Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about the role of Agent Orange in certain cancers with Doctor Rory Shallis. Dr Shallis is an assistant professor of medicine in hematology at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology. So Rory maybe we can start off by you telling us a little bit more about yourself and what it is you do. I’m originally from New Jersey, South Jersey and in particular for those that know there are difference. Graduated from Rutgers College with a BA and cell biology, neuroscience, medical degree at the same place, residency at Brown and then Fellowship and Hematology Oncology at Yale was privileged to stay on as faculty and currently I currently specialize in the...
management of acute myeloid leukemia and myelodysplastic syndromes. Otherwise known as AML. And MD S. So that’s generally my practice. Tell us a little bit more about your research, my research is mostly focused. As I said on patients that are unfortunately afflicted with AML and MD S but not dissimilar from other folks that consider themselves specialists in this area. I do see, you know, a fair bit about other myeloid malignancies and other forms of leukemia as well. Most of my research is and is by way of clinical clinical trials, but I do maintain an interest in outcomes research as well, and perhaps you know on some of the topics that you wish to speak of. Yeah, so so why don’t we dive a little bit more into myeloid leukemias and and you can tell us a little bit more about what they are, what causes them, how common they are, and what the prognosis is. Them all you know pretty
important questions and all. Could be pretty lengthy answers, but I’ll try to summarize it as best I can, especially just considering you know what I presume is going to be. The audience here.

Myeloid leukemia is a general term actually, and taken simply refers to a malignant state of the white blood cells. More specifically, those that are not lymphoid, 2 general types and this is not perfectly stated of white blood cells, myeloid and lymphoid. The myeloid group of cells originate in the bone marrow or the essentially what I tell patients is the factory for. Where these are made and once assembled or mature, leave the marrow to enter the bloodstream and perform their duties, including fighting off infections among a few other roles. This is a near continuous process. Unfortunately, this process can be disrupted by a number of mechanisms that basically injure the machinery that make healthy myeloid white blood cells that can cause a ruckus on the factory floor so that they’re
really not made into the same quantity but also the same quality. We think with enough.

Injury to specific parts of that machinery. The process can be stalled entirely in certain areas where you know they are. There's a backlog of the of the myeloid white cell building blocks or precursors that we call blasts when in excess. This generally heralds a typically aggressive form of disease and at a certain point defines what we call an acute myeloid leukemia. AML not every form of myeloid leukemia or or even amount for that matter, or are identical, so you know this might be related to the fact that there are different. Parts of the machinery, whether they are specific genetic mutations in these cells or disruptions of larger portions of these cells, DNA called the chromosomes, are detected and drive the cells towards this usually unequivocally problem problematic. State. How common are they? It’s I mean it’s all relative, you know, in the hematologic malignancy world,
there are some that are more common than others. When it comes to MD S and AML, generally we regard the incidence as being in the order of maybe three to four per 100,000 population or person years, so I wouldn’t call them rare, but I wouldn’t call them common, and the prognosis for each of these diseases there’s a lot of variance, and this depends on. Really a lot of variables and some of which were really refining. You know progressively and perhaps some we haven’t even really figured out just yet. It can range from, you know, from just a patient being recommended for observation. recommended for observation. You know it’s something that can be regarded as a chronic illness. Like you know, blood pressure issues or cholesterol issues, often doesn’t really cause any problems. Conversely, there are patients that you know have disease, which is clearly aggressive and comes with a whole host of problems for which we have to be a bit
And our management approach. And so what? What causes us? I mean, when we think about other kinds of cancers, sometimes we know an etiologic factor. So for example, I think everybody kind of knows that smoking can cause lung cancer. We know that exposure to sunlight can cause melanoma. We don’t know too much about AML, so talk a little bit about what we do know and what we don’t know about factors that cause this. Great question and happy to help there. There is evidence that some AML is what we call quote UN quote de novo, meaning it arises quote from nothing and quote to take the Latin literally. But really, every you know every day our marrow stem cells and their cousins or related cells are replicating and there are inherent errors in the DNA that come about and are usually, you know, repaired via our really innate mechanisms. But sometimes these aren’t repaired, you know? So this is where some of this machinery. Can be damaged and put the cells in the path to become leukemic. So it’s really through no
fault of you know of their own, but this is still kind of a theory. Beyond this we do know that as you stated there are several causes to these disruptions to the biology that previously normal cells you know can become leukemic. Probably the most well defined exposures to things that are really meant to damage the cellular DNA and for good reason. These are certain chemotherapies. And radio therapies. Therapeutic radiation that you know is used to be solid tumors like breast cancer, lung cancer, relatively common cancers, and for which these therapies are game changers. These are effective therapies and can cure a lot of cancer, but there’s a small but appreciable risk that the marrow cells are exposed to these therapies and the damage they induce, and these cells acquire these abnormalities and this increases the risk of developing a myeloid leukemia. Non therapeutic exposures which I think is more to what you’re getting at,
are also described, however, so one of the clearest examples is unfortunately I don’t wanna say a good example. I’ll say a clear example is are there studies that have shown or or looked at sort of the long term outcomes of individuals that were exposed to the radiation from the atomic bomb explosions from, you know, the 1940s and Nagasaki and Hiroshima. This is particle radiation, specifically beta particles, also gamma radiation with regards to. Other forms there is electromagnetic radiation in certain settings that are implicated. Non therapeutic chemical exposures are also shown in some studies, including benzene. Dioxin is formaldehyde as well. Obesity has been linked to a slightly higher risk of AML. Other non modifiable risk factors as we call them contribute as well, one being male as there is a slight predominance. The other is age. AML is a disease. Sorry for saying is a disease that the elderly,
the median age at diagnosis is. Around 68 years, but the risk is higher the older you are. And this might be because people that have been on Earth longer, they’ve had longer time to be exposed to the things that you know we just discussed. So you know, unpacking a few of the things that you mentioned, the first thing, and I’m sure that listeners who may be on chemotherapy for a variety of reasons or may have undergone therapeutic radiation for a variety of cancers, often think that you know these therapies are are really trying to treat whatever their malignancy is, whether it’s breast cancer, colon cancer, lung cancer, others that are are more common, so when you said there’s a small but still appreciable Risk of developing AML with these therapies? How small is small and should people really be scared that they are now trading one cancer for another? It’s a very, very poignant and important question, and it’s certainly relevant one, you know, the risk depends on a number of things.
The agents use the dose of radiation, and to where these you know.

