together the rare disease patient community. NORD was organized by patients and families who had been connecting for nearly 15 years having bonded over a common frustration with the lack of progress to better understand and develop new treatments for rare disease.[13] This coalition of patients and families was the core driver for establishing the Orphan Drug Act (ODA) of 1983.[14] The ODA aimed to promote drug development for diseases that occur in less than 200,000 people by providing tax incentives, subsidies for research and market exclusivity for an extended period to pharmaceutical companies.[15] A review of the impact of the ODA published in 2019, noted as more subtypes of common diseases/common cancers fall into orphan drug status, rare diseases that were initially envisioned to be addressed have been diluted.[15] While the ODA was well intended to assist in development and approval of new therapies for rare diseases through incentives, as the landscape of cancer has evolved to more rare distinct subtypes, there is opportunity for the cancer patient voice to encourage revisiting these incentives especially given the high price of many new therapies (profit for industry) and the financial burden for patients (limiting or prohibiting access).

Engagement of the patient perspective by the National Cancer Institute (NCI)

The clinical trial program of the NCI, the National Clinical Trial Network (NCTN), has programs to engage patient advocates in cancer research. The involvement of patient advocates has evolved within the cooperative group network. An example that exemplifies the NCTN commitment to involving patients can be found in SWOG. They have developed and implemented a robust program for orientation and training, providing mentorship along with relevant supporting written materials to ensure patient advocates are well prepared for their role as patient advocates within SWOG.[16] Within their mentorship program they model for advocates specific areas that their perspective can enhance and strengthen SWOG research. In an evaluation of the program, patient advocates identified 2 key areas they positively influenced, (1) study objectives that reflected patient priorities and (2) study procedures that were sensitive to patient concern/burden.[17] Areas that patient advocates felt could be improved included the quality and consistency of communication with the investigators and the inclusion of advocates in study conduct, interpretation, and dissemination of results.[17] This review focused on the evaluation of the patient advocate engagement and did not report the evaluation by the investigators on the team.

The Cancer and Leukemia Group B (CALGB) evaluated the engagement of patient advocates in 2012 by surveying both the patient advocates and investigators. Results showed patient advocates were more likely than investigators to report benefit of their involvement in several areas including, in the clinical trial process (100% of advocates vs 72.1% of investigators; $P < 0.05$), in protocol development (92% vs 33.8 % respectively; $P < 0.001$) and assistance with patient accrual (78.6% vs 23.4%, respectively; $P < 0.001$).[18] These findings underscore the importance of developing tools to regularly evaluate the impact of engagement so that improvement measures can be implemented to address deficits or gaps.

The NCI Council of Research Advocates is a program designed to solicit patient advocate input into the research strategy of the NCI and is led by Doug Lowy, MD, Principal Deputy Director of the NCI. The Council focuses on 4 key functional areas: advise, design (evaluating and identifying barriers), review and disseminate.[19] The organizational structure of the NCI Council of Research Advocates provides a framework for areas of engagement with clearly defined roles and responsibilities of the research advocates.

Food and drug administration patient engagement

There are several active FDA programs aimed to better understand the patient experience with rare tumors including, (1) Public meetings led by the FDA that systematically obtain the patient perspective on specific diseases and their treatments; (2) Listening Sessions whereby patients with rare diseases schedule a meeting time with the FDA staff to discuss their rare disease, the symptoms and impact; and (3) A Patient Engagement Collaborative which is a forum to discuss and share information on drug development and regulatory matters.[20] These sessions are an opportunity for research advocates to share their unique experiences for consideration as the FDA weighs the evidence for drug approval.

Sarcoma patient advocates become sarcoma research advocates

In 2019 the SARC Sarcoma Research Advocacy Council was established. The program was launched with an in-person full day educational seminar. Twenty-two patient advocates participated. Patient advocates represented subtype specific and pan sarcoma patient advocacy groups. Faculty included a research advocate from the NCTN and NCI Council of Research Advocates, a research advocate from Patient-Centered Outcome Research Institute (PCORI), a medical oncologist, basic researchers, NCI leadership from My Pediatric and Adult Rare Tumor (MyPART)

network, a pharmaceutical company medical officer, a nurse practitioner and a research manager. The curriculum included the following topics, (1) Research Process, (2) Clinical Trial Research (Protocols and Informed Consent), (3) Process for New Drug Development, (4) Clinical Trial Research in Sarcoma, (5) Challenge of Rare Cancer Research, (6) Strategies for Sharing Your Patient Story, and (7) Purpose and Structure of Sarcoma Research Advocacy Council. Following the training session thirteen participants were interested in becoming members of the research advocacy council and have continued to meet monthly via webinar to study more in-depth aspects of the research process including early concept review, structure of a protocol including objectives, eligibility, schedule of events and the process of informed consent. These research advocates have participated on research teams, doing a variety of activities including, developing a subtype specific sarcoma clinical trial, engaging with study principal investigators to disseminate information about activated trials as outreach to raise awareness amongst the community, recruiting participants for focus group to evaluate patient reported outcome tools for a clinical trial. The facilitators of the council provide educational sessions and connect the research advocacy council with the research team and stakeholders to ensure the voice of the sarcoma patient is incorporated. Going forward we will continue to refine meaningful and constructive engagement.

