Interview with Prof. Naoto T. Ueno, an inflammatory breast cancer expert

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Editor's note

As an emerging journal in the field of clinical oncology, *Chinese Clinical Oncology* (*CCO*) has published a number of special series in recent years, receiving overwhelming responses from academic readers around the world. Our success could not have been achieved without the contribution of our distinguished guest editors. Taking this opportunity, this year, *CCO* launched a new series, "Interviews with Outstanding Guest Editors", to highlight our active contributors. We hope to express our heartfelt gratitude for their tremendous effort and further uncover the stories behind the special series.

The special series "Inflammatory Breast Cancer" (1) led by Prof. Naoto T. Ueno (*Figure 1*) from The University of Texas MD Anderson Cancer Center has attracted numerous readers since its release. This special series was a summary of the presentations from a session on inflammatory breast cancer (IBC) management which was part of the 4th International IBC Conference. Gathering the pioneers in this field, it aimed to optimize the approach for diagnosing and treating IBC. At this moment, we are honored to have an interview with Prof. Ueno to share his scientific career experience and insights on this special series.

Expert introduction

Prof. Ueno is a tenured Professor of Medicine at The University of Texas MD Anderson Cancer Center; his research is on IBC/triple-negative breast cancer (TNBC), the molecular mechanism of metastasis, and the tumor microenvironment in breast cancer. He is best known for his varied preclinical research and the identification of several biomarkers, which led to novel investigator-initiated clinical trials related to breast cancer. He is the Executive Director of the Morgan Welch IBC Program and Clinic and Section Chief of Translational Breast Cancer Research at the Department of Breast Medical Oncology.

The projects in his laboratory include elucidating the role and the underlying mechanism of several signaling pathways, including epidermal growth factor receptor (EGFR), transforming growth factor beta (TGF-β), c-Jun N-terminal kinase (JNK), and Axl receptor tyrosine kinase (AXL), in promoting the progression of TNBC and IBC. His research also focuses on determining the impact of the tumor microenvironment on the efficacy of targeted therapy and establishing novel therapeutic approaches by modulating the tumor microenvironment. His significant current extramural funding includes R01 and R21 grants from NIH, as well as grants from the Cancer Research and Prevention Institute of Texas, the US Department of Defense, and the Breast Cancer Research Foundation. He also has more than six ongoing investigator-initiated clinical trials for patients with IBC and TNBC.

Interview

CCO: As a reputable expert in translational breast cancer research, what drove you into this field in the first place?

Prof. Ueno: My passion has been treating aggressive breast cancer. I initially started my career by trying to understand how immunotherapy or high-dose chemotherapy with an autologous stem cell transplant could help in metastatic

Figure 1 Prof. Naoto T. Ueno.

breast cancer. As most of the audience knows, eventually, this did not become a part of the standard care for breast cancer. Then, I transitioned into an area where there was not much interest—IBC. At the same time, I was trying to identify a place where I may be able to help, which further drove me to study IBC.

CCO: What kind of projects are you recently working on? How is the topic of this special series associated with some of them?

Prof. Ueno: That's a good question. In some way, we did not show exactly what we do in the special series. The special series focused on how to provide the best care. For this interview, I could give you a context of both current clinical and basic research, where we think there is a need for emphasis. The special series was essential because IBC represents about 2% to 4% of breast cancers.

In the United States, the rate is probably lower than in Asian countries, but once it is diagnosed, it represents about 10% of breast cancer mortality in the United States. Therefore, its highly aggressive nature could result in a fatal situation. Many clinicians know about this disease. They know the name, and they think that they know how to manage it; however, the surprising part was that until ten years ago, when we looked into the US data, about 25% to 30% of practitioners in the United States did not follow the standard care, systemic treatment followed by surgery and radiation. We have data showing that if you do not follow standard care, the survival rate is lower than when standard care is followed (2). This happens in the United States, but I do not think this problem is unique to the United States. Many countries probably will have a similarly poor standard of care. Basically, the special series focuses on many different controversies. Even though standard care seems very easy, a lot of complicated fine-tuning is needed because of the aggressiveness of IBC.

Now in terms of my research, it is to develop a novel treatment by understanding the biology of IBC. Historically, people have tried to understand the omics, particularly the genomics, of IBC to determine whether there is something unique in IBC compared to more common forms of breast cancer. There are indeed some genomic differences; however, it does not appear so far that one gene drives everything. It is not a straightforward story that tells you why this disease is very aggressive. Most of the changes we notice that may explain why the disease is so aggressive involve the tumor microenvironment and the surroundings of the tumor. The immunological changes in the microenvironment really impact tumor aggression, and we found that the well-known EGFR pathway regulates this area. We are dissecting this at the molecular level using animal studies to understand how the EGFR pathway regulates the tumor microenvironment. We are also trying to enhance immunotherapy by combining it with EGFR targeting. Those are the kinds of research projects I mainly invest in.