These agents are really being applied. They’re not very specific for tumor tissue, they’re just hopefully preferentially. You know, damaging those cells.

Which are, you know if they’re malignant, probably you know more apt to undergo the pathways that drive them to death in a good way.

But if I had to kind of give a specific number, it’s in the order of single digit percents, probably in the order of probably no less than 1%, but probably no higher than the than 9%, depending on the setting.

So you know there’s a difference. Say 1% is not 0% and it’s not 0.001%, there’s always a a risk benefit calculation on the provider side and always a risk benefit discussion that should be had.

You know, in conjunction with the patient you know before us. Hopefully this conversation is open.

As it should be and thorough, because this is like I said, it’s you know I don’t want to call it a nominal risk, it is appreciable.
But as you’ve kind of just echoed, you know these are effective therapies that are shown to unequivocally increase the risk of prolonged survival, not only the risk of prolonged survival, but cure for many many patients and you know, as it stands right now, these are still gold standards. You know of care may be in the decades to come, and hopefully in the not too distant future, you know the need for these therapies. Might be maybe pushed aside or slowly phased out with more specific and less toxic therapies, so which brings us to one or two further questions to kind of unpack that even further, so one is, you had mentioned that the prognosis of AML really varies, and for some patients it’s just a chronic illness. It’s kind of it just follows along. Just like you know, hypertension or something else. And it really doesn’t cause a whole lot of problems. And other patients, it can really be problematic.
Do we know whether the prognosis is linked to the etiologic factor? So, for example, some people may be more willing to trade one cancer for another potentially or even the risk of developing AML if we knew that the AML that was caused by people who had been exposed to chemotherapy for therapeutic intent was really more of the benign. Indolent kind of AML rather than the more aggressive. Do we know whether there's any linkage based on ideology? I probably say that biology matters, and when I'm, you know, that's sort of a, you know, vague statement. But really, it's you know what damage has been induced in these leukemia cells or the cells that eventually promote you. Know the development of leukemia. There are some exposures that are more classically associated with particular, you know, damage damages to the damage to the DNA of these leukemia cells some. Are unfortunately, you know pretty well described as being predictive of stubborn disease when it comes to things like prior
chemotherapies in particular,
classes of chemotherapies as well as radiotherapy.
There are these are therapies which are probably more associated with what we call adverse disease,
adverse risk biology,
some things that can induce a lot of DNA damage or chromosome like large segments of DNA which other chromosomes can be.
You know it just in and of themselves sort of removed, duplicated and there are some poor risk lesions,
specifically one in TP 53 which unfortunately is among those that.
Are the kind of the the worst to have in a leukemia cell among other cancers,
and you know this is 1 lesion,
which is unfortunately the most commonly observed across all the tumor types,
so it’s not necessarily that the the treatment itself is independently predictive of prognosis.
It’s more, say,
the the middle man that induces the damage and the damage itself is really what predicts more stubborn,
you know, disease, biology,
biology that would predict a lack
0:13:21.66 –> 0:13:22.752 Therapies and unfortunately,
0:13:22.752 –> 0:13:25.13 among patients that are, you know,
0:13:28.35 –> 0:13:28.613 Unfortunately,
0:13:28.613 –> 0:13:30.454 don’t stay in remission for that long,