Rare cancer research: Opportunities for research advocacy

The gold standard for cancer clinical research is a randomized controlled clinical trial which often is not feasible to conduct in a reasonable timeframe given the small number of patients with rare cancer.[21] The need to explore alternative approaches to trial design in rare cancers like sarcoma is an opportunity for research advocate engagement. For example, exploring patient reported outcomes (PRO) as an endpoint is feasible only if the PRO is relevant.[22] Patients alone are positioned to explain their experience and provide insight into relevancy of specific patient symptoms. Research advocates can more effectively provide needed and valuable information, if provided details about patient reported outcome measures, what they are and how they are collected.

A useful resource to understand the nuances of trial design in rare diseases is the FDA guidance document entitled; “Rare Diseases: Common Issues in Drug Development.”[23] While drug approval criteria are not the sole consideration for designing research, this guidance outlines the pros and cons of various study designs and endpoints for testing drugs in rare diseases. For example, the guidance addresses the value of understanding the natural history of a rare disease in defining the disease population of a study. Research advocates can assist in defining data elements that will adequately describe a rare disease when conducting a natural history study. Resources like this guidance document help prepare research advocates to address the challenges of designing rigorous scientifically sound research in rare cancers.

Conclusion

From the early actions and drive of the breast cancer patient advocates, fueled by First Lady Betty Ford bringing cancer into an open public arena, recognition of the importance of the patient perspective was sparked. Patient advocacy engagement has evolved over time in scope and impact with programs established at the NCI and FDA to engage patients. The lessons learned from these programs provide important information for research advocacy in rare tumors such as sarcoma including the importance of education, definition of roles and responsibilities, evaluation, and communication skills.

Tailoring education will help patient advocates understand the most important points in the research process to express their perspective to add value and strength to the research. With information and understanding about scientific methods, research process and drug approval,

Table 1
Research advocate points for Input.

Trial Design	• Is the hypothesis posing a question that is important to patients? • Can I describe the primary objective? What do the investigators hope to learn from this study? • What standard is the trial intervention being compared to? Does it seem appropriate? • Is it inclusive of the appropriate population? • Is anyone group being inappropriately excluded? • Is the schedule of events reasonable, doable, and explainable to ensure patient participation and compliance? • Is there a role for patient report outcomes? ○ If so, what symptoms or patient perspectives should be included?
Informed Consent	• Is it readable, clear in description of the objective and what will be required of someone enrolling? • Who will have access to the information collected on the trial? ○ Does it seem appropriate for this group to have access? • Does it describe how participants and their information will be protected (privacy, IRB approval review etc.)?
Information Dissemination: Active Trial	• Share publicly available appropriate information about the activation of a trial (approved by the study Principal Investigator). ○ Identify which groups may have interest in the trial for dissemination.
Information Dissemination: Study Results	• Upon completion of trial, develop patient friendly summary of findings ensuring those who participated are provided this information. ○ Did the trial meet goal (primary endpoint)? ○ If not, what was learned? • How will the information gained from this trial be used to design future research?

patient advocates can become research advocates, effectively and appropriately bringing their patient voice to research. Many of the early experiences cited provide insights and pave a way forward for rare tumor research advocates to strengthen and enhance their engagement.

Building upon the experience of others, Table 1 lists specific points within the research process that the sarcoma research advocates will provide their patient perspectives.

(Insert Table 1 Research Advocate Points for Input)

Evaluation tools will be developed to regularly assess the effectiveness of the research advocate engagement within the research team. All team participants will be asked to complete the forms so that perceived value and effectiveness as well as the process of engagement can regularly be assessed. Modifications to research advocacy will be done based on the feedback.

Education will be provided on a regular basis and will include topics relating to communication skills, scientific method, and research process. The research advocates and all members of the team will be asked to provide suggestions for educational programs. Problem solving and conflict resolution plans will be developed and shared with the team. Table 2 summarizes approaches to enhance engagement of research advocates.

(Insert Table 2: Approaches to Enhance Research Advocate Engagement)

Continuing to publish patient advocacy engagement experiences, evaluation data including perceived value of the interactions, effectiveness of communication and program modifications based on feedback is an opportunity to learn from each other. Connecting groups to develop common evaluation tools would permit comparison across groups who have similar goals of effective patient engagement. Collaborative efforts can help patient advocates across disease states enhance effectiveness and impact through continuous self-evaluation and improvement strategies.

Rare cancers like sarcoma present a challenge that necessitates bringing researchers and patients together so that strong, well designed rigorous research is done. With limited resources of funding, patients, researchers, we must maximize the opportunity to learn as much as we

Table 2
Approaches to enhance research advocate engagement.

1. Provide education on scientific method and research process.
2. Explain areas that the patient voice/perspective most useful? a. Describe experience with disease. i. This can aide in determining how to measure benefit of interventions for example. b. Explain the importance of research participation. c. Describe the value of correlative science. i. Expanding understanding of basic biology of a disease. ii. Assist in determining why or why not an approach was or was not effective. d. Evaluate developing protocols (inclusion/exclusion, relevance of question being asked, feasibility of the schedule of events) as well as the informed consent.
3. Provide clear definition of the role of research advocate.
4. Solicit evaluation of research advocate engagement from all members of the team.

can from each patient who is willing to share their perspective, enroll in a trial, provide biological samples, complete questionnaires, provide funding, and/or participate at the research table advocating for meaningful, scientifically sound research.

CRediT authorship contribution statement

Denise K. Reinke: Conceptualization, Writing – original draft, Writing – review & editing.

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