

Bevacizumab (Avastin®)

The drug bevacizumab (Avastin®) is a biological therapy, meaning that it works on processes within our cells such as cell division. Whilst bevacizumab has proved effective for some types of cancer, its effectiveness in brain tumour treatment is under much debate. For this reason it is not authorised in the UK to treat brain tumours.

It is thought that the drug may be helpful for the short-term treatment of some brain tumours, particularly glioblastoma (grade 4 astrocytoma) that have relapsed (returned) after treatment. However, there is concern that brain tumours that relapse following treatment with bevacizumab often do so by invading surrounding healthy tissue more aggressively. This fact sheet looks at the current evidence relating to bevacizumab.

In this fact sheet:

- What is bevacizumab?
- How does bevacizumab work?
- Is it effective for brain tumours?
- Can I have bevacizumab?
- How do I take it and what are the side-effects?

What is bevacizumab?

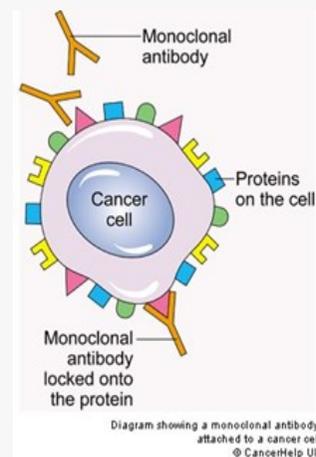
Bevacizumab (pronounced bev-ah-siz-oo-mab), brand name Avastin®, is a type of monoclonal antibody.

What is a monoclonal antibody?

Antibodies are naturally occurring proteins within our bodies. Our body's immune system makes these antibodies when it detects harmful substances. The antibodies work to remove or kill the harmful substances, that are referred to as 'antigens'. Examples of antigens include chemicals, bacteria, viruses, pollen, or other proteins produced within the body e.g. those on the surface of tumour cells. An antibody works by binding (sticking) to the antigen and then causing it to die.

To bind to the antigen effectively, the antibody needs to be the 'complementary' (matched) shape to the antigen - like a key fitting a particular lock. As each antigen is a different shape, there needs to be many different types of antibody to help protect us from many different harmful substances. Each type of antibody, therefore, is unique and defends the body against one specific antigen.

Researchers have learned how to design antibodies that target specific antigens, such as certain proteins found on the surface of some tumour cells. They can then make many copies of that antibody in the laboratory. This is known as cloning and the antibodies are called Monoclonal Antibodies (MABs). ('Mono' means 'one', and 'clonal' refers to the cloning /copying of the antibody to make numerous copies of the same type).



Different tumour cells have different proteins on their surface, so each tumour type acts as a different antigen. As a result, different MABs need to be made to target the different proteins. To make these MABs researchers have to first identify the right antigen (protein) to attack.

This is often not easy with some tumour cells, so MABs have proven to be more useful against some cancers than others.

Bevacizumab (Avastin®) is one of these types of MAB. It is currently authorised in the UK to treat some types of cancer for which it has been shown to have some positive effects, particularly when used alongside chemotherapy. These include breast, advanced bowel, kidney and ovarian cancers.

Bevacizumab is not, however, authorised in the UK for the treatment of brain tumours, but it is being used in clinical trials for high grade gliomas in both adults and children, particularly in combination with chemotherapy and/or radiotherapy. (*For information on grading and types of brain tumours, see 'What is a brain tumour?' fact sheet*). (*For information about clinical trials, see the section 'Can I have bevacizumab?' further on in this fact sheet*). It is approved for use with recurrent glioblastomas (GBMs) in the USA.

How does bevacizumab work?

There are three main types of monoclonal antibody - each working in a slightly different way. They can:

- trigger the immune system to attack tumour cells
- block signals to the tumour cells that help them grow or divide
- carry drugs or radiation to the tumour cells

Bevacizumab uses the method of blocking signals.

