Podcast Transcript
Dr Geoff McCowage & Dr Caroline Bateman

CAR T-cell therapy targets specific cancers

An innovative treatment that will soon be at the Cancer Centre for Children

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Dr Geoff McCowage: Hello everyone, I'm Geoff McCowage, I'm a paediatric oncologist here at the Children's Hospital at Westmead, and perhaps you know me from my podcast 'Understanding Childhood Cancer with Dr Geoff'. Today for the first time I'm going to interview someone, which is pretty exciting. I've got someone here to speak with me about an exciting new treatment that is going to start being given here at The Children's Hospital at Westmead and it's my great pleasure to welcome Dr Caroline Bateman. Hello Caroline.

Dr Caroline Bateman: Hello Geoff. Thank you for inviting me.

1. Introducing Dr Caroline Bateman (0:30 min)

Dr McCowage: It's a pleasure. Thank you for coming. Dr Bateman is going to speak to us about a really exciting new treatment and it's called CAR T-cells. So, we're going to hear all about these things - CAR T-cells, that have a funny name amongst other things if you ask me. But first of all, what about you Dr Caroline Bateman, you're a doctor are you? What do you do for a living?

Dr Bateman: Well, I'm the same as you Geoff, but I've probably got a few more qualifications than you, if you don't mind me saying. So, you can tell by my accent that I'm British, so I trained in Britain, and I'm a paediatric oncologist, but I'm also a paediatric haematologist, so I'm also trained just primarily in blood disorders. But, I also do pathology as well which means I can look down the microscope and look at blood cells et cetera.

Dr McCowage: Wow, now hang on a bit. Let's just go back here. So, you're a paediatric oncologist like me, so that means you're one of the people that treat childhood cancer and leukaemia and all that with chemotherapy and all that.

Dr Bateman: That's right.

Dr McCowage: So that means you became a paediatrician first, didn't you? Did you do that in England?

Dr Bateman: Yes, that's right.

Dr McCowage: Premature babies, asthma …

Dr Bateman: Yes! Yes, loved it!

Dr McCowage: Was that in London?

Dr Bateman: Yes, primarily in London. In and around London. We had to go outside London for short periods.

Dr McCowage: So, you became a paediatrician. Then you did the paediatric oncology, and you did some of that here …

Dr Bateman: Yes, I did. Quite a while ago, and I was still training then. I was allowed, under the British training scheme, to come and get extra experience outside the UK and I chose to come to Sydney.

Dr McCowage: Right. So, you did some time with us and completed that paediatric oncology training in England, and then you did haematology pathology.

Dr Bateman: Yes, but actually what I did after I completed paediatric oncology is I did a PHD.

Dr McCowage: A PHD? Is that a research sort of degree?

Dr Bateman: Yes, that's right. A PHD is sort of something you've done on top of your university degree and it's a period of time which I describe as being dedicated towards answering a specific

question, and it usually involves a period in a scientific laboratory trying to answer that question so I did that for four and a bit years.

Dr McCowage: Four and a bit years of pure research, at the bench, with the test tubes. Wow.

Dr Bateman: Yes, absolutely. I mean lots of scientists do a PHD after their primary degree, and medical doctors do it too, but it's a bit of a challenge going into the laboratory for medical doctors.

Dr McCowage: Yes, we're all used to wham bam quick things, whereas research just moves at a different pace.
(4:00)
Dr Bateman: Yes, but it's a good thing because it gives you time to really ponder and think about the question you're trying to answer.

Dr McCowage: And what was your PHD researching?

Dr Bateman: I was really fortunate that I was in the laboratory of Professor Sir Mel Greaves and he is someone who, his last 40 or 50 years of his life, has been researching into the aetiology of childhood cancer, particularly childhood leukaemia. I did a PHD trying to work out more information about how childhood leukaemia develops in children and I did that using a very unique scenario where identical twins both have leukaemia.

