Reducing the risk of flu infections in cancer patients

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Yale Cancer Center Answers is a weekly broadcast on WNPR Connecticut Public Radio Sunday Evenings at 6:00PM  
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Welcome to Yale Cancer Center Answers with your hosts Drs. Anees Chagpar, Susan Higgins, and Steven Gore. Dr. Chagpar is an Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on myelodysplastic syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about flu infections in cancer patients with Dr. Andrew Branagan and Eamon Duffy. Andrew is a Postdoctoral Associate in Hematology and Eamon is a Medical Student at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar: Maybe I will start by having both of tell me a little bit about yourselves and how you got involved in this field? Andrew, let’s start with you?

Branagan: Thank you very much. My interest in these types of cancers, which are multiple myeloma and other plasma cell disorders, really has a long history even before medical school. I came from Boston and worked at the Dana Farber Cancer Institute and it was during my time there at medical conferences when I first met Dr. Dhodapkar who is Chair of Hematology here and one of the world experts in these types of diseases and that is what got me to go back to school to become a physician and I finished my subspecialty training in Medical Oncology and Hematology but Yale has a very unique program where you can get a PhD in Investigative Medicine and become better at research and that is what I am doing right now.

Chagpar: And so this project was part of this investigative studies initiative?

Branagan: Yes, exactly.

Chagpar: Eamon, how do you fit into the picture? We know that this was part of Andrew’s research but for a medical student to get involved in this level of research, is that common?

Duffy: I think it is more common than you would think at a Medical School. Yale is a special place and has what is called the Yale System where they support and encourage medical students to get involved with medical research from day one and so the Office of Student Research supports me going to conferences and they have been great in every way. I met Andrew sort of randomly at the cafeteria; I was working in a flu lab in the summer between my first and second year of medical school, I mentioned flu and he told me about the trial and then at the end of the summer, I reached out to him and said, “hey if you need a hand, I would be happy to help out,” and here we are almost two trials later and it has been an incredible experience and a really wonderful way to complement my time in

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the classroom to be able to learn about these disorders and get lectured by people like Dr. Madhav Dhodapkar and then go into the clinic and see the patients and into the lab and process the samples, and to be able to see all aspects of trials like this has been really a special experience.

Chagpar Is it your interest after Medical School to pursue Medical Oncology and do clinical scholar things like Andrew?

Duffy We will see. I am in my third year so I am rotating through all the different specialties, I am on neurology right now, for example, which is wonderful, but I do have a special interest in hematology and oncology. I worked at Fox Chase Cancer Center before Medical School and was eager to get involved. I did not expect it would turn into this but my dad is a hematologist, so it is in my blood I guess I would say.

Chagpar Andrew back to you, can you tell us a little bit more about the project itself and the genesis for that project?

Branagan Sure, these types of cancers that we are talking about, multiple myeloma and other plasma cell disorders, are really disorders of the immune system or cancers of the immune system itself, and one of the hallmarks of these diseases are risks of infections and that is one of the major causes of death in these patients, so this is a huge problem in the disease, and this is something I noticed early on when my step-father actually died of an infection shortly after being diagnosed with multiple myeloma, so one of the passions I have had is trying to find ways to reduce infections in these patients and the flu itself is about 10 times more likely in myeloma patients, all viral infection such as a flu, so it seemed like a good place to start. Looking at prior research, we know that we recommend every year for myeloma patients to get a flu vaccine but we know it probably is not working that well because we still see so many infections.

Chagpar And even though we tell myeloma patients, get your flu vaccine, these patients still get the flu and why is that? Is it that myeloma patients just do not have an immune system to mount against the flu and other infections?

