Yale CANCER CENTER answers

WNPR Connecticut Public Radio

The History of Chemotherapy

Guest Expert:
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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a medical oncologist specializing in pain and palliative care. He also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening, Ed Chu welcomes Dr. Vincent DeVita, the Amy and Joseph Perella Professor of Medicine at Yale University. Dr. DeVita is also a former Director of the National Cancer Institute and of Yale Cancer Center and he joins Ed this evening to discuss the history of chemotherapy.

DeVita — Chemotherapy was first coined as a word by Paul Ehrlich, a chemist who was well known in the early 1900s. He defined it as using chemicals to treat syphilis. His major contribution was that he developed the rabbit model of human syphilis and developed a series of compounds, one of which was compound 606 (Salvarsan), which was used by medical professionals to treat syphilis. This was the birth of trying to find chemicals using animal models as screens so that you could treat a disease. He had a wing in his laboratory where he did the same kind of work trying to find chemicals that might effectively treat cancer. He had a sign over the door that said "Give up all hope, you who enter." So he was not optimistic about the likelihood of finding chemicals that would cure cancer, nor did he ever actually find one during his lifetime.

Chu — When was chemotherapy first developed and then applied to treat patients with cancer?

DeVita — There is an Egyptian papyrus that actually talks about using topical chemicals, herbs, and extracts of herbs and so forth. So you can go as far back as you want, but it was really not until around the mid 1930s that people began to think you could realistically use chemicals for cancer. The first major screening program was started in around 1935, but frankly, the date that people use for the birth of chemotherapy is 1943, and it was here at Yale. Based on experiences in World War I and then an accident in World War II with mustard gas, data showed that people who died had an atrophy of their bone marrow and their lymph nodes disappeared. It was then thought that maybe they would be useful chemicals for treating a group of diseases called lymphoma, or cancers of the lymph nodes. Alfred Gilman, here at Yale, and Gustaf Lindskog, who was a thoracic surgeon at that time, used an animal model of lymphoma and screened these chemicals. They found that it actually worked and so they convinced Dr. Lindskog, who had a patient who was having trouble breathing because of a large tumor mass in their neck, to let them test it. This was before the

3:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

FDA was involved in these things, and they got a very dramatic response that started the whole interest in cancer chemotherapy. That paper was not published until 1946 because of the secrecy of the war gas program, but it is generally regarded as the beginning of human cancer chemotherapy.

Chu It is interesting, as you just commented that it came out of the chemical warfare program that we had here in this country.

DeVita As a matter of fact, later in 1955, because of the interest in nitrogen mustard another drug was developed called methotrexate, which was also worked on here at Yale by Joe Bertino and people like you in the lab. The Cancer Chemotherapy National Service Center was started on 1955, which was a national program to begin to screen chemicals for cancer in a major way so that the birth of chemotherapy here lead to development of a national screening program.

Chu It is fascinating to me as I learn more about the history of cancer chemotherapy having the privilege and honor of working closely with you. The whole concept of cancer chemotherapy was not widely embraced when these first discoveries and treatments of patients with cancer came about.

DeVita You are being very polite, but no, it was not widely embraced. In fact, the critics were vitriolic about it. It was something about the self-fulfilling prophecy. Cancer is a fatal disease, if you do not treat it, it is indeed a fatal disease. People just did not believe you could ever cure cancer with a drug. Nitrogen mustard worked, but it worked very briefly. The people who were involved in developing nitrogen mustard became harsh critics of cancer chemotherapy because they were so disappointed after getting their hopes up that they were going to finally have a drug that will cure cancer, that they never believed that you could cure cancer with drugs. The original pioneers are the people who started using chemotherapy. The original pioneer would probably be Alfred Gellhorn who was Director of a cancer center that was attached to Columbia University. People like him were driven out of town. I interviewed him at age 94; last November he passed away. I interviewed him in his office. He was working at age 94 and he told me about the great Robert Lurb who was the chairman of medicine at Columbia. He was a great man, a great teacher and a great academician. He used to say to him in front of people, "Alfred you are part of the lunatic fringe." The impact of having someone of his stature say something like that, even if it was partly in jest, is really enormous. Eventually, he was run out of town and the Hospital was closed because people did not like the idea of cancer patients being treated and having

6:34 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

their house staff being exposed to this. There are many other examples of that kind of thing happening.