Dr McCowage: That sounds really interesting. Maybe the subject of another interview sometime.

Dr Bateman: Of course! I could go on for hours about that.

Dr McCowage: It sounds like you could after four and a half years! Sir Mel Greaves is a giant in this field. Even I've heard of him. So, then you did the haematology pathology, so this is the one where you do the bone marrow tests and look down the microscope and look after all those other conditions like iron deficiency and haemophilia, and you know how to do all that stuff.

Dr Bateman: Yes, that's right. So, general haematology training in the UK is both looking after patients but also yes, looking down the microscope and work out what's going on in someone's blood or bone marrow, but it's not only malignant haematology, you're right, it's also non-malignant, so it's the bleeding disorders, red-cell disorders, iron deficiency, B-12 et cetera, in both adults and children. So yes, I did that as well.

Dr McCowage: You're fairly seriously qualified. I think I'll push for a pay rise for you. Would that be okay?

Dr Bateman: Yes, sure! (laughter)

2. What are CAR T-cells? (5:30 min)

Dr McCowage: All right. Let's get to this thing, CAR T-cells. Why don't you tell us all about CAR T-cells, then I'm going to go back and go over all the details because I don't know if we're all going to understand it the first time through.

Dr Bateman: Okay, so CAR T-cells are a very different way of trying to get rid of leukaemia, the cancer I'm going to talk about specifically, forever. So, we're all very familiar with chemotherapy

which treats many cancers, and is very successful in many cases, in getting rid of the cancer so it goes away forever. However, when cancer comes back a problem is that sometimes you can't get it to go away again by giving a lot more chemotherapies. You have to use a different approach, and CAR T-cells is this different approach. And, what it's doing is, it's really using the power of the immune system to kill the cancer cell.

So, it will be really exciting for CAR T-cell therapy to be given at The Children's Hospital at Westmead shortly. It is using part of the patient's immune system which is called a T-cell, hence CAR T-cell, and then you genetically engineer that CAR T-cell to be able to find the leukaemia by a very specific way in the patient's body and then that T-cell kills that cell.

Did that make sense to you Geoff?

Dr McCowage: It makes sense to me, but we might go through it a little bit. So the cells come from the patient, and you take them out of the patient's body?

Dr Bateman: Yes, that's right. Not in all scenarios, but the one we're talking about specifically is it comes from the patient, and you take the T-cell out of that patient by an apheresis procedure.

Dr McCowage: Apheresis is that thing where you're on a machine right and it takes blood out of the body, and it takes the white cells into a bag, and sends the rest of the blood back into the body. You watch TV for five hours while this machine extracts these cells.

Dr Bateman: Yes.

Dr McCowage: Okay, so that's how you get the cells out of the body. And then what do you do, you engineer them? What does that mean?

Dr Bateman: For the CAR T-cell that we're talking about it is tisagenlecleucel.

Dr McCowage: Can you say that again?

Dr Bateman: Tis-agen-lecleu-cel.

Dr McCowage: That's catchy!

Dr Bateman: That's its generic name. Its trade name is Kymriah. It's manufactured by Novartis. So, what happens is, you take the cells out through the apheresis procedure, as you described beautifully, and then they get sent to the United States, to Morris Plains in New Jersey, and then they get genetically engineered to be able to identify the leukaemia cell in the patient's body.

So, T-cells are taken, they're frozen down, they're shipped over to the US, and then the CAR T-cell is manufactured by genetic engineering.

Dr McCowage: Okay, so this company Novartis, they have a big lab in New Jersey and they do this genetic engineering part to it, and then send them back to us.

Dr Bateman: That's absolutely right. To go, obviously, into the patient that they came from.

Dr McCowage: So, each patient gets their own cells given back to them.

Dr Bateman: Correct.

Dr McCowage: Okay. Wow. Do you just give them back to the child or do you give them drugs as well? Tell us a bit about that.