0:13:31.29 –> 0:13:34.45 and so you know the the last question
0:13:34.45 –> 0:13:38.074 I’ll ask you before we take our break is.
0:13:38.08 –> 0:13:40.996 In the patients with AML who
0:13:40.996 –> 0:13:43.52 have a more aggressive form,
0:13:43.52 –> 0:13:45.39 is it treated with chemotherapy
0:13:45.39 –> 0:13:47.415 and radiation, and if so,
0:13:47.415 –> 0:13:49.54 couldn’t that induce even more
0:13:49.54 –> 0:13:51.658 toxicity like it does this
0:13:51.658 –> 0:13:53.638 then become a vicious cycle?
0:13:56.08 –> 0:13:57.55 If you were to ask a leukemia
0:13:57.55 –> 0:13:58.4 specialist 20 years ago,
0:13:58.4 –> 0:14:00.199 this would have been a shorter answer.
0:14:00.2 –> 0:14:01.992 You know we’re learning about this is
0:14:01.992 –> 0:14:03.784 about the biology of disease and how this
0:14:03.784 –> 0:14:06.115 can be sort of sub route based on the
0:14:06.115 –> 0:14:07.419 mechanisms and classical combination,
0:14:07.42 –> 0:14:08.74 chemotherapy has been the gold
0:14:08.74 –> 0:14:10.312 standard for for many patients since
0:14:10.312 –> 0:14:11.761 the early 1970s and this is still
0:14:11.761 –> 0:14:13.437 the case for many subsets of disease.
0:14:13.44 –> 0:14:15.407 This is what we call quote intensive
0:14:15.407 –> 0:14:16.955 therapy and quote meeting and
0:14:16.955 –> 0:14:18.893 has the potential to strain major
0:14:18.893 –> 0:14:20.32 organs including the GI, tract,
0:14:20.32 –> 0:14:21.76 kidneys, liver, heart, lungs,
and it will undoubtedly injure the bone marrow, both bad cells. In good cells, just we hope the bad cells are the ones which are preferentially yeah exposed and die. As you can imagine, at every patient can accept these risks that come with intensive therapy. The older patient or the the person that already has strained organ function might not be best suited to really receive intensive therapy. We do have less intensive therapies that are reasonably effective and this is really served as the backbone upon which some of these newer agents as you were alluding to, you know, have been studied and have been shown to be better and and quite tolerable. With the older intensive therapy quote, UN quote ineligible patient this then fosters newer combinations and even the study of these combination therapies in younger patients, perhaps even those that are eligible for intensive therapy at the starting line. Well, we’ll dive a little bit more into all of the exciting developments there right after we take a short break for a medical minute.
Please stay tuned to learn more about AML, its treatment, and about Agent Orange right after we take a break.

Funding for Yale Cancer Answers is provided by Milo Cancer Hospital where you can view videos from their integrative medicine team by searching Yale Cancer Center Integrative Medicine playlist on YouTube.

There are many obstacles to face when quitting smoking. As smoking involves the potent drug, nicotine quitting smoking is a very important lifestyle change, especially for patients undergoing cancer treatment, as it’s been shown to positively impact response to treatments decrease the likelihood that patients will develop second malignancies and increase rates of survival. Tobacco treatment programs are currently being offered at federally designated Comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital all treatment components are evidence based and patients are treated with FDA approved first line medications as well as smoking cessation counseling that
stresses appropriate coping skills.

More information is available at yalecancercenter.org you’re listening to Connecticut Public Radio.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest Doctor Rory Shallis. We’re talking about a ML and you know how this cancer of white blood cells really is? The result of derangement of DNA that can occur due to a variety of causes, and we talked a little bit about the fact that one of those causes is actually therapies from cancer. Treatments like chemotherapy or radiation, which inflict DNA damage.