Branagan Exactly, as I mentioned these can be considered cancers of the immune system themselves. These patients have low protective antibodies, so the good antibodies that all of us have to fight off infections are low in myeloma patients and also other dysfunctions in the immune system that we are trying to explore in our lab as well and so what you can do to improve the response to the flu vaccine, there are several different approaches, and a couple examples are increasing the dose of the flu vaccine itself and another might be to use a booster strategy as we see in other vaccines that we commonly get in children. So, there is a higher dose flu vaccine that has been approved since 2009 in older adults and
that is actually recommended to anybody who is 65 and older and these types of cancers are actually cancers of older age, the average age is into the 70s for people with this cancer, so we know that they are getting a higher dose and still getting the flu, so this probably will have some benefit but it also probably will not be enough, so we took the strategy of a booster which is adding an extra dose after a certain period of time and generally at least 3 weeks later, so we chose to use a 4-week period and in terms of evidence to use boosters in this population, somebody did look at boosting flu vaccine in blood cancers. They looked at all blood cancers and this was several years ago and it actually was not successful, so this was aborted for several years, but a couple of years ago in Germany a group gave a double standard flu vaccine and focused specifically on myeloma patients rather than just all blood cancer patients and they did see a benefit, so the protective antibody levels that you can measure against a vaccine called HAI titers, they saw that double from about 15% to 30%, so that told us that there might be something to that booster strategy and so we took both of those concepts and combined them together by giving high-dose flu vaccine and then after 30 days, a second high-dose flu vaccine.

Chagpar Eamon, some people may be listening to this show and wondering first of all, for the vaccine itself, we talk about vaccines that are live vaccines and vaccines that are not and so do myeloma patients, if you are giving them a higher dose of a live vaccine, could that not actually cause the flu in these patients?

Duffy I do not think patients have to worry about this vaccine causing the flu.

Branagan We are just introducing an inactivate vaccine. And so what that means is there is part of a surface of the virus itself as a protein and that protein has been purified and used to stimulate the immune system, so there is really not a risk of getting the flu.

Chagpar I think that is really an important point.

Branagan It is a great point, right.

Chagpar When we think about vaccines oftentimes people are told that these vaccines are live vaccines or they are smaller dose of whatever it is that they were vaccinating against, and that idea is that your body mounts an immune system, so this is an inactive form of the flu that people get.

Branagan And even though we know that and we say that to our patients, it is a very common fear that they are still going to get the flu and in fact, we hear this over and over again.

Chagpar The next question though is, if we talk about myeloma being a cancer of the immune system and that being the reason why people are more prone to infections because they simply cannot mount an

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immune response, an immune attack, I am still struggling with why you would think that giving a larger dose or booster would help, is it that maybe they mount a baby response and so two baby responses equals a normal response to a flu vaccine, because if they cannot mount any response, then it should not matter how big the dose of the flu vaccine or how many boosters you give, they will always be prone because they do not have sufficient immune activity?

Branagan It is a great point and it is something that is still not quite fully known but because of some of these prior studies that I showed you where we are getting incrementally better response, it does show that there is somewhat of a response and it is possible to augment that, but we do want to understand what are the exact dysfunctions in the immune response, so as part of these flu vaccine studies, we are actually collecting immune cells from the patients and we are looking before and after vaccine and looking at the critical blood cells, in particular, we are looking at the T cells that work together with other cells to make an immune response. We know that they are dysfunctional in myeloma but we are really going to do some tests that have not been done before in myeloma specifically involving the flu vaccine, so it might be the case that more is needed and just a higher dose or an extra dose is not enough and we need something else to boost that response like live vaccine as you were saying or maybe something called adjuvants that can help augment and wake up the immune system a little more.

Chagpar And to that point, have you looked at whether there are some myeloma patients who have a particular kind of T-cell or a particular kind of response in their T-cells such that they are the ones who are more likely to prompt an immune response to a vaccine and for them a vaccine would be beneficial whereas others in whom there really is not that kind of reserve, so that they do not make that response, I am trying to get around some of the contradictory studies that you had mentioned earlier.

Branagan These studies again were focused at blood cancers in general. Very few people have focused studies on myeloma or other plasma cell disorders and that is why the studies we have been doing in the last couple of years I think are so crucial, we have larger numbers than have ever been studied, specifically for flu vaccine, so we can do some of the exact things you mentioned, we will look at those patients who actually get the flu and what is different from those who do not get the flu, so we can actually have clinical end points because we have more patients and that is what is missing in prior studies.