Dr Bateman: That's right. It sounds like a very straightforward procedure but obviously it is very regulated, because when the cells come out of a patient they need to make sure they go back into the right patient. But also the patient needs to be prepared for the reinfusion of these CAR T-cells and how that is making sure that they're fit and infection free and as tickety-boo as possible. But also, you need to give them some chemotherapy to immune-suppress them further, so when the CAR T-cells get infused into the patient it gives it the better chance for the CAR T-cell to expand, and that's what we need, we need them to expand to be able to go around the body to find any residual leukaemia cells and kill them.

Dr McCowage: Okay. So, the cells come back from America. They're in the freezer, and then when we're ready to go, the child is given some chemotherapy to just sort of knock out some of their own normal blood cells.

Dr Bateman: That's right.

Dr McCowage: And then you thaw out the others and give it to them, and then they circulate through the body and hopefully find the leukaemia and kill it.

Dr Bateman: Yes, and expand. The CAR T-cells should expand.

Dr McCowage: Expand so that when they meet a leukaemia cell, one cell turns into two, and to four, and so on to hundreds.

Dr Bateman: And it's important that they expand, but when they do, that's when you can get some of the side effects.

3. What do CAR T-cells do? (11:00 min)

Dr McCowage: Side effects, right, we're going to come to side effects. But first, I want to know what this CAR thing is about. It's C-A-R T-cells. What is this CAR thing?

Dr Bateman: CAR is just an abbreviation of Chimeric Antigen Receptor. Chimera means a fusion of two or more things, and the antigen receptor is because what you're actually doing is telling the patient's T-cells to have a receptor on the top, and they don't normally have a receptor of this type on the top, and that receptor is a thing that goes around the human body and finds its matching partner, the fancy name of which is an antigen, on the surface of the leukaemia cell.

What we're talking about is CD-19 which is on B cells, so B cell leukaemia.

Dr McCowage: Alright, so CD-19 is a chemical that is on the outside of the leukaemia cells, and some normal cells.

Dr Bateman: Yes, normal B cells.

Dr McCowage: For this B cell type leukaemia, CD-19 is the target. So the CAR T-cell is manufactured to now have an antibody against CD-19. So, as it circulates it finds this CD-19 and sticks on it, and that's what gets it revved up to multiply and kill things with CD-19 on them.

Dr Bateman: That's correct.

Dr McCowage: That's pretty cool! Okay, well that's what the CAR is about.

Can you tell me a little more about which patients might get this? Which patients with leukaemia, or brain tumours or bone tumours, or neuroblastomas? Who might get this particular CD-19 CAR T-cell?

4. Who gets the CD-19 CAR T-cell? (13:00 min)

Dr Bateman: So, the CD-19 CAR T-cell is universally for patients with CD-19 positive which is a B cell acute lymphoblastic leukaemia but it's not at the time of first diagnosis. So the indications are if the disease comes back two or more times, if you have not had a bone marrow transplantation, or if the disease comes back after bone marrow transplantation it may be the first time the disease has come back, if the disease never came back before your transplant.

And there are rare patients, even though you're initially diagnosed and most patients go into what we call remission, which means looking down the microscope we can't see leukaemia any more, some patients don't do that, and they're what's called refractory, and those patients would be considered for tisagenlecleucel.

So just to be clear, it's patients who are what we call primary refractory, so they have not gone into remission early on after being diagnosed, it's a second or greater relapse, or first relapse post bone marrow transplantation.

Dr McCowage: Okay, but it's always only these patients that have leukaemia in the B cell family. Is that right?

Dr Bateman: That's right, for tisagenlecleucel (or Kymriah), for this CAR T-cell.

Dr McCowage: So there are other CAR T-cells in the world?