Now all of us know that. The majority of these treatments tend to be more targeted towards cancers, which are rapidly dividing. But what about people who don’t have cancers and who are inflicted with DNA damage causing agents like chemical weapons or doctor Shallis? You mentioned before the break things like radiation from nuclear accidents or worse yet, atomic bombs like Hiroshima and Nagasaki. Can you talk a little bit more? About how those have an implication in terms of developing myeloid leukemias.
You said it quite nicely there. Unfortunately, many patients are, you know, unbeknownst to them and folks around them, exposed to things that. It might just take time in the order of years to decades to understand that these can be detrimental to the genetic machinery you know, DNA damage, and even some of the things that aren’t necessarily DNA damage. This is often accidental. There are, you know, chemical spills, contamination, events and things that are used in a weaponized sense as well. There is also an implication that there are. Ambient forms of these potential carcinogens or leukemogenesis you know as we call them as relates to the development of myeloid leukemias. There are several examples radiation. We mentioned, things like dioxin wins and you know you had mentioned earlier the break that you wanted to discuss a little bit about ancient orange as well. This is, you know, one of the most infamous, if not the most infamous sort of vehicle by which one of these
agents leukemia genic agents, was delivered to. Unfortunately, I would say innumerable individuals, since we don’t really know the full. The full number. So talk a little bit more about Agent Orange. What is it? What do we know about its implications in terms of developing AML? You know pervasive term, but you know, in my experience, many folks don’t understand what it actually is. It’s a combination of herbicides. 2 herbicide herbicides specifically in one to one mixture, both of which were commercially available as early as the 1940s, you know. And because it was an effective. Herbicide it was used by the US military during the Vietnam conflict. As early as I want to say 1961 or 1962 as a defoliant meaning it would rapidly clear thick areas of vegetation to allow our forces to be more effective. It was delivered by both air but as well as ground there were, you know, manual.
You know applicants going on and throwing the same time, but the herbicide spray missions you know the aircraft were part of what was called Operation Ranch Hand and an estimated it was at least 15. They wanna say 15 to 20 million gallons were delivered over these areas over. You know the years that you know the forces were in that area. Agent Orange however, was found. It took some time to realize this was found to be regularly contaminated by a chemical known as TCDD. This is a specific form of a benzo dioxin. These are as a group. These are substances that are made up of two benzene rings that are joined chemically and really could be. Unique by additions to, you know, usually through chlorine substitutions. Unfortunately, TCDD is a known carcinogen and teratogen as well. One of the first means by which
It was realized that Agent Orange was a delivery mechanism for a known toxin of this magnitude. The fact that these areas of Vietnam over the next few years did see an increase in the rate of birth defects, and unfortunately a lot of stillbirths as well. Further study, and this is mostly like lab and mouse based studies in the United States. And around the same time, given these findings clinically in those areas led to the appropriate conclusion that this was a problem, and the US eventually did end these missions and the use of Agent Orange altogether, and in 1971 as it relates to cancers. And, you know, I hope I get to talk about myeloid leukemia realm. A number of studies have found an increased risk of breast cancer, GI cancer, some lung cancers, kidney cancer, you know these were well done studies that showed that were basically,
you know, among patients that were exposed to TCDD, and not necessarily Agent Orange. There is an appreciable risk regarding the hematologic malignancies or or blood cancers, which is my area of expertise. TCDD is linked to an increased risk of both Hodgkin and non-Hodgkin lymphoma, as well as another malignancy known as multiple myeloma. The one rub is that you know exposure to TCDD is uncommon and the disease is of interest. You know are also uncommon and so and some people also don’t live long enough to get these diseases of interest. So you’re studying an uncommon. Among uncommon, with perhaps not enough time, and this is likely why some other studies have shown quote no increased risk to which you know many of us say, you know, have a you know, raise an eyebrow. However, the weight of evidence you know in some is really clearly established. That CD is a known carcinogen. Its most critical designation you know among some of the very well respected communities and organizations. The most I’d say weighted is the
International Agency for Research on Cancer or IR, which is the agency of the World Health Organization. And another relevant organization, you know veterans, the Veterans Administration VA also recognizes that there’s enough evidence to conclude that you know exposure to TCDD via Agent Orange, you know, was causative, and sorry, it was associated in some cases causally associated with the development of. Several cancers. And so if you’re a vet and you’re listening to this show, you knew that you were exposed, what kinds of things should you be doing? So number one? Are there particular tests that you should be doing in terms of screening? We know about screening tests for breast cancer and colon cancer, but not so much for leukemias #2. Are there symptoms that you should be looking for and #3? Is there anything you can do now that the exposures already
happened to lower your risk?
Good questions and I would probably start by saying that you know more than the patient shares the burden.
This is up to the provider to really be mindful of exposures you know, including you know Agent Orange exposure, which at this point is usually well documented and in fact the VA really concedes that anyone serving during a certain period of time in a certain area has been exposed to Agent Orange with regards to, you know, cancer in general. You mentioned some of the you know, the clear. You know, screening procedures for certain cancers at the moment. There's really no evidence to suggest that you know that these practices should be changed or altered in a way just based on an exposure in the past. When it comes to a new diagnosis of myeloid leukemia like AML or I would even consider MD S, you know, patients can come to attention in a number of ways. We do see patients who have, you know, as you said, quote UN quote, routine blood work, and there are abnormalities that you know
that eventually prompted evaluation. But this is not common. Typically, there is a symptom that prompts blood work. Whether this is something as nonspecific as fatigue. But also shortness of breath, which is usually a consequence of anemia, uncommonly bleeding, which is usually a consequence of low platelet count. There are patients who present with other complications of the disease, either by way of it’s inflammatory nature such as fever or with true infection because of a lengthy and low white blood cell count that predisposes a patient to such. Unfortunately, some patients, you know do come to us much sicker, with the clearly more aggressive forms of the disease. You know others, like I said, with an isolated asymptomatic. Blood count immorality but the need for treatment is usually always sorry. Is is always the same for pretty much every patient. So at the moment exposure doesn’t really buy the book by anyone. Any change to sort of screening procedures,
but I would as a provider just knowing that there’s a history out there, either documented or through you know, our routine history and physical just has me a bit more mindful in looking out for things and maybe in a biased sense. I do sort of change my monitoring.

