Gene Editing questions 11th Feb 2025 Webinar

Hi, what is the max age for this treatment ? Is it 35?

NICE have not set a maximum age. We know that in general that as people get older their bodies are going to struggle more with the strong chemotherapy but this would be looked at on a person-by-person basis rather than just looking at their age. So far people treated on the clinical trial were under 35 so we do not have experience yet of treating older people, and that would also have to be taken into consideration.

Can cancer be a side effect of the chemotherapy - If so, which cancers

Yes, unfortunately it is true that cancer, especially blood cancers such as leukaemia, are more likely in people who have had busulphan chemotherapy than people who have not had chemotherapy. The risk is relatively small but is a long-term risk.

Is there screening for unintended on-target and off-target DNA damage that could give rise to leukaemia in the longer term? This is not a question of if unintended DNA damage will occur but how much and how risky this is.

On the clinical trial there was screening for off-target DNA damage caused by the gene editing and they did not find any, but they did target their screening at particular areas of the genes rather than looking at all of the genes. The treatment works by disrupting an area of the BCL11A gene so they looked at how many cells had this change in as well – that would be the 'on target' effect and this is how the treatment works. However, we know that the chemotherapy itself also causes a risk of damage to the DNA which is why there is a small increased risk of cancer.

what is the potential of the age profile further changing? (I'm 47!!)

I think that it is likely centres will start by treating younger patients but there have already been approvals for people around 40 and a little over, and as we gain more experience with this treatment we will understand more about its effects in slightly older people as well. I would recommend for anyone over 35 who is interested in this treatment to see their specialist team for discussion as soon as possible, to discuss whether this might be a good option for them or not – I would not recommend waiting.

Is fertility preservation free for clients needing gene therapy??

Yes, fertility preservation, for people meeting the criteria, is free on the NHS. However, there may be a time limit for the number of years that sperm, eggs or embryos are stored free of charge before someone has to pay for extended storage. I would suggest discussing this with your clinical team as there can be some regional variation with this.

If sperm/egg freezing is included, how many rounds of IVF are allowed? Currently it depends on local authority.

I agree that IVF funding arrangements vary between region and therefore it would be best to check with your local team. IVF would be for after Exa-cel treatment. If the question is related to how many rounds of hormonal cycle therapy would be given to stimulate egg or sperm production, this would be a bit different and would depend on someone's response to that treatment and whether it was felt that further treatment would be likely to be successful.

If I understand correctly, the NHP ultimately decides which patients will receive the treatment and in which order?

For approval, a specialist team first has to get approval of the regional centre (HCC) – often this would be the centre delivering the treatment. The NHP then also has to give approval. However, each centre which is delivering Exa-cel treatment will have its own waiting list and would manage that themselves. There are not currently long waiting lists for treatment, but if these develop then the NHP might help with advising centres on how to decide who should be prioritised to go first or later on for treatment – this currently has not happened though.

If you have already have a sibling matched donor, are you eligible for the gene editing?

If you have a fully matched and healthy sibling donor who is available and willing to donate, then unfortunately you would not be able to receive gene editing treatment. Currently we could only offer the option of donor transplant in that case. However, even if there is a fully matched sibling, if they were not fit enough to donate or not willing to donate then we would consider you did not have a donor and you could be eligible for Exa-cel gene therapy.

"If someone was said to have been diagnosed with liver cirrhosis but now the levels have returned to normal 5 years after being diagnosed, will an mri/t2/ultrasound scan be sufficient to see if they are eligible for gene therapy or is anything more needed???"

For someone with a history of liver cirrhosis, a standard ultrasound or MRI / T2* / Ferriscan would not be enough (although these are still important). There is a risk of having a bad liver complication of the treatment called 'venoocclusive disease' with this chemotherapy, so we need to make sure people have healthy livers before starting treatment with Exa-cel. Therefore if there is a history of cirrhosis then further tests would be recommended to get more information on how healthy the liver is today. These are likely to include specialised ultrasound scans such as a Fibroscan, and also very likely to include a liver biopsy. The liver biopsy takes a small sample of the liver tissue to examine it in detail under the microscope and make sure the cirrhosis has completely gone away.

Why 6 months to produce the gene edited bone marrow stem cell product? With gene addition gene therapy it's a fraction of this time - 1 week!