Dr Bateman: Yes, there are other CAR T-cells in the world, and this is the really exciting thing. Kymriah has really been proof of concept of using this immunotherapy to treat children in a situation where it normally would have been very difficult to treat them. So now it's really expanding into other childhood cancers, and also adult cancers, so lymphoma, but also more childhood cancers such as neuroblastoma, and there will be other cancers as well. And there are other studies to do with different types of leukaemia, acute myeloid leukaemia for example. But those will not be coming to Australia as soon as the tisagenlecleucel.

Dr McCowage: So for each cancer you presumably have to find a target on the surface of the cancer cell that you can design this CAR T-cell for. So if it's breast cancer you'll have to find a breast cancer one.

Dr Bateman: Correct, And although that sounds relatively easy to do, you have to really find a target that's not on other important cells in the body. So it really has to be on the breast cancer cell, but not on a target that also happens to be in the eye or something.

Dr McCowage: Right, because the CAR T-cell would attack the normal tissue then, and we don't want that.

Dr Bateman: And that's why it's very complicated and clinical trials have to be done, to be making sure there are no other effects of the immunotherapy for the specific target.

Dr McCowage: So just going back again now. In paediatric oncology the leukaemias are normally acute leukaemia, and so we're talking about acute lymphoblastic leukaemia and we're not talking about the T-cell form of acute lymphoblastic leukaemia?

Dr Bateman: No.

Dr McCowage: And most children with acute lymphoblastic leukaemia, when we first find the disease, they're not going to go for CAR T-cells, they're going to do what they do now and go on to normal chemotherapy. And it's only if that doesn't work, so if the leukaemia doesn't go away, or if it keeps relapsing, or after a transplant it relapses.

Dr Bateman: Yes.

Dr McCowage: Well that's only a small proportion of children with leukaemia that we give this too.

Dr Bateman: Yes, absolutely. So only a tiny amount of people will need this therapy and if we think about numbers in New South Wales, for example, I would imagine that's only five to ten children per year maximum. So really it is a small amount of patients. And as time goes on though, I'm hoping, and this is not for now, but as time goes on, is that this therapy may be able to reduce the amount of chemotherapy that we give, and we move it further down and include different groups of patients with the same diagnosis. But that's not how it is at the moment because chemotherapy for the majority of children with B cell acute lymphoblastic leukaemia is curative first time around.

A significant burden of treatment, absolutely, but it's very effective for the majority of patients.

5. Possible side effects (18:00 min)

Dr McCowage: But one day, maybe we could get rid of one of the nastier drugs and put in this. Now, you did mention side effects. So we give these cells to the child, say this child still has leukaemia from the relapse, and we've given some chemotherapy, and that will have some side effects, and then we give these cells and things can go wrong can they?

Dr Bateman: Well, not really go wrong, it's just a consequence of the treatment, and its something that we expect to happen. So obviously whenever you're infusing anything into a patient you can always have a mild or sometimes severe reaction to the infusion of the CAR T-cell itself. But that's not too much of an issue. The main side effects we worry about is something called Cytokine Release Syndrome.

Dr McCowage: Hold on. Cytokine Release Syndrome?

Dr Bateman: Yes.

Dr McCowage: Okay. Tell us more.

Dr Bateman: Cytokine Release Syndrome is partly what I was describing before. The CAR T-cell finds its partner, so it finds its CD-19 on the leukaemia cell, or other normal cells which it's okay to be on, and then the immune system is activated to kill the leukaemia cell. At that point we can have a clinical picture, which means what we see in the patient with Cytokine Release Syndrome, and it usually presents around day three after the infusion of the CAR T-cell with a fever. So it mirrors, very much, an infection with a fever so we would start antibiotics but sometimes the fever can become very high at 40 or 41 degrees and we often talk about 38 degrees as the baseline for thinking someone has a fever.

So, the patient can become very hot and they may get palpitations, and their heart may race, and then sometimes their blood pressure gets quite low. And normally we would treat this as an infection but now we know it is an immune response that means the patient needs some extra treatment to dampen down the immune response.

Dr McCowage: So, this happens because the treatment is working.

Dr Bateman: Yes. One would expect.

