Yale CANCER CENTER answers

WNPR Connecticut Public Radio

Advances in Cancer Treatment

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller specializes in pain and palliative care. 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 we look at current trends in cancer research with Dr. Vincent DeVita, the former Director of the National Cancer Institute and Chairman of the Yale Cancer Center Advisory Board..

Miller Vince, for years during my training my mentors would always refer back to the beginning of combination chemotherapy and some of the amazing work that you did back in the 60s at the National Cancer Institute. You are the source of a legend among oncologists. Can you tell us about that adventure of what happened in the 60s?

DeVita It is interesting because we did this with great trepidation. Nowadays combination chemotherapy is given in the outpatient department in every way you can imagine. In those days, it was considered very risky business and we actually put the first few patients in the early laminar airflow rooms because we were worried about what was going to happen to them. The most important part of those experiments that we were doing in those days, when I came into the field, the thought was chemotherapy was toxic, it probably did not help anybody and therefore why bother to give it. The word cure never crept into the language and the group that I landed with at the cancer institute was of a different mind. They wanted to set out and prove that you could cure cancer with drugs. They were working on leukemia. We started work on Hodgkin's disease and we followed a lot of the experiments of a man named Howard Skipper who was doing the same sort of thing in mice. He was a mathematician turned biologist and in 1964 he reported the first cure of leukemia in a mouse. Around that time we were using the same principles to treat childhood leukemia and Hodgkin's disease, and ultimately, by 1970, it was clear that in a significant fraction of Hodgkin's disease the patients were cured by combination chemotherapy when they had an advanced cancer. That's the experiment that was at the heart of everything that we were doing. It was very exciting to see because it was quite in contrast with beliefs at that time.

Chu It is interesting because back then, being a product of the National Cancer Institute myself and having trained under Dr. DeVita, the National Cancer Institute was viewed as the center of the universe for medical oncology and cancer chemotherapy, not just for leukemia and lymphoma but for a lot of other solid tumors. To some degree they have the same freedom that we had in those days.

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DeVita

But in those days we could do things nobody else could do. First of all, we had stable financial support. Secondly, we could admit patients to the clinical center from anywhere and keep them there for as long as we needed to study them; something you cannot do anywhere nowadays, except maybe in the clinical center to some degree. You were limited by your ideas, where in the current research environment you are limited by the financial resources and other resources that are at your disposal. Even if you have a good idea, you may not be able to get the resources to carry it out. The clinical center was the Mecca for working and translating your ideas into practice.

Miller In the early 60s, if someone came to you with Hodgkin's disease, what were they treated with and what happened after? Also, what kind of changes did you see in terms of treatment outcomes?

DeVita There was a funny meeting that was chaired by Tom Fry when we did our first study which was called MOMP, because one of the drugs was methotrexate at that time; we then switched it to Procarbazine. We were going around the table, and I was a youngster and Tom wanted me to tell everybody what I was doing. He was very clever doing this because the environment was a little bit hostile. He went around the table and asked everyone what they were doing and everybody went around and said they were testing one alkylating agent compared to another alkylating agent and that was the drug, you either gave them chlorambucil, or you gave them Cytoxan. There was no effort to ask if we can eradicate the disease, it was more which alkylating agent will be easier to use. Then I got up and presented the combination. There was a very famous oncologist, now passed away, but remained a good friend of mine, he raised his hand and asked me, now he's this famous professor, “Dr. DeVita, do your patients speak to you after you do this to them?” I was a bit shaken and Tom had to smooth it all out. Years later, I was invited to his institution to give a Grand Rounds and I started out by saying, by the way he was the developer of chlorambucil, I said, “Do you remember when you asked if my patients speak to me after I do this?” then I said, “Yes, for a lot longer.” It actually was assimilated very quickly. It was one of the first tools where you could actually offer patients a cure. The full assimilation of combination chemotherapy into the medical environment took 11 years. It was a very wonderful paper that came out and looked at diffusion into practice. Initially it was a very big blip on the radar and then gradually was administered to virtually every patient with Hodgkin's disease or advanced disease. Then what happened, and is happening still, is the conversion from radiotherapy for earlier stages to chemotherapy for earlier

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stages. We're now in a bit of turmoil about whether or not you need radiotherapy and whether to use both in combination; that's the focus of most of the studies.