Tumours need a blood supply to be able to grow and spread. Bevacizumab targets a protein, on the surface of the tumour cells, called VEGF (vascular endothelial growth factor) that helps to make blood vessels grow. When bevacizumab reaches the VEGF protein, it binds to it. There are a variety of possible mechanisms by which it then works. One suggestion is that bevacizumab blocks the VEGF from creating new blood vessels for the tumour. By cutting off the blood supply to the tumour and depriving it of the nutrients and oxygen it needs to survive, bevacizumab causes the tumour to shrink and die or, at least, slows the growth of the tumour.

Another theory is that rather than starving the tumour, bevacizumab restores the abnormal blood vessel growth to a more normal state. The advantage of this is that cytotoxic (cancer-killing) treatments, such as chemotherapy and

radiotherapy, can then be delivered more efficiently to the tumour by the, now more normal, blood vessels.

Bevacizumab, therefore, is known as an 'anti-angiogenesis' or 'anti-angiogenic' drug. 'Angiogenesis' means the formation of new blood cells. Anti-angiogenic means it blocks this process.

Is bevacizumab effective for brain tumours?

The effectiveness of bevacizumab for the treatment of brain tumours is under debate.

Most of the research so far has been on high grade gliomas, such as glioblastomas. This is because these high grade gliomas are often highly 'vascularised' (have many blood vessels) and bevacizumab targets new blood vessel formation.

Recurrent glioblastomas

Initial investigations with bevacizumab were on recurrent glioblastomas. These are glioblastomas (GBMs) that have returned after initial treatment. This treatment for tumours that have recurred is known as 'second-line use'.

Some studies produced promising results in shrinking these recurrent tumours. This led to accelerated approval of the drug in the USA, to be used on its own as treatment for recurrent GBM. However, in Europe it was felt there was insufficient evidence for this effect on the tumours. It was felt that the shrinking may be due to bevacizumab's effect of reducing oedema (water retention/swelling) within and around the tumour, rather than reducing the size of the tumour itself.

The reduction of oedema does have beneficial effects. Swelling in the brain can be life-threatening as it directly causes increased pressure on the brain, or blocks the flow of fluid within the brain, making the swelling worse. By relieving the increased pressure on the brain and the symptoms this causes, reduction of oedema can help you to live without your symptoms worsening (known as 'progression free survival'). It can also reduce your need for corticosteroids (given to reduce swelling) and their side-effects. (See the 'Steroids' fact sheet for more information).

However it has been found that in many patients treated with bevacizumab, when the tumour relapses it grows more quickly, with more aggression, than comparable tumours where patients did not receive bevacizumab.

The reason for this is thought to be that by cutting off or altering the blood supply and so depriving the tumour cells of nutrients, bevacizumab therapy acts like a switch and activates another substance in the body - an enzyme called 'Src kinase'. (An enzyme is a substance that causes chemical changes in other substances in the body.)

The production of Src activates proteins around the edges of the tumour. These proteins allow the tumour to move more quickly to other healthy parts of the brain in search of a new blood supply, where it continues to grow.

In this situation the glioblastoma is unlikely to respond to any further bevacizumab, chemotherapy or radiotherapy. The result is little or no difference in overall survival for patients treated with bevacizumab, compared to those who have 'standard' chemoradiotherapy. This means it does not appear to prolong life.

It is due to such lack of efficacy (effectiveness) that bevacizumab is not authorised for use in the UK (or Europe) to treat brain tumours.

Dasatinib

New research is looking at whether a drug called dasatinib (Sprycel®) could help to treat these recurrent glioblastoma that have returned again after treatment with bevacizumab.

Dasatinib is currently authorised to treat some blood cancers. It is thought to work by 'switching off' or de-activating the Src kinase, which scientists hope will make the tumour no longer able to move to other parts of the brain. Promising studies into this drug are in their early stages - in phase 2 of the clinical trial process. (See 'Clinical trials' fact sheet for information about trial stages).

It is hoped that dasatinib used together with bevacizumab will provide an effective treatment for recurrent glioblastoma, but far more research is needed before dasatinib could become authorised for this treatment.

Currently, as a brain tumour patient, you can only get dasatinib if you are eligible to enter a clinical trial investigating the drug. (For information about clinical trials, see the section 'Can I have bevacizumab?' further on in this fact sheet).