Chu So what turned things around in the evolution of cancer chemotherapy?

DeVita Well, as you know, you needed evidence that you could cure cancer and that was provided by two diseases, childhood leukemia and Hodgkin's disease. More than one drug became available and work was done in childhood leukemia combining several drugs, one of which was the drug vincristine, which became available in the late 1950s. The first program that was developed and was quite successful was called VAMP, the initials stand for the drugs in the program, and that increased the remission rate in leukemia to about 50%. The striking thing was that these people now stayed in remission for long periods of time. By 1970, people were saying you could cure childhood leukemia. At the same time, we were doing work on Hodgkin's disease and developed the MOPP program. The complete remission rate went from virtually 0 to about 80%, and that is just the 40-year follow-up on that original study. 55% of the original groups of patients are alive 40 years later. By 1970 it was also apparent that Hodgkin's disease was very likely cured by chemotherapy. That provided the spark that had been missing. Then what happened after that, which is a very important thing, was that people went out willing to test drugs in the postoperative period for patients whose tumor had been removed, but we knew they would have a high risk of recurrence, particularly in breast cancer and colorectal cancer, and so the early studies, and what we now call adjuvant therapy, came right on the heels of that adjuvant to surgery, and of course these studies have been brilliantly positive. The mortality rates from both colorectal cancer and breast cancer are falling. At least 50% of the decline in mortality is due to the application of chemotherapy as an adjunct adjuvant therapy to surgery. I think the big impetus was what I call the concept of cure, that you could actually cure cancer with drugs.

Chu The important concept was that combination chemotherapy was essential to being able to cure cancer.

DeVita Indeed, and of course it was a dirty word in medicine at that time. If you gave combinations of antibiotics, for example, you were considered a sloppy practitioner. Combination chemotherapy was not something that was accepted at the time when I worked with the two founders in this field. I watched them being criticized in unbelievably vitriolic ways. When I got to Yale, I used to talk about their work and there was no acceptance of it at Yale either, because it was just something that was not done. The important message, however, is that now that we have targeted

9:31 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

therapies, combination chemotherapy is still required. Cancer is such a complex derangement that you need to target more than one pathway. In very rare exceptions, for example with the disease chronic myocytic leukemia, it is treated with Gleevec. It has one abnormality so you can treat the one abnormality. Take a cancer like cancer of the pancreas. There are about 12 different key abnormalities and you are going to have to make different kinds of combination chemotherapy, but the principle is the same.

Chu — As we are now seeing this era of targeted therapy, which perhaps we can talk more about later in the show, is that it does look like we need combinations of targeted therapies and combinations of targeted therapies in combination with chemotherapy to perhaps have the greatest effect on killing the tumor cells.

DeVita — Yeah, absolutely, because what the targeted therapy does, that we see now, is it resets. I do not know if the audience is aware of the word apoptosis, but it means cell death, cell suicide. We have built-in mechanisms in our body for cells to commit suicide when they are no longer functional. For example, as an embryo we have webs between our fingers, but we are not born with webs between our fingers normally because these mechanisms make sure that the cells that are not needed any longer die. Every cell on the body has an apoptotic mechanism. A lot of the targeted therapies actually reset that mechanism so that when you damage it with chemotherapy, the cells commit suicide. So the combination of the targeted therapy and chemotherapy is going to be part of the future for combination chemotherapy. The problem we have with that is that all the regulations in the Food and Drug Administration process are contrary to allowing you to do that kind of thing. It is very difficult to develop these innovative therapies today. There is a study coming out very shortly looking at the time it takes for a protocol to be approved, to go through the process at a cancer center at the National Cancer Institute and the FDA. If you want to guess, you will never get it right on. It is 800 days.

Chu — Wow! 800 days.