Chu — And that's really the model that we followed not only for Hodgkin's lymphoma and non-Hodgkin's lymphoma, but for all other solid tumors as well.

DeVita — I've got to give credit to Dr. Skipper who just recently passed away. It was designed using drugs that worked in combination and scheduling them around the growth of the bone marrow. We did studies in humans on their bone marrow and we calculated the interval in which we could safely give the combination chemotherapy. We did not have GCSF and factors that are used to protect the bone marrow in those days. We had to schedule around the most vulnerable organ, which is the bone marrow. It turned out that for many years it was a very effective schedule for any combination program. We actually developed the CNF program for breast cancer on the same principles and my friend in Italy tested it on breast cancer. It was the first effective adjuvant program in breast cancer as well. It was a very exciting time and a very exciting environment that captured all of us. I think those of you who went through the National Cancer Institute could feel the electric environment there. We were aiming at something different than other people. We had the means to do it and we did it.

Miller — What are some of the basic principles that you learned and established that we are still using now in terms of combinations, efficacy and side effects?

DeVita — One that I think is very important is combination chemotherapy which is required for any tumor that is cured by chemotherapy, with rare exceptions. You may ask yourself that with all the new therapies, such as Dr. Foss and her biologic therapies, and with targeted therapies, is it still true? And I think the answer is yes. It turns out that except for a very few tumors, most of the molecular targets in tumors like cancer of the pancreas and colon, there are multiple targets in any single tumor. My guess, and this is purely my opinion, is that you are going to have to block more than one target no matter what you use. We are going to have to learn how to use kinase inhibitors, monoclonal antibodies and cytotoxic drugs in the most effective way to destroy the cancer cells. So I would guess that combination chemotherapy is with us to stay, at least for the foreseeable future. That is one lesson that I have learned. The other lesson that I learned is to be careful. When I first came to Yale I told the faculty, "I don't really want anybody using MOMP and I am not promoting MOMP." My great fear was that we would set something into motion and then

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people can't get off the track. If this is old fashion then you should not be using it, or if I am wrong about combination chemotherapy, and I have been wrong before, you should not pin people down to the old ways, you have to be able to change. I always think of the famous Hopkins surgeon Dr. Halstead who developed the radical mastectomy which stayed around for 75 years. I have the feeling that if William Halstead had lived he would have been the first to change from the radical mastectomy to something else. But his disciples stuck to it as if it was a religion and it was a very difficult transition from the radical mastectomy to other things that are much more effective. I do not want to be the person who is responsible for pinning people down to old fashion ways.

Chu Back in 1971 president Nixon signed the National Cancer Act which many viewed as a landmark act. Could you tell our listeners what that was all about? You obviously played a key role, what was the importance of that National Cancer Act?

DeVita It was a very unique experiment and what we have been talking about played a role in it. Up until the 1970s, we had surgery and we had radiotherapy. The missing link was apparent when all the results from surgery and radiotherapy flattened out. We realized it must be that cells are getting outside of the field. We needed something to give to patients that would treat the cells that had escaped from the primary site. When we were able to show you could cure Hodgkin's disease and childhood leukemia, Mary Lasker, who is the philanthropist responsible for many health initiatives including the high blood pressure program that saved many people from strokes, said, “Wow! Now we have got critical mass and it is time to start a war on cancer." She put a lot of pressure on her friends in politics and the war on cancer was initiated. It was an effort that was unique during its time and poured enormous amounts of resources into the cancer program and into the NIH. The NIH budget in general rose as the Cancer Institute budget rose. It laid out a blue print for what we should, and needed to do to eradicate cancer. It is a very interesting document to read. It is one of those documents that is extremely wise, you wonder how prescient these people were when they wrote it because they used the phrase “in so far as feasible” very often. They knew that we did not have the resources to do some of the things they wanted to do, but they anticipated we would and therefore we should do the following things 'in so for as feasible'. When I became director in 1980 I looked at the cancer act and a lot of the 'in so for as feasible' had became feasible. We began to implement and frame the cancer institute in a way so that it could approach the mission of the cancer act.

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Miller How do you think we're doing collectively as you look back on the blue print that was laid out?