Summary

More research and more clear-cut results are needed before bevacizumab could be authorised for use with recurrent glioblastomas.

It is important to note that the Avastin (bevacizumab) website itself states:

"Currently, no data have shown whether or not Avastin improves disease-related symptoms or survival in people previously treated for GBM."

www.avastin.com/patient/gbm/benefits

Newly diagnosed glioblastomas

The initial apparent success of bevacizumab in treating recurrent glioblastomas led to researchers also looking at bevacizumab in patients newly diagnosed with glioblastomas.

The results on this 'first-line use' are starting to come in and while some have shown a positive effect on progression-free survival (no worsening of symptoms), others have shown little or no effect. There has also been no effect on overall survival.

For example, one phase 3 study looked at treatment with chemoradiation (temozolomide and radiotherapy) plus bevacizumab compared to chemoradiation and a placebo ('sugar pill'). All had undergone surgery before chemoradiation. Whilst in this study the bevacizumab group showed a 'significantly increased PFS' (progression free survival), there were more side-effects in this group. These included:

- low platelet counts (with increased risk of bleeding)
- blood clots ('deep vein thrombosis'/'pulmonary embolisms')
- high blood pressure
- greater decline in cognitive functions (concentration, memory, reasoning, thinking)

For less common, but sometimes fatal effects, see the 'side-effects' section further on in this fact sheet).

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Another multinational phase 3 trial demonstrated that bevacizumab only modestly increased progression-free survival and also did not increase overall survival for newly diagnosed patients. It also demonstrated similar side-effects.

Summary

Due to a greater increase in side-effects, disputed effects on quality of life (progression free survival) and no definite benefits of using bevacizumab earlier, the evidence currently suggests it may not be suitable for first line use in newly diagnosed patients.

In September 2014, the European Medicines Agency concluded a re-examination of Avastin® and decided not to approve its use in the treatment of adult patients with newly diagnosed glioblastoma, as any improvements shown in studies in progression free survival “could not be considered clinically relevant”. Further investigation via scientifically rigorous clinical trials is needed.

Other brain tumours

Research into whether bevacizumab is helpful in treating other brain tumours is ongoing.

Grade 2 and 3 gliomas

There is currently a UK clinical trial looking at whether the drug could be helpful in treating grade 2 and grade 3 gliomas (astrocytoma, oligodendroglioma or oligoastrocytoma) that have come back after treatment. The trial is investigating bevacizumab in combination with temozolomide chemotherapy.

Paediatric grade 3 and 4 non-brainstem gliomas

There is also a UK trial investigating the use of bevacizumab in newly diagnosed children between the ages of 6 months and 18 years, with grade 3 and 4 non-brainstem gliomas. (These are most frequently anaplastic astrocytomas and glioblastomas, but also include other tumours such as anaplastic oligodendrogliomas, anaplastic ependymomas and choroid plexus carcinomas.)

(For information about clinical trials, see the section ‘Can I have bevacizumab?’ further on in this fact sheet.)

Summary

Bevacizumab is not a cure for brain tumours. It may increase your ability to live independently in the short run (though this is under debate). There is also no evidence that the drug is able to prolong life. Finally the burden of the side-effects of this treatment may reduce your quality of life.

It is hoped that continued research will lead to the identification of biomarkers (particular genes) and patterns of genes that will identify a sub-set of patients who may benefit from anti-angiogenic agents, such as bevacizumab. *(For more information about biomarkers, please see the ‘Biomarkers’ fact sheet.)*

Future clinical trials that identify the best dose, the timing of its use, combinations with other drugs and length of treatment will also be very helpful. The effect of anti-angiogenesis on normal cells in the brain also needs to be established.

Can I have bevacizumab?

Bevacizumab is not authorised in the UK for patients with brain tumours. However, if you want to take bevacizumab and your medical team is willing, they may be able to help you to access to the drug via the following routes, once all the risks have been discussed.

Independent Funding Requests (IFRs)

An IFR is where your clinician can make a request, on your behalf, to your local health body, for treatment that is not normally available.