Chagpar Let’s talk more about the trial itself, can you walk us through what the trial is, how you recruited the patients and what the randomizations were and so on?

Duffy Sure, patients were recruited from Yale Cancer Center and these are patients of Madhav’s and Andrew’s and all the hematologists there and for the most part, they were really excited to get
involved with a research project like this. I did a fair number of the consents last year and I was really encouraged by how willing so many of the patients were to get involved with research like this so that was really wonderful to see and to be able to explain to them that this is going to benefit you, but this is really a long term mission of ours to improve vaccine strategies and patients with cancer. We took blood on day #1 from the patient, gave them that first vaccine and then 30 days later, they came back. We took blood again. We gave them the booster vaccine on day #30 and then a month after that, they came back, we took blood once again and then we were able to measure the response throughout that several month period, looking at anti-flu titers and T-cells that Andrew mentioned and be able to watch their response on a molecular level and also we were constantly checking in with them to see the end-point that we care about which is, are they getting the flu? That is the most important thing, so we were in close contact with the patients. We know all their names. We know them well, and that has been a fun side to it as well is getting to know all these people who are on an important trial with us, so we see, do they get the flu and that is the main end-point I would say.

Branagan And this was a pilot study since it was the first time this exact strategy was used in patients like this. Safety was really one of the biggest end-points.

Chagpar We are going to carry on this story and learn more about these trials with the flu vaccine in myeloma patients’ right after we take a short break for a medical minute. Please stay tuned to learn more information with my guests, Andrew Branagan and Eamon Duffy.

Medical Minute The American Cancer Society estimates that over 1500 people will be diagnosed with colorectal cancer in Connecticut alone this year. When detected early, colorectal cancer is easily treated and highly curable and as a result it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for colorectal cancer. Tumor gene analysis has helped improve the management of the disease by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in a more patient-specific treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guests Andrew Branagan and Eamon Duffy. We were talking about some really cool research looking at flu vaccines in myeloma patients and right before the break, Andrew, you were saying that
this study that you had done, I guess it was last year, was a pilot study to look at safety and titers, and could myeloma patients actually mount a good immune response to the flu vaccine? What did you find?

Branagan 51 patients were enrolled in this pilot study and in terms of safety, we found no unexpected serious events that were related to the vaccine. It was the usual side effects that we get from the vaccine which are mainly soreness at the arm where you receive your vaccine, sometimes a little bit of tiredness and feeling unwell for a short time after the vaccine and that was the most important thing to us. It did really show this was safe because everybody got the intervention, it was a pilot study. What surprised us was actually how effective this strategy seemed to be, so as I mentioned before, myeloma and other plasma cell disorder patients do not mount a very good immune response. We know that their serologic protection is in the order of 5-19% after a standard dose of flu vaccine. What we found is after a high dose, we saw 49% with protective titers and after the second high dose that rose to 66%, so that was really the highest ever reported value, specifically for these types of patients. The other thing we did look at was the number of clinical infections and we saw 6% and that is lower than we would expect. We do not have great numbers of exactly how many to expect in the population, as I mentioned flu infections including all viruses is about 10 times more common and it is probably in the order of 20% or more based on our experiences in the clinic, so 6% is also very exciting but again this was a small pilot study and to really be sure if there is a clinical benefit, we thought we need a larger study to look at that specifically.

Chagpar And is that what happened next?

Duffy Yeah, so that was last year as you mentioned and this year, we have embarked on what is called SHIVERING 2 and that is a randomized clinical trial where one group of patients will receive our novel strategy, the high-dose flu vaccine followed by the booster, and then a second group of patients are the control arm and they will receive standard of care, so if they are under 65, they receive the normal flu vaccine that you and I get and if they are over 65, they will receive the high-dose vaccine and so that started in September and we are working daily on it now and it has been going really well and we will see how it unfolds in the spring but we are very hopeful.

Chagpar So I have to ask you, how is it named SHIVERING 2?