Practices from a CBC standpoint or you know looking for different things on exam that might lend weight to hey, we should be looking. You know at this thing next or do additional testing. Is there anything that people can do to prevent cancers? Many, many patients kind of ask about that, right? Like, is there something that I should eat? Should I try antioxidants? What about hyperbaric oxygen? What is your advice to to people who have been exposed to Agent Orange who are listening to this show and are worried about the fact that this increases their risk and want to do something proactively to reduce that risk? Important, it starts with establishing care.
and in particular many are not really taking advantage of the services to which they are entitled. You know there is a framework known as service connection that is can be navigated with some of the patient advocates and the provider charged with the care. For a veteran. You know, especially one that was exposed to Agent Orange that can secure you, know additional benefits just based on that exposure, and anything that comes. Down the road, which at this point we can for the most part, presume was related to that exposure. So it starts with just establishing care you know at the VA. Or you know if you’re not a veteran and you know another, another facility that can provide really the same level of services, what can be done otherwise beyond the things we we talked about. I don’t want to sound like a nihilist and forgive me for saying this. But it’s, you know, and it’s unlikely it is sorry. It’s likely that there will always be cancer and and always be anal.
mostly because of you kind of harking back to what you had just kind of mentioned. You know the you know there are things that are natural. You know the natural world in which we live is brutal and we're likely being continually exposed albeit at low levels to ambient things that are, you know, likely naturally carcinogenic. Unfortunately such as background radiation from radon for instance, which is the leading cause of the thought to be the you know, the second leading cause of lung cancer or cosmic radiation, to which we will likely always be exposed to some degree. These are. Extreme examples I'll give you, but I think they serve the point. This does not mean we should be lax in coming up with alternatives, you know. To spare exposure, you know if we're talking about, you know occupational exposures as well as medical exposures or the ambient setting. It would be nice to have solvents that are as efficient as a starting material to make plastics, resins, and spare workers to benzene,
to which we really don’t know the true quote,
unquote safe level.
You know, which I think is a misnomer.
Or chronic low dose exposure that
you know a body like like OSHA,
for instance, establishes.
It’s possible that there may be
no safe exposure to anything out
there which can be invoked as a
carcinogen or leukemogenesis to bring
it back to my my area of interest.
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If you have questions,
the address is canceranswers@yale.edu
and past editions of the program
are available in audio and written
form at yalecancercenter.org.
We hope you’ll join us next week to
learn more about the fight against
cancer here on Connecticut Public.
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