DeVita — In some cases 1000 days, this means that the study that you are starting that was written 800 or 1000 days ago, is out of date. We have a logistical problem that I am trying to solve, how cancer cells grow and how can you kill them?

Chu — We would like to remind you to email your questions to

12:09 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

canceranswers@yale.edu, or call on *1-888-234-4YCC.* At this time, we are going to take a short break for a medical minute. Please stay tuned to learn more information about the history of cancer chemotherapy with our special guest, Dr. Vincent DeVita, from the Yale Cancer Center.

Medical Minute

The American Cancer Society estimates that in 2008 there will be over 62,000 new cases of melanoma in this country and about 2400 patients are diagnosed annually here in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths, but when detected early, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale to test innovative new treatments for melanoma. Patients enrolled in these trials are given access to newly available medicines, which have not yet been approved by the Food and Drug Administration. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR health forum from Connecticut public radio.

Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am here in the studio this evening with our special guest expert Dr. Vincent DeVita discussing the history of cancer chemotherapy. Vincent, before the break you were mentioning how long it now takes in order for protocols to even get up and running, let alone actually help us get an answer to whether or not a particular treatment actually works for a particular cancer. What is really quite fascinating to me, having been a product of the National Cancer Institute, and having been one of your fellows when you were Director at the NCI, is that the NCI was a very different place that allowed these clinical trials to get up and running in a very timely fashion and to get us some key answers. What, in your view, were the special qualities about the NCI? What made it so special that it was able to get answers that we really needed for our patients?

DeVita That is a very important question, because in the answer to that question is the description of what we should be doing now. Cancer centers were designed in the National Cancer Act "The War on Cancer" to play a special role in The War on Cancer. What was the strength of the NCI? We were limited primarily by what was between our ears. If we had ideas, we could act on the ideas very quickly. We did not have to get approval for protocol modification, which was something that could be handled internally at the National Cancer Institute. We could make modifications very quickly and what now takes 800 days, would take less than a week at the cancer institute. We could develop new therapies, modify them on the run, and come up with very novel ways of doing things. I look at the young people now and think why they even want to do this because you can't spend 800 days waiting while your protocol is being

15:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

approved somewhere else. I think what needs to be done is that the Food and Drug Administration and the National Cancer Institute need to delegate the responsibilities for protocol development approval for early trials to the cancer centers through an internal review mechanism so that you can move around very-very quickly. There is a wonderful book by Robert Weineberg on the biology of cancer. In the back of the book he has a large chart that I love to use. It is the most complicated thing in the entire world; he did it for a reason. We know a huge amount about the signaling pathways of cancer cells. When you look at it you realize how complicated it is for us to do anything to interfere with the signaling pathways. We need to be able to use the scientific talent at a cancer center to be able to make modifications to treatment regimens to block various pathways, and when they do not work, we need to be able to make another modification very quickly to adjust the treatment. You cannot do that by having the protocol submitted back to Washington to the cancer institute and then back to the Food and Drug Administration. Somebody might say, "Dr. DeVita aren't you concerned about patient's safety?" I am concerned about patient's safety. I think we are not doing something safely for cancer patients when we make them wait 800 days for our next best idea. We are in a very difficult situation and the model from years ago would be a very good model for us to use again to readjust the environment of cancer centers like Yale and Harvard. We have lot of talent at these places and we are not using it as effectively in this modern age with all the knowledge we have.

Chu You mentioned the National Cancer Act, which you played a key role in when you were director of the National Cancer Institute. One of the key features of the National Cancer Act was to have these NCI designated cancer centers around the country. One thing that maybe is confusing to a lot of listeners out there is that there are so many here in the State of Connecticut, they hear about various community centers that call themselves cancer centers, but clearly there is a difference. Could you help our listeners kind of go through that?