DeVita I am asked that question a lot. You see a lot of articles saying that the war on cancer failed and so forth. You have to ask people what their criteria for success are. If your criterion for success is that no one dies of cancer, then the war on cancer failed. If your criterion for success is to look at the mandate that is written right in front of the act that says, "To support research and the application of the results of research to reduce the incidence, mortality and morbidity from cancer," it has not failed. It does not say tomorrow or 10 years from now, it just says to support research and the applications of research. That was new at the NIH. NIH never supported applications of research to reduce incidence, morbidity and mortality from cancer. In 1990, the incidence of cancer began to drop. The mortality from cancer began to drop and morbidity of cancer is far less. If you look at breast cancer, in 1970 women went through radical mastectomy, postoperative radiation therapy, big swollen arms and their survival did not change. It was a very, very morbid treatment. Any woman diagnosed today with breast cancer views the treatment as a very difficult exercise. It is so much better having a lumpectomy and radiation therapy. You preserve the cosmetic effect, receive chemotherapy that does not cause nausea and vomiting and the national mortality from breast cancer is falling. The mandate has been fulfilled. The timing of that fulfillment has been the critical issue. It takes time. There was a lot of flurry about having this done by the bicentennial, which was not possible in anybody's mind because the labs were not even set up from the cancer funds by the bicentennial.

Chu We are now beginning to see the fruits of your labor over the last 20-30 years trying to understand the molecular biology and the underlying genetics of cancer. Now we have identified all these interesting targets.

DeVita Well one of the good things about getting older is that you can look back and see things that seemed so incongruous at the time. In 1983, the cancer institute was 23% of the NIH budget and we were supporting 55% of all the molecular biology research in the country and most of the world. I was warned that we were putting too much emphasis on molecular biology. Of course now that we know the big pay off of the investment on molecular biology, that seems silly, but in those days' people worried. We were weighting the institute's resources in favor of one area that might not pay off. The molecular revolution in medicine that came from the cancer war spilled over into other areas of medicine. The good news is that the best is yet to come. The fulfillment of the mandate is largely from the 15% of

dollars that went into the clinical programs and the combination chemotherapy making them more widely available drugs. The 85% that went into the laboratory gave us the molecular revolution which is just now hitting the clinic. Gleevec for chronic myelocytic leukemia and monoclonal antibodies is just coming along. The next ten years are going to be the most exciting in the history of the cancer institute.

Miller We would like to remind you to email your questions to us and Dr. Vincent DeVita at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about cancer treatment with Dr. Vincent DeVita from the Yale Cancer Center.

Over 170,000 Americans will be diagnosed with lung cancer this year and more than 85% of these diagnoses are related to smoking. The important thing to understand is that quitting even after decades of use can significantly reduce your chance of developing lung cancer. Each day patients with lung cancer are surviving. Thanks to increased access to advanced therapies and specialized care and new treatment options lung cancer survivors have new hope. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale, to test innovative new treatments for lung cancer and patients enrolled in these trials are given access to medicines, not yet approved by the Food and Drug Administration.

This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut pubic radio.

Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller, and I am here with my co-host Dr. Ed Chu, and Dr. Vincent DeVita. We are discussing trends in cancer treatment. Vincent, I'm going to ask you a relative question, but on a different topic. When we have such wonderful advances being made here in the United States, what is the status of oncology worldwide, both in third world and in other parts of the world?

DeVita That's interesting because I saw an article in the New York Times not too long ago and it suggested that our healthcare system is not as good as people think it is and that cancer care here is suffering. The fact of the matter is that our cancer care is unsurpassed in the world. People from all over the world come here for cancer therapy and lot of other countries have not invested the same way we have. They benefited from what has been discovered here, but they do not always implement it. I am in interest of full disclosure here and I am no longer on the board of the company ImClone anymore, but the drug Erbitux, which ImClone makes,

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is a drug that has produced the first data showing improvement and survival in head and neck cancer in 30 years. It has been approved by the FDA here and is being used for head and neck cancer quite vigorously. In Great Britain, the drug has not approved been for years. They have decided not to use it because it is too expensive. You have a situation where you have a drug that clearly helps a category of patients, but if they want it they have to go somewhere else; either to a European continent where it is approved, or to the United States. This is because it is a form of rationing due to the healthcare system. We are in better shape than elsewhere if you look at the mortality rates. Great Britain, which is our closest cousin, compared to the United States, we are way ahead in terms of survival and mortality rates for cancer, for obvious reasons. We should be very proud of our system. We need to fix the system to make it easier to navigate but in large part our companies have developed drugs very vigorously and I think we have better care.