Dr McCowage: So, it is sort of a good sign, but sort of a bad day or two.

Dr Bateman: Yes, that's right. But not everybody gets Cytokine Release Syndrome and it's graded one to four, actually, and with grade 1-2 you'd still be on the ward for example, but with grade three to four you might be in intensive care and needing a bit more support with your blood pressure for example. But not everybody gets it, and a little bit is okay, but the problem is you don't know at what point it's going to stop, and you might have a little bit and then it gets better and you might not have Cytokine Release Syndrome again. Or, it might start off not so bad and then progress quite rapidly.

But we have good treatments for it and we know how to treat it. We expect about 70 per cent of patients, so about seven patients in ten will get some form of Cytokine Release, but maybe only one in ten patients will go to intensive care.

Dr McCowage: And you've got a wonder drug to turn it off if you have to. Is this right?

Dr Bateman: Yes, that's right.

Dr McCowage: It's got a funny name as well I guess?

Dr Bateman: Yes, it's called tocilizumab and basically as the immune system is activated, we know that it is driven by something in your blood, an interleukin called IL-6, and tocilizumab can essentially turn that off. We also have other things we can use if that doesn't work. And I think one of the good things about tisagenlecleucel (or Kymriah) is that we are getting better at managing Cytokine Release Syndrome (CRS) and also getting better at getting patients in the best possible clinical condition and disease status condition to minimise CRS.

So, you were saying about CRS 'oh, does that mean it's working?' Well, yes, that would be an assumption, but you also have the opposite of that. If you don't get CRS, it doesn't mean it hasn't worked.

Dr McCowage: Alright. And by the way, are the children getting CAR T-cells the ones with a tiny, tiny amount of leukaemia that is still detectable, or are they the ones that have lots of leukaemia in the bone marrow (an overt, full-on relapse)?

Dr Bateman: It can be either, or. You can have CAR T-cells even when you only have a small amount of leukaemia, and ideally you would not want to have a huge amount as that is associated with severe CRS, so going to intensive care CRS, which can be dangerous. So that's part of what I'm saying, that we're getting better, because we're identifying patients earlier, and we're getting them before they have a lot of disease.

We've talked about the collection of CAR T-cells by the apheresis procedure, where you said we'd be sitting watching TV for five hours, which I think is roughly true, and you can potentially collect the CAR T-cells and then keep them in your freezer for 30 months.

Dr McCowage: And wait for the exact right time to give them …

Dr Bateman: Correct. That's right. So this is how we're becoming clever really at using this sophisticated product.

So, it is really exciting for patients, because a lot of these patients need CAR T-cells as an avenue for good therapy to get disease control otherwise their options are potentially more limited, or not as effective as CAR T-cells.

6. More about side effects (25:00 min)

Dr McCowage: Okay. Now, tell me more about side effects. Are there any more side effects in the weeks, months, or years following CAR T-cell therapy?

Dr Bateman: Other type of side effect that can be quite disturbing, but actually is almost universally reversible is neurological side effects. Neurological side effects are things to do with your brain and your nerves. You can get neurological side effects with CRS, or without CRS, or the CRS is getting better and you get neurological side effects. It classically is a picture of being confused and the patient stops speaking and you can manage it with the antidote very similar to CRS, or other medications, but it almost universally gets better on its own.

Dr McCowage: So, a pretty scary few days with the patient not talking and confused, but they get better …

Dr Bateman: Absolutely, they almost universally get better. So yes, scary for everybody, but we have to remember that they get better.

Dr McCowage: Okay, that's good.

Dr Bateman: Other side effects. We talked about CD-19 on leukaemia cells but you also have CD-19 on some normal cells and one of your other type of white cells that fights infection in your body is a

cell called a B cell, and your B cells are particularly good at producing your own antibodies in your body, which we all do all the time to protect us from infections.