DeVita I had the privilege of dedicating a number of cancer centers, including other ones here in New Haven at St. Raphael's Hospital. Community cancer centers have a responsibility for delivering state-of-the-art therapy for particular tumors. The cancer centers that were approved and developed by the NCI, like Yale, have been responsible for developing the state-of-the-art therapy so being at a cancer center like Yale brings you closer to the newest developments and since cancer is an evolving field, you want to stay as close to that if you have a cancer that is not easily treated at the present time. The community cancer centers sprang up, and national mortality rates have come down for a lot of cancers, and survival rates have improved because you have been able to take the information from the cancer centers and spread it out into

the community, but there is a major difference. The difference is that one develops the therapy and the other delivers it. In the process of developing it, you deliver it as well. The Yale Cancer Center has to deliver state-of-the-art treatment, but in the process of doing that, we also have studies that look at modifying the state-of-the-art therapy to take advantage of the new biology. For example, when we developed MOPP it took 11 years fully. There is a nice paper published on this subject. It took 11 years for full dissemination of MOPP into the community; that was 1967 through 1971 so we did not have all those community cancer centers out there now. Now, the modification of a protocol that is advantageous to the patient can be disseminated very quickly.

Chu As you always taught me, translational research is the key to making new discoveries and bringing new treatment strategies into the clinic. Maybe you can tell our listeners out there, what does translational research mean to you?

DeVita I am being facetious because translational research is the current buzz word, so right now when I review grants I never see a grant that is in transitional research presented to me as transitional research. But basically, I think what we are trying to say is that ultimately you have to test new things in patients. There is a friend of mine in Boston who always made the rather crude statement that when he saw a mouse with cancer, he would step on it, that mouse models do not particularly fit well for humans. You have to eventually do your studies in humans. Taking basic information and designing studies in humans is the ultimate goal in translational research, but most scientists in the lab who are doing something they think may be relevant will tell you they are doing translational research as well. It is a very broad definition that primarily means, let's try to get something out there to help people.

Chu One of the exciting aspects these days for those of us who are involved in cancer drug development, is the ability to work very closely with the pharmaceutical companies.

DeVita Yes.

Chu Which I think may be a bit different than when you were developing MOPP chemotherapy back in the late 60s and early 70s.

DeVita There was no pharmaceutical industry in those days. We were the pharmaceutical industry. We had the National Cancer Institute Drug Development Program. It was Bristol-Myers Squibb that was the company that began to put money into and investing into anticancer drugs, and they did some heroic stuff and came out with some very good drugs, including the drug Taxol. They do a very good job and I think we go a little bit overboard the other way in trying to avoid conflict of interest in putting ourselves at arms

length with pharmaceutical companies. I think we need to stay close to them. We cannot do at Yale or Harvard or Duke what the pharmaceutical industry does. They have the capacity to develop the drugs, to do the toxicology and to market the drugs, we don't. So we need to have a partnership with them and what we just have to be careful about is the extent of that partnership.

Chu I think that is an important point that you raise, because unfortunately, with all the press and the media hoopla, pharmaceutical companies tend to get a very bad reputation, which sometimes is quite unfair.

DeVita It is unfair. I think I have mentioned this to you before. I have a pet peeve that is, when you read about these drugs, new targeted therapies, monoclonal antibodies, the cost of them can be as much as $100,000 a year, which is a lot of money, and that is why people pick on the pharmaceutical companies. Then you hear that they are tested in cancer patients and they only prolong life by about 3 months, and the public rightly says, you pay $100,000 a year and you will get a 3 month prolongation of life. What is not often said in these articles is that you are testing it in patients with advanced cancer where it is beneficial and it is expensive. When you take the same therapy and put it in the postoperative period, when there are fewer cancer cells and the patient can be cured, you may actually only require about $30,000 worth of drug and the patients are alive for the rest of their normal life. So the transition is always from the expensive and a little bit helpful in advanced cancer, to less expensive curative approaches in people who have early stage disease. I wish when the stories came out in the newspapers about the big bad companies charging $100,000, is first of all, it costs about 800 million dollars to develop a drug and get it to the market. It is happening in breast cancer and it is happening in colorectal cancer.

Chu In my own area, in colorectal cancer, where the initial approaches were to treat metastatic disease, are now actually moving into the adjuvant setting after surgery and finding remarkable results.