Your clinician will have to follow the procedures laid down by your local health body, which will differ from region to region. The application, which is often very complex, will have to include detailed medical information about you and show that there is an exceptional clinical need for the drug in your case. It will also need to show that you would benefit significantly more from the treatment than other patients not meeting the funding criteria.

It is important to note that the outcome of any application will differ from region to region and also from case to case.

Your neuro-oncologist or Clinical Nurse Specialist (or key worker) will be able to explain the local system to you.

(In some areas of the UK, these requests may be known as IPFRs (Individual Patient Funding Requests) or IPTRs (Individual Patient Treatment Requests)).

Cancer Drugs Fund (CDF)

If you live in England, you may be able to apply for bevacizumab through the Cancer Drugs Fund (CDF). These applications are known as Individual CDF Requests (ICDFRs).

This fund was set up in 2011 by the government, and is now run by NHS England. It will run until March 2016. It provides money for cancer patients living in England to have drugs that are not authorised by NICE (National Institute of Clinical Excellence) and are not available on the NHS. This could be because the drugs have not been looked at yet or because NICE believes they do not work well enough or are not cost-effective.

The CDF has a list of drugs for which it provides funding. However, for brain tumour treatment, bevacizumab is currently only on the list for use in low grade gliomas in children, with additional criteria that need to be met.

www.england.nhs.uk/wp-content/uploads/2014/03/bevaciz-gli-ch-mar14.pdf

It is possible to make applications for drugs not on the list, or to use them in different circumstances. Bevacizumab was previously on the list for recurrent/ progressive glioblastoma in adults, but has since been removed, due to the evidence for its effectiveness in these patients being “extremely limited”.

Should you decide to apply, your neuro-oncologist will need to apply to the fund on your behalf - you cannot apply directly. **Applications can only be made if your doctor feels you will benefit significantly from the treatment and all other options for accessing cancer drug funding, such as IFRs, have been explored.**

The panel, to which your specialist applies and which makes the decision, recognises that these decisions need to be made quickly. They will usually reply within 10 days.

If unsuccessful, your neuro-oncologist can appeal against funding decisions, but only if they believe that the CDF panel did not follow the right process or did not take all the available evidence into account.

It is important to note that the CDF only applies to England. The governments of Scotland, Wales and Northern Ireland

currently do not have similar schemes to the CDF. You can, however, apply to your local health body for a drug or treatment via an IFR (previously described in this fact sheet.)

Clinical Trials

Another possible way to access bevacizumab is by entering a clinical trial. Clinical trials are experimental and look at whether a new treatment is better than an existing one. Each clinical trial has a specific set of eligibility criteria, which participants must meet in order to take part in the trial.

If you are interested in finding out about bevacizumab clinical trials, please speak to your specialist about trials that may be suitable for you.

In addition, The Brain Tumour Charity has an online clinical trials database that you can use to search for clinical trials. You can find it on our website: thebraintumourcharity.org/about-brain-tumours/clinical-trials.

You can also call our Research and Clinical Trials Info Line on 01252 749 999 or email clinicaltrials@thebraintumourcharity.org (Please also see the 'Clinical trials' fact sheet for more information.)

Other options

In Europe, including the UK, there are regulations that allow patients with life-threatening illnesses to access unlicensed medicines in certain circumstances.

These include 'compassionate use' (for products that are not licensed at all) and 'off-label' access (for products that are licensed, but only for other diseases, doses, means of giving the drug, or against listed warnings).

In both cases, there must be no alternative licensed treatment available or they must have all been tried and failed. In addition, your doctor must judge it to be in your best interest based on the available evidence, as it will be your doctor who has to apply for the medicine on this basis.

Bevacizumab, therefore, might be available off-label (as it is licensed for other tumours/illnesses). This will depend not only on whether your doctor feels it would benefit you but also on the professional codes and ethics of their statutory bodies and the prescribing policies of their employers (local commissioning group).

Many doctors may also be reluctant as the responsibility for the prescribing, and any adverse effects, will lie with them. You can always speak to your doctor about this.

Some people may consider other options such as paying themselves for drugs or treatments that they can't get through the NHS or their local health organisation. In this instance it is always important to consult your doctor.