Using CAR T-cells means you don't have any of your normal B cells in your body anymore. And actually, we use that as a biomarker to see whether your CAR T-cells are still working because if they're getting rid of your B cells then they must be getting rid of any leukaemia cells that keep popping up here and there, like they do unfortunately.

But what it means is that you do have to have a supplement of immunoglobulin, which is like an antibody that you can produce in your own body, but because you can't produce it, you have to have it as an additional administration. It's usually given by an injection once a month.

Dr McCowage: So the normal B cells are normally meant to be making your antibodies. Antibodies against the cold, the tetanus, and the flu, and you stop making those antibodies so the blood bank gives you the antibodies to have by an injection.

Dr Bateman: The other thing is we need to monitor for disease coming back, because CAR T-cell therapy is not a cure for everyone, and so we still have that as a significant problem. We expect that about 50 per cent of patients should be okay, and so there will be a period of surveillance which almost universally is done by bone marrow tests.

Dr McCowage: Okay, so these were children where all of our treatments so far had failed, and we were sort of running out of options, and used CAR T-cells. In what proportion will you see an improvement in the situation, in the short term at least? A reduction in leukaemia, or maybe going into remission?

Dr Bateman: It's very dependent on where you're up to, for example, post-transplant or primary refractory, but the majority of patients do have some response, and that is measured at 30 days post infusion. But, the key is keeping that response maintained, that is, maintaining CAR T-cells in the body, and that is something we don't have a lot of control over at the moment.

7. Leukaemia can adjust the chemical target (30:00 min)

Dr McCowage: So, in 50 per cent of the time we don't see the leukaemia again, and in the other half it does start to emerge again, so maybe we talk about transplants again or CAR T-cells again. Can you give them twice?

Dr Bateman: Well, the simple answer is no. But there are situations where potentially you may be able to give a different type of CAR T-cell, or a top-up of the CAR T-cell you've already had because sometimes too much is made. So there are other options, but I think once you've relapsed post CAR T-cell it will be really down to if you have had a transplant and your mechanism of relapse because sometimes we can have the very frustrating situation where we can see your CAR T-cell is still there and still working but unfortunately leukaemia is really, really clever and it can get rid of the chemical blob on of top of it, CD-19.

Dr McCowage: You're kidding. So, the leukaemia gets rid of the target, just so it can keep growing.

Dr Bateman: Yes.

Dr McCowage: Well, that's not fair.

Dr Bateman: It's incredibly frustrating, but then that does happen in some patients.

Dr McCowage: To give them again would be a bit experimental.

Dr Bateman: Yes, and that's a very difficult situation.

Dr McCowage: So, these cells, they could last in the body longer than a drug lasts for instance. Like drugs we think might last a few days or a week and then the drug goes away. But these CAR T-cells, they can persist. Is that what you're telling me?

Dr Bateman: Yes, that's right. They also get called a 'living drug' so they live in the body and we don't actually know how long they're going to last because, and I think we can say her name because she's very famous as the first young girl who got Kymriah administered, Emily Whitehead. She was six or seven, I think, when she was infused and now she's a young woman of the age of 15 or 16, and she's the person that we know has had the CAR T-cell for the longest and she still has CAR T-cells detectable in her body. So that's how long we know they can persist for.

Dr McCowage: So those cells are still circulating and maybe if a leukaemia cell does crop up, they're waiting ready to go …

Dr Bateman: That's right, and we know with leukaemia that cells can sometimes be sleepy, or what we call quiescent, and that's part of the philosophy around maintenance therapy which can be either eighteen months or a year. Where you'd have small amounts of chemotherapy, and if a leukaemia cell wakes up … zap! But, with the CD-19 on the surface, if the cells are detectable, then the CAR T-cell can also just … zap!

Dr McCowage: And that little girl, Emily Whitehead, was the first person to get CAR T-cells. There is a very interesting picture on the internet. She meets Barack Obama at the White House and Barack Obama says to her, is there anything I can get for you? Meaning a glass of water or something, and she tells him she needs a note for school. So he writes her a note for school (as she missed it to attend the White House). You can look it up!