Chu I am just curious, what are your thoughts about the socialized nature of medicine that obviously is practiced in Europe and Asia. I know some of my colleagues in France, Italy and UK are very limited by what types of novel biologic target therapies they can offer to their patients because of the fact that everything is nationalized.

DeVita This is exactly the point. The decision with Erbitux was not the only drug. Avastin may be approved now, but it was not approved right away. I think the decision not to approve it was made by a bureaucrat who was looking at the budget as opposed to a doctor looking at the patient. They are the ones who have a patient with head and neck cancer where their mortality could be reduced using Erbitux and radiotherapy, but they cannot give it. That is a terrible thing. That would not happen in this country. We can find ways to do it. Therefore a nationalized health system has potential limitations and I am not in favor of that. I am in favor of improving the system but I am not in favor of nationalized healthcare.

Miller Going back to 1993 when you became director of the Yale Cancer Center, what were some of the challenges that you faced, or some issues that were being faced nationally in cancer?

DeVita Before I left the cancer institute part of the mandate was to build cancer centers to carry out the mandate of the cancer act. Before I left we looked at cancer centers and decided that we needed to tighten up on the guidelines so that the institutions could fulfill certain responsibilities uniformly across the country. It took 5 years to implement and when I left Memorial Sloan-Kettering and came to Yale, it was one of the first two

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cancer centers having to live up to the new guidelines, my job was to make sure the cancer center was up to speed on those guidelines and to restructure it. The first site visit was pretty tough. I remember one of the site visitors, when I brought up how ironic it was that I had to live up to these guidelines, said in sort of a stage whisper, "Poetic Justice." I had a tough job changing things. Institutions like Yale look very carefully before they make changes in the institution. Structurally there were a lot of things we had to do, especially trying to get the clinical trials program functional. It is remarkably good now thanks to people like Ed and Rick Edelson, but I think we needed a little bit of work at that time and spent a lot of time doing that.

Chu It is interesting, and we actually underwent a recent site visit by the National Cancer Institute, the mandate now is on clinical translation research, translating ideas from the laboratories into the clinic, which I think is the essence and the spirit of what was taking place at the NCI.

DeVita Exactly, we are using application of the results of research, which is something that scientists did not always pay attention to, but now they are more than ever. Yale has always had strong science. The image that the hard part is the strong science is not correct. The hard part is the application of the science. It is extremely difficult to set up programs that translate laboratory work into the clinical practice. Every center in the country has struggled with ways of doing that. Some centers have done better than others, but some of the centers that have done better, do not have much science to translate. We are in a unique position of having an extremely strong science base and being able to match it with the program that can apply the results of that science. In this day and age with molecular revolution roaring down at us, this is the way you want to be.

Miller What are the barriers between the lab and clinical care? What are some of the things that stop us?

DeVita There are a lot of things that you would not normally think about, for example the Food and Drug Administration. If you look at it globally, not from say Yale's perspective, the ability to develop drugs is very much dependent upon how flexible the Food and Drug Administration is. The Food and Drug Administration is not a particularly flexible organization. They have a tremendously difficult job, but I think they need to look at how they handle cancer relative to say, arthritis. I mean patients with arthritis have a different kind of disease and they live a very long time and testing drugs in arthritis has a different dimension to it. When testing drugs in patients with advanced cancer, which is where we are forced to

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start, we are dealing with people who have a very limited life span. We are much too restrictive in terms of access to drugs. The current environment in general is a very heavily regulated environment that is not conducive to getting an idea and running with it. Once you get an idea, you have got tons of paperwork and things like that. It is necessary to some degree, but I think we need to continue to examine it to let the science and clinical science flourish.

Chu Another challenge is, and Dr. Edelson and I are dealing with this now on a daily basis, is funding and resources. It is important for people out there listening to understand it is quite costly, and to be able to take the best ideas from the laboratory and bring them into the clinic you need funding from federal sources like the National Cancer Institute which is being limited; it is not so easy.

DeVita That's true. It takes $25,000 a patient to do a clinical trial. The entire 25,000 may not be required to do the study, some of this is used by the drug company, but I would say anywhere from $10,000 to $15,000 per patient. If you have to do a study on 100 patients, or 1000 patients, you are spending a lot of money on and there are very few mechanisms at the NIH for supporting that kind of research. Philanthropy is key because you have the flexibility with philanthropy to be able to move the funds the way you think is appropriate. You do not have that with the federal government; it is a very rigid funding system.