DeVita Remarkable results, you can say national mortality from colorectal cancer has plummeted in the last couple of decades. By the way, even in advanced diseases you are now starting to see patients with metastatic disease go into complete remission. Some of those are lasting a long time and I think we are coming to the point where we will see the ability to cure patients with metastatic cancer. However, keep in mind that 90% of the time breast cancer presents as a local disease. When you develop these therapies in advanced disease and then apply them in the local situation, you are dealing with a great majority of the population, and that is why mortality rates from breast cancer are coming down in this country as well. We need to be careful, but the pharmaceutical industry in this country is marvelous and the world owes them

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a great debt of gratitude. I think we should continue to work with them because we cannot do what we have to do without them.

Chu I think it is fair to say that the pharmaceutical companies are quite smart and they partner up with the cancer center programs that they feel give them the best chance.

DeVita Yeah. They do not have the same science that we have and they can afford to invest into that kind of scientific program. They need the scientific input and it is inefficient for a cancer center to invest in large scale toxicology chemistry programs to develop drugs, and so we now use them. The cancer institute did that for centers for a long time, but it is largely done by the pharmaceutical industry now.

Chu Just a minor switch in topics, as I mentioned at the beginning of the show, you are the senior author of the definitive text in oncology called *Principles in Practice of Oncology,* PPO, now in its eight edition. This is viewed as the Bible by all of us who practice oncology. What made you decide to actually write this book?

DeVita I just came out last week with the eight edition, so I am very pleased. It is a very beautiful book. We were looking at the field and we noticed that textbooks came out for surgeries, medical oncology and radiotherapy, but there was not one textbook that said, this is cancer, and we put it altogether in one package. So I sat down with my colleague, Steve Rosenberg, who is the Chief of Surgery at the Cancer Institute, and we convinced Sam Hellman, who by the way was trained here at Yale but at that time was at Harvard and is one of the preeminent radiotherapists in the country, to do the book. I remember Sam Hellman's comment when I asked him, he said "Are you out of your mind?" Because it was obviously going to take a lot of time and effort and since the first edition it has been very popular because I think it filled a need and we like to think, though we're slightly biased, that the national mortality rates have been nudged down by making information available to all oncologists in a very good textbook. Now there are other books that are doing the same sort of thing and I think it is delightful to see the book doing so well. For me, it keeps me sane because what it does is it forces me to look at the entire field, and we only have a year or so between editions. You are constantly looking at what is changing when you put it together and getting new authors and making sure that all the new information is in the text. It has been a delightful experience. I do not measure my life in editions, but I think I would not change working on the text for much.

26:45 into mp3 file http://www.yalecancercenter.org/podcast/Answers_July-06-08.mp3

Chu Vincent, you have got great perspective. Where do you see the landscape of cancer therapy heading over the next 5 to 10 years?

DeVita My personal feeling, and I have said this publicly, is that we have in hand a critical mass of usable knowledge. By that I mean we have enough information to do what we need to do for most cancers. The problem is, as I said, that big diagram in the back of Robert Weineberg's book is very-very complicated, and sorting it out and putting it together in effective ways in order to prevent cancer, diagnose cancer and treat cancer, is very complicated. We need to be able to develop the machinery to do that. We paid 55 billion dollars for this information in terms of support for the cancer program, and right now that is a problem that I am approaching. We have a grant that is under review at the moment looking at the structure of cancer centers and at the regulatory agencies and their interaction to see if there is a way we can change things so that we can make use of this knowledge and move very fast. If we do, I think the next 10 years are going to bring startling revelations. We are going to see tumors we never thought would fall, fall, and it will happen at a great rate of speed if we can build flexibility into our programs.

Chu Vincent, as always, it has been great having you on the show and hearing your perspectives. We look forward to having you come back for a follow-up session.

DeVita Thanks.

Chu Until next week, this is Dr. Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our Podcast, go to yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, we look at the latest information on kidney cancer with Dr. Harriet Kluger and Dr. Edward Uchio. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.