Branagan I was just going to say, we never actually told you the name of the study, which is one of the most exciting parts. We came up with SHIVERING, obviously when you get the flu you could have the chills and shivers, that actually stands for the Study of High-Dose Influenza Vaccine Efficacy in
Gammopathy Patients, so these types of patients have lots of names, plasma cell disorders, gammopathy patients, monoclonal gammopathy patients and so that is the creative way to have everybody remember our trial.

Chagpar I was beginning to wonder whether I had missed the part where you put the patients in the ice box and they start shivering, so you have embarked on this randomized control trial, how is it going?

Branagan It is going great. We have now 125 patients on the study which is a lot more than every other trial in the Hematology Department, so we really thank the patients for their interest and it is open at all the different Smilow Care Centers throughout Connecticut and they are actively involved and half the patients are coming from sites other than the one at York Street where we work.

Chagpar How many patients are you targeting to enroll in this study?

Branagan We were very happy to have over 100, which we already have. The full target would be 150, so there is still room for 25 more patients. Most patients have already been vaccinated because we do recommend that in the fall and now we are getting into the winter, but this is a slow start to the flu season this year, so there are some patients that have not been vaccinated yet and then they would still be eligible for the trial, so we do expect a few more to still join on.

Chagpar Eamon, what are the endpoints of this trial, is it still the same thing, you are looking at titers before and after each dose of vaccine and still checking in with patients as to whether or not they got the flu?

Duffy Yes, the primary endpoint of SHIVERING 1 as Andrew mentioned was safety and now that we feel that has been addressed, SHIVERING 2 is really looking at clinical outcomes. Does it really decrease the number of patients who get the flu? And those similar more molecular outcomes we are studying in parallel, so those outcomes the same, but as I mentioned SHIVERING 1 was primarily safety and SHIVERING 2 is really, does our new approach work? And with this number of patients, and it being randomized, the control versus the experimental arm, that allows to compare our strategy directly with the control strategy and as I mentioned we’re very hopeful.

Chagpar I would imagine that you do not have results as of yet until you reach your target accrual, but any hints as to (A) Whether you think you see a difference, is the trial blinded and (B) When do you think these results should be expected?

Branagan That is one of the things that we love about focusing on the flu, we get an answer in a short time, because flu seasons are less than a year. So after a year we definitely will have the results, but this is a
double-blinded study, so we do not know which intervention the patients got and the patients do not
know and one way we control for this blinding is obviously if you had a flu shot, you would know you
are in the control arm, so people in the control arm got a placebo saline booster, so nobody knows who
got which interventions. We have no idea this season how it is looking. The complicating factor is
that it has been a slow flu season and there is not a lot of background of flu. Last year was a very bad
flu season and there was a lot of flu and so the fact that this strategy with the background of a lot of flu
is very exciting. This year, I hope that that is not too much of a challenge in interpreting the results.

Chagpar So this year if you get results that showed the two strategies are equivalent because the background of
flu is so low, does that mean that you will embark upon another randomized SHIVERING 3, which is
essentially SHIVERING 2 and hope that the next flu season is worse.

Branagan I think it is too early to say, but we will have to see at the end of the year what the results point to, and
I do want to thank all the people involved in this research because, as I mentioned, this is a very high
accruing trial, lots of efforts went into the design, especially Dr. Dhodapkar, working with us in
planning the trial and the patients themselves; it is amazing that they actually drive great distances,
some of them, to be on this trial. Some came to Yale just for the trial, actually living in another state
and the Cancer Center itself sponsored the trials, Dr. Hochster and Dr. Eder were really supportive in
getting this to be a sponsored trial which we really appreciate and there is a whole team of research
coordinators led by Stephanie Ladd that has been excellent in keeping track of all the data points for so
many patients and I really thank all the clinicians for putting people on the trial, the physicians, nurses
and even the statisticians and research pharmacists involved in the trial.