Miller Most of us in our offices have *Yearbook Cancer Principles and Practices of Oncology*, which I understand you have just finished the 8th edition of, what are some of the latest updates of focus in this edition?

DeVita The 8th edition will be out this coming December. I cannot believe it. I sort of meter my life in editions of the book. It has been a joy because you can see the whole field reflected in the content of the book and as you might expect the molecular revolution is very heavily reflected. We have a chapter for every disease, and before each chapter we have a chapter on the molecular biology of that disease. Then we have the front section of the book which is the basic science part that has completely changed. It is amazing to go back and look at the first edition and then look at the same subject matter in the 8th edition; it is just like night and day. The other thing that we have done is we have a journal that is called *The Cancer Journal*. We have renamed it and it has been taken over by the publisher. The book is now called *The Journal of Principles and Practice of Oncology*. It matches our text, but what we are doing is combining the journal and the book so that the journal will be used to update the book

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periodically. Every issue will have updates of sections of the book to keep people abreast of the science. We are looking at online versions of the book and other ways to get information to people through all the various devices that are carried by doctors in training and non-training.

Chu I think it is fair to say that Dr. DeVita's book is viewed as the Bible of Oncology. It is a must for everyone in the field to have.

DeVita Thank you, I have enjoyed it. It is great to see the book everywhere I go. When I go to some place, look in the shelf and there is the book, it is really a kind of fun.

Chu Another interesting project you are working on with your daughter is your memoirs and kind of looking at the historical perspective of this war on cancer. How is that coming along?

DeVita My daughter is a writer and has written a book herself. It is coming along quite well actually. It should be about a year or so before we are finished. I happened to be in the right place at the right time. I took care of the person who actually wrote the Cancer Act and his response to cancer treatment was what stimulated Mary Lasker to look at what we were doing. I watched it being written and I was a skeptic like everybody else, and then I ran the entire program and came out and watched it by running a couple of cancer centers. I have an unusual perspective of what happened and the people involved. I know what was going on behind the scenes. This book is for lay people because we have spent over 60 billion dollars of their money on the war on cancer. I think the public who paid for it has a right to hear how it happened and why it happened and what has been done. It is a massive program and there have been a lot of critics. It is very hard for anybody to start a new program and get their arms completely around it. I have a little different perspective and I am having a lot of fun. If you had 3 or 4 more hours to talk on your show, I could fill it with all the stories that are floating around my head. My daughter is the one that gets the brunt of that at the moment.

Miller A word that we do not use often is cure. It is nice to hear it on this show, but what does the future hold in terms of the chance of curing people with cancer?

DeVita We cure the great majority of patients right now with cancer. The problem is you do not know them when you see them, which is the way we want it. Somebody who has had colon cancer and has received surgery and adjuvant chemotherapy is perfectly normal and when you see them,

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you would never know they have colon cancer. What the public sees is the patient who is failing which translates to everybody who has cancer and that scares them. That is not a real picture of it. By the year 2000 mortality rates had dropped about 10%, and the cancer society has set a goal for reduction in mortality by 50% by the year 2015. They have recently projected where they are, and if not another thing happens, the mortality rates by 2015 will drop by 23.8%, But a number of things have happened since they made those projections. They are probably closer to 30% to 35% reduction mortality by 2015 and a 50% reduction is not impossible. For some tumors they are going to be beyond the 50% goal predicted; such as colorectal cancer mortality rates which are falling very fast. Even breast cancer seems in line with getting a 50% reduction by the year 2015. We are doing well, but if you have cancer or somebody in your family has it, and they are not doing very well, we are not doing well enough for those people. I think that is a problem we face in the public perception of this.

Miller I would like to thank Dr. Vincent DeVita for joining us on Yale Cancer Center Answers.

Chu Vince, thanks so much for being with us this evening.

DeVita Great pleasure.

Chu It is always a pleasure to speak with you and to get your perspectives on the state of cancer research. Until next week, this is Dr. Ed Chu and Dr. Ken Miller 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 also find transcripts of past broadcasts in written form. Next week, we examine new developments in the prevention and treatment of lung cancer.