Dr McCowage: So, while they're just circulating, maybe every time a leukaemia cell crops up, they kill it.

8. CAR T-cell treatment will soon be at the Cancer Centre for Children (34:00 min)

Dr McCowage: So Caroline, Novartis is a big international drug company, and they've approved now for us to be a site that delivers the treatment. This is pretty expensive, am I right?

Dr Bateman: The tisagenlecleucel? Yes, absolutely. So, it is a very expensive treatment and currently I understand the cost is in the region of half a million dollars. That's just for the product. So that doesn't include the cost of care for the patient in hospital, or the staff that need to be employed, because this is a highly regulated process, which is a requirement by the Australian Government but also by Novartis, to make sure that this product goes from the right patient to America and back into the right patient.

Dr McCowage: And that it doesn't get infected over there, and the cells grow properly, and there's quality control.

Dr Bateman: Absolutely, so it's a highly complicated process. So yes, the product itself is expensive, but there is a whole other layer of expense. That's partly why not everybody gets it, but we don't know that everybody needs it at the moment. Like you said before, it would be really nice if one day, if you're diagnosed with leukaemia, rather than having two years of chemotherapy treatment, which is significant and burdensome for families and young people and children, you may have a month of treatment to get your disease down a bit, collect your T-cells, have your CAR T-cell infused when it comes back in a month (it takes a month to manufacture) and then that's it. You've got your living drug in your body for the rest of your life, so your leukaemia doesn't come back. Doesn't that sound fantastic?

Dr McCowage: It sounds nice.

Dr Bateman: But we're not in that situation at the moment.

Dr McCowage: Maybe in 2040 or something we'll be there …

Dr Bateman: Well me and you will be retired I think, Geoff …

Dr McCowage: How are these families going to pay for this, or who's going to pay for this?

Dr Bateman: The Australian Government, and NSW Health, pay for it so there is an agreement between state government and the federal government to pay for this, but you're only allowed one.

Dr McCowage: Okay, so families don't have to pay for this.

Dr Bateman: Absolutely not.

Dr McCowage: No crowd funding, no selling raffle tickets, no selling the house …

Dr Bateman: No. This is a Medicare related expense. There is no expense to the family. It will be administered in a public hospital, such as The Children's Hospital at Westmead. There will be no difference in expense than there would be for chemotherapy, other than the federal government noticing the expense.

Dr McCowage: Well that's great news isn't it?

Dr Bateman: Yes, that's fantastic. Because previously it was not available potentially for free for patients.

Dr McCowage: There were patients travelling to America, and paying with their own money, and there is no more of that needed. Now tell me, Novartis has agreed to your program being one that can deliver the drugs, so what did you have to do? Did you have to prove to them you were capable?

Dr Bateman: Yes, absolutely. We underwent a very rigorous audit. An audit is a very clear process of looking at all your processes in the hospital, in the laboratory where your cells go before they're packed up and go to America. And for every step of that process you have to prove you know exactly what is going on. I'll give you an example. We collect some cells from a patient, and we say

they are collected at 10am on the 11 November 2020. You're asked, how do you know it's that time and that date?

Dr McCowage: You're kidding.

Dr Bateman: No, it comes down to that. These are actually quite philosophical questions. Well, of course, we know that in a hospital because we have all our clocks on systems, and those systems know the time is correct. So that's the answer. But saying, "because my iPhone or any other device says that's the time" is not adequate. So that's the nitty gritty, that's the level of the audit, and it has to be like that. Of course, we are in agreement with that. And they have passed that we are okay.

Dr McCowage: So, you had to have a fully functional, fully fleshed out, bone marrow transplant program, lab, and all of that as well, and convince them.