This was answered in the webinar

I have a nephew 22 years old now, in Manchester. He had transplant when he was 2-3 years old. His organs stopped working due to chemo. Is there any other hope or way.

I am very sorry to hear about everything your nephew has gone through. Unfortunately it is not likely he could have Exa-cel treatment because once someone has already had strong chemotherapy with busulphan or similar treatment it would be too risky for them to have more of the same drugs. It may be that in the future we can give gene therapy without the strong chemotherapy – people are working on this already, but it is still quite a way off being available to treat people unfortunately. There might be clinical trials or new treatments of different approaches though which could help your nephew, for example by making transfusions less frequent. I know the team in Manchester are looking to open more clinical trials, so I would suggest he speaks to them directly about this.

I heard Thalidomide and hydroxyurea would activate the fetal hb...there are people without transfusions with these medications. Could you please elaborate

This was answered in the webinar

Could you summarise again the duration of each stage of treatment

Once someone is ready to start treatment, they would have 'hypertransfusion' for 2 months – this is extra transfusions to keep the haemoglobin higher than usual (often

over 110 g/l). Then they will have 4 days of injections called G-CSF to bring the stem cells out into the bloodstream, and after that will go into hospital for around 3 days of stem cell collection – on that first day they will have an additional injection of another medication called plerixafor to help release the stem cells as well.

After that, there is approximately a 6 month wait until the stem cells are ready, and for the last 2 months there would be more of the hypertransfusion. After that, you would be admitted to hospital and would have to stay in an isolation room for around 4-6 weeks to receive the chemotherapy, the gene therapy treatment and then to wait for the stem cells to regrow in the bone marrow. Once you have enough white blood cells to protect you from infection, you could come out of isolation and go home but you would be seen in the hospital regularly (at least twice a week to start with) for the first few months at least, and likely up to a year.

Is the same chemo drug used for bone marrow transplant i.e. as strong?

Yes, the chemotherapy drug used for gene therapy is called busulphan and is also used for some bone marrow transplants

Does it all have to be done via a hickman line? Is there risk of infection

Usually you would have a Hickman line or something similar for the time you are in hospital during the gene therapy treatment. The line itself does carry a risk of infection, but it is needed to make sure you can receive the chemotherapy, the gene therapy treatment and all the other treatments you will need during your hospital stay safely. It could come out once your blood counts have come back up after the treatment. The main cause of infection during this time however is the strong chemotherapy itself and the fact that it causes your white blood cell levels to be very low, so that you can't fight off infection in the normal way.

Roadmap for gene therapy ..would chemo still be part of the equation

In the long term it would be the aim to deliver gene therapy without strong chemo. There is work being done to accomplish this, but it is not ready to be applied to people yet and probably quite a long way ahead at the moment.

is the IVF/egg collection funded even if you have a child already

Access to funded IVF is unfortunately still postcode-dependent therefore I would recommend the interested individual asks their team regarding local arrangements.

any idea to the number of patients the NHS will be able to finance

They have not set a cap on the number of people who can have this, and once NICE makes a treatment available they have an obligation to make sure it can be provided equitably to everyone who meets their criteria for receiving it. It is a very expensive treatment, but actually if you compare that to the cost of all the treatment needed when people need lifelong transfusions and all the extra possible complications and care caused by this, it is perhaps not a very big difference. You would also want to factor in the financial benefits of someone being able to spend more time in education and work, because they are feeling well and not having to come for transfusions, which will benefit the economy.

Is this treatment stopping after 5 years?

NICE have said they will re-evaluate after 5 years. If at that point they have good information to show the treatment is working well and is not causing any unexpected problems, I would hope that they will make it available long term after that.

Which centres are being used? Which are the London centres?

Currently the six centres which are delivering this treatment are: Manchester, Birmingham, and the 4 London centres are UCLH, St Bart's Hospital, King's College Hospital and Imperial (St Mary's and Hammersmith).

Newer treatments have been developed to avoid harsh chemo work up, so why does this therapy involve the total irradiation of the bone marrow? Why is chemo required for this treatment?

Unfortunately, all types of bone marrow transplant including gene therapy still need chemotherapy. This is to clear space in the bone marrow to allow the new cells to grow, and to prevent the body from rejecting them. People are working on different ways to be able to give treatments like this without the harsh chemotherapy, so I hope that in the future we might be able to give gene therapy without the strong chemo but at the moment unfortunately this is not close to being trialled in humans yet.