CCO: As you mentioned in the editorial of the special series, MD Anderson Cancer Center is often involved in convening new consensuses or updating treatment guidelines to the public every year; what problem do you think shall be set as a priority in moderating the IBC guidelines in the coming year?

Prof. Ueno: MD Anderson has the largest IBC clinic, followed by Dana Farber Cancer Institute. They are the two significant places in the United States that set the standard of care for IBC. We recognize that many patients do not have access to large cancer centers, so one of our goals is to ensure that the same value of care can be provided in any location. In our program, we have a network called "IBC Connect", and strategically, we have about 14 domestic and international sites, including ones in China and Japan. And then, we are trying to ensure that standard care can be provided at any other places. We are spreading clinical case discussions every two months, and we discuss standard care constantly. Those are probably the main efforts that we are currently

conducting. Reading this special series is also very important.

Meanwhile, the treatment algorithm related to IBC is in the public domain on the MD Anderson website. Every change, every standard of care that we defined is there. There are other guidelines like National Comprehensive Cancer Network (NCCN); however, they are not very detailed. Our guideline probably provides the most detailed information on providing care to IBC patients.

CCO: Of the three necessary treatment modalities you mentioned in the editorial of the special series, which one do you think is the most commonly overlooked in the conventional treatment of IBC?

Prof Ueno: Each treatment modality has its issues in the community. One of the major issues is systemic treatment. The best outcome is a pathological complete response. This is what we need to achieve. We have seen patients receiving a limited amount or duration of systemic treatments and quickly moving to surgery. I think that is a serious mistake. Doctors need to pick the optimal treatment, ensuring that patients receive plenty of systemic treatments to maximally shrink the tumor and only then proceed to surgery. Speaking of surgery, we sometimes see people who have not had a mastectomy because they had a good response to systemic therapy. Sometimes doctors take only part of the breast, which may result in a challenging situation. Sometimes they will remove the normal contralateral breast because the patient wishes to do so, or they are worried that the disease will come back on the other side. Sometimes they perform immediate reconstruction, which is not the optimal thing to do because if the patient has any surgical complications, it does delay the radiation therapy. You could perform the reconstruction later on. And we also do not recommend skin-sparing or partial mastectomy. When it comes to radiation, we do see some people skip it. I do not know why, but it does happen.

All three disciplines must see the patient together at the first visit to know the extent of the disease. Additionally, they should take a picture so that they can remember where the redness had spread. After treatment, most times, redness will disappear, and then it is difficult to remember where the edge of the tumor was, so taking a picture is very important.

CCO: Which part of the content impressed you most in this special series? What do you think is the unique advantage of this special series compared with other similar projects?

Prof. Ueno: The series is unique. The opportunity for this series came to work out very well because we were supposed to have our 4th International Conference on IBC, for which all the experts would get together to discuss clinical, basic, and translational research. However, because of the pandemic, everything had to go virtual. It was December 2020 when we decided to focus on clinical management, so that was what we did. The content of the special series originated from that session which was only almost a little more than a year and a half ago. I think it is probably the most up-to-date in terms of the content.

CCO: To make a quick takeaway for clinical doctors, what are your suggestions on diagnosing and managing IBC based on the special series?

Prof. Ueno: The appearance decides whether it is IBC or not. Therefore, if you see redness or early signs of redness, you have to suspect a diagnosis of IBC. Unfortunately, there is a misconception that the redness has to spread to the entire breast to diagnose IBC. Recently, because of the improved awareness of this disease, people may catch the redness early. However, if it is small, they may think it is not an IBC. The surprising part is that sometimes small areas of redness spread. After you use a diagnostic image, such as a mammogram, magnetic resonance imaging (MRI), or ultrasound, you will see diffuse erythema and edema. Occasionally, you cannot see the skin thickening with the naked eye, and I think you must be suspicious first and keep looking at it because if you make that first mistake, it could have a disastrous outcome. If you are not quite sure about the diagnosis, reach out to us or reach out to any local IBC experts. There is always somebody willing to help.

CCO: If there is a chance to update this particular series, what content do you want to moderate, add, or emphasize more?

Prof. Ueno: We have to update the continuing changes of the systemic therapy part, particularly for triple-negative IBC. We will also need to update the information on CDK4/6 inhibitor usage in the adjuvant setting in IBC. How to apply these new data to this aggressive disease is something that needs an update. Our latest IBC treatment algorithm (3) by MD Anderson is up-to-date in terms of how we should deal with these issues as this kind of treatment comes out.

CCO: As we know, the content of this particular series mainly came from the 4th International IBC Conference, and the 7th Conference (4) is going to be held. Could you talk about some important topics which will be presented at the coming conference?

Prof. Ueno: I think this upcoming conference will provide more updated information related to the tumor microenvironment, immunotherapy, and the progress that we have had in the past two years. So, implementing standards here is essential. At the same time, it is necessary to understand the biology of how the tumor and its surrounding environment interact. There are a lot of different hypotheses, and many are going to be presented at the coming meeting. If you have an interest, please join the meeting.

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