Dr Bateman: Yes, that's right. So we have our own bone marrow transplant service and we have a big BMT (bone marrow transplant) laboratory, where all sorts of cell products get processed, and we actually share that with the adult hospital next door, Westmead Hospital, who are also going to be giving Kymriah, and we're doing our audit in consort with them so we can both start at the same time in the lab.

Dr McCowage: Adult patients with CD-19 positive leukaemia …

Dr Bateman: Who are under 25. It's not all adult patients, there's a bit of an age cut off. Which doesn't really affect us as we only have up to 17 or so, but for adults there is a defined cut-off age.

Dr McCowage: You mentioned an audit, and from what I could see it looked like they were putting bamboo under your fingernails and shining a bright light in your eyes. That's how an audit looked to me.

Dr Bateman: Lots of paperwork!

Dr McCowage: Hmm, I bet.

9. CAR T-cells and other cancers (40:00 min)

Caroline, you mentioned we may be able to have CAR T-cells for other cancers in the future. Can you tell us something about that?

Dr Bateman: Well, actually Geoff, why can't I interview you, because you've been playing that you know nothing about CAR T-cells, but tell me about your CAR T-cell.

Dr McCowage: It's true. I have been acting very ignorant, but we do actually have a CAR T-cell that we're working on here in our labs. So this is a CAR T-cell, but it doesn't attack CD-19, it attacks a different chemical. It's a chemical we find on certain of the bone tumours, like Ewing sarcoma and osteosarcoma, and certain brain tumours, and it's a chemical called EphA2. We've made a CAR T-cell against EphA2, and when we mix the CAR T-cells with tumour cells in test tubes, or in other lab systems, it's really good at killing the cancer.

Dr Bateman: So, you're using essentially the same technology that I've been talking about, just changing what the target is.

Dr McCowage: That's right. Our target is a target on different tumours. Otherwise it's an identical system to what they're using on leukaemia, and like I said, it works really well in the lab, and we're actually we're trying to get towards a clinical trial to treat children with bone tumours, and maybe brain tumours, with this CAR T-cell.

Dr Bateman: Do you have any idea when that might happen? And, which patients specifically you would be including in your clinical trial?

Dr McCowage: I think we're a few years off being able to give it to children, and we would reserve it, really, for those patients where the existing chemotherapy, surgery and radiotherapy hasn't worked. So, it would be small numbers, but it would be a trial, first off we would have to move very carefully and just prove it was safe to do this.

We've got this incredible program here at The Children's Hospital at Westmead in making the gene delivery systems. This isn't just in Oncology, this is a whole separate program here in gene therapy, and they're the ones that can make the systems to do the genetic modification of the T-cells, and they work on all sorts of diseases including diseases of the eye, and diseases of the nerves and muscles and livers. They are a whole separate story we can talk about another time.

But we're really well placed here on the Westmead campus to do exactly this sort of research. It's pretty exciting times. But, anyway, with the leukaemia CAR T-cell, the CD-19 one and Kymriah, do you think you'll be ready to potentially treat patients later this year?

Dr Bateman: I'm hoping either late 2020, or early 2021, we'll be ready. And I think it will be absolutely fantastic to have the opportunity for our patients to have this treatment if they need it.

Dr McCowage: It's very exciting. I'd like to congratulate you for getting us this far. I know it's been a lot of work, and a lot of it very, very tedious paperwork, and meticulous attention to detail, but certainly very exciting times. So well done, and we'll all be very interested to follow what happens next.

Dr Bateman: Thanks Geoffrey. And I'm part of a big team

Dr McCowage: Thank you Dr Bateman.

Well that was a pretty exciting thing to hear about. We'll stop there, and just to remind you, I'm Dr Geoff and my podcast is Understanding Childhood Cancer with Dr Geoff. And I've been speaking with Dr Caroline Bateman, a paediatric oncologist here at The Children's Hospital at Westmead, and I am going to push for her to get a tripling of her pay because she seems very, very qualified.

Dr Bateman: Thanks Geoff!

(44:30)