Chagpar Clinical trials are always a really big group effort. One of the questions that I have for these last 25
patients, because there may be people who are listening who think, I have got myeloma and I do not
want to get the flu and this seems like a pretty sensible low risk kind of trial to participate in, do the
patients need to come down to New Haven to participate or can they participate at one of the other
care centers in Torrington or Orange or wherever it might be.

Branagan That is a great point. They can go to any Smilow Care Center, in fact, like I said, half the patients so
far have come from other sites and it is not just myeloma, we did focus a little bit on myeloma because
that is the most common of these types of disorders, but even the pre-malignant condition, monoclonal
gammopathy of undetermined significance (MGUS), which is quite common in the community, are
open for the trial and could enroll if they were interested.

Chagpar Let’s suppose you get the results and later this year the results come out, the trial finds that there is a
great new strategy to reduce flu in patients with MGUS or with myeloma by having this booster high-

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dose strategy. What happens then? Clearly you will publish your results and hopefully this will then spin a national or international response, so a few questions, Eamon, do you think that there would need to be a multicenter trial to validate these after the results of a positive trial here? And the next question is, are there questions that remain unanswered that you would need to or would want to look at after this?

Duffy Yeah, absolutely. I think that if our results hold hopefully this would become standard of care and that we have enough patients where it should be, that being said, a multicenter trial throughout the country will hopefully continue to prove what we have shown here at Yale Cancer Center, but as you mentioned, I think there are a lot of outstanding questions that we still hope to pursue with regard to vaccine strategies in patients with cancers. One of the additional layers of this trial that I find to be particularly interesting is that myeloma patients are constantly getting chemotherapies, they are on a lot of different medications and some of those medications can tamper down the immune system and we are trying to build that up with a vaccine, so what we are also looking at is maybe there is timing with when you should be getting this vaccine and when you should be getting chemotherapy and those are just some other questions that we are looking at.

Branagan Like which therapy, maybe some of the newer therapies for myeloma might actually boost the immune response, the so called immunomodulatory therapies.

Chagpar And so with those immunomodulatory therapies now that you bring that up, do you think maybe in those patients who are getting immune therapies that are boosting their immune system that actually the revised strategy of high-dose vaccines and multiple boosters might not be needed in those patients?

Branagan Nobody has looked at this formally in a large trial with myeloma. Some people have postulated that immunomodulators could help immune response to other vaccines and it has been somewhat disappointing as a whole in the field, so I do not think that is going to be quite enough but there might be some components of potential benefit from immunomodulatory drugs, that is why I am so excited we have so many patients we can actually look at the end-points like what type of therapy and what is the timing of the therapy.

Chagpar Are the patients who are on the trial all currently being treated or are these patients who have been in remission and are not on current therapies now?

Branagan It is a whole mix of patients. Most patients are actively being treated and have clinical disease, but some have pre-malignant disease, like I mentioned, MGUS or asymptomatic myeloma, for instance. We really wanted to look at everybody since there is evidence that even the pre-malignant states have some immune dysfunctions. We really wanted to see if this is applicable to all sorts of patients.

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Chagpar Right, so you might be able to pick up some signal looking at that wide array of patients to see who is on immunotherapy, who is on standard chemotherapy, who has been in remission and whether the responses are different in each of these cohorts. I guess the next question is, does this have applicability for other patients and other patients with cancer because as you say, Eamon, a lot of patients whether they have got breast cancer or colon cancer or lung cancer or on chemotherapy for at least a portion of the time, it knocks your immune system down a little bit and should those patients be getting a revised or different strategy in terms of flu vaccine?

Duffy That is a dead-on question and in fact, I just want to highlight the fact that infections are a problem for all cancer patients. The American Cancer Society did a study in 2005 and looked around the country at patients with cancer who are hospitalized from the flu and found that 9% of those patients died from the flu. So we know complications from the flu are higher in all types of cancer patients, so we chose to first study plasma cell disorder patients because we think that the risk is the highest, but if we do see a benefit to the strategy in these patients, it is worth exploring in other conditions and other types of cancers definitely.

Dr. Andrew Branagan is a Postdoctoral Associate in Hematology and Eamon Duffy is a Medical Student at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.