Second opinion

With all the options, it is important that you consult with your specialist. If your neuro-oncologist doesn't think you should have the drug, you may wish to ask them to outline their reasons. You are always entitled to request a second opinion from another health professional if you would like to. Either your GP or your neuro-oncologist can help to arrange this.

It can feel a bit daunting to ask for a second opinion. Please remember that, although you do not have a legal right to a second opinion, a healthcare professional will rarely refuse to refer you for one, and it will not affect your treatment. If you have any concerns or want to know how to ask for a second opinion, please talk to us via our Support & Info Line - 0800 800 0004 or support@thebraintumourcharity.org

How will I take bevacizumab?

Bevacizumab is taken 'intravenously' which means it will go directly in to your vein. You may have bevacizumab through a cannula (a small tube that goes in to a vein) or a long plastic tube that goes into the vein in your chest (central line or portacath) or arm (PICC - peripherally inserted central catheter).

You would usually have bevacizumab over a series of sessions every two to three weeks. The first session is likely to take longer (around 90 minutes) than subsequent sessions (which typically take around 30-60 minutes). This is because the drug is given more slowly the first time to keep a check on any problems or reactions you may have to the drug.

Bevacizumab may be taken alone or in combination with chemotherapy and or radiotherapy. (Some studies have shown positive results on progression free survival for combined therapy, whilst others have shown no difference. More research is needed).

What are the common side-effects?

The most common side-effects of bevacizumab include:

- Hypertension (high blood pressure)
- Fatigue
- Constipation, diarrhoea and abdominal pain
- Nosebleeds or rectal bleeding
- Dry or inflamed skin
- Back pain or headaches

The most common **serious** side-effects of bevacizumab include:

- Serious bleeding. Symptoms include vomiting or coughing up blood, bleeding in the stomach, brain or spinal cord, nosebleeds, vaginal bleeding.
- Wounds that don't heal. Bevacizumab should not be used for at least 28 days before or after surgery and until surgical wounds have fully healed.
- Gastrointestinal perforation (hole in the stomach or intestine). Symptoms include pain in your abdomen (gut), nausea, vomiting, constipation or fever.

Other serious side-effects include:

- Severe high blood pressure. Blood pressure should be monitored every 2 - 3 weeks while on bevacizumab and after stopping treatment.
- Kidney problems. Caused by too much protein in the urine.
- Infusion reactions. These include high blood pressure that may lead to stroke, serious allergic reaction, chest pain, trouble breathing, excessive sweating.
- Arterial thromboembolism (blood clots in the arteries that can lead to severe stroke or heart problems). Symptoms include chest pain, breathlessness, light-headedness, changes in your vision, difficulty speaking or moving, swelling, pain, redness, warmth in arm /leg.
- Fistula . A hole develops between two organs creating a passage between them e.g. between the trachea (the windpipe / tube to the lungs) and the oesophagus (the food pipe / tube to the stomach).
- Nervous system or vision problems. Symptoms include headache, seizure, high blood pressure, sluggishness, confusion and blindness.

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These side-effects can sometimes be fatal. Contact your health care team if you have any signs of side-effects.

The full list of side-effects should be given to you before you have the drug. You should talk through possible side-effects with a member of your health team before taking bevacizumab and ask as many questions as you would like to.

Important points to consider

Immunisations

It is important that you do not have live vaccines (which contain small amounts of live cells from a disease) for at least six months after you have bevacizumab.

In the UK, these vaccinations include:

- Measles, mumps and rubella (often given together as the MMR vaccination)
- BCG
- Yellow fever
- Shingles vaccine (Zostavax)

You can still have the flu vaccine.

We would strongly advise that you check with a member of your health team or your GP before having any vaccinations.

Pregnancy and contraception

Bevacizumab is known to increase the risk of birth defects and can lead to a miscarriage, so it is important not to become pregnant or father a child if you are having this drug. This continues to be the case for 6 months after treatment. Speak to your doctor or nurse about reliable contraception before having the treatment.

Contraception is also important to protect your partner, as it is not known whether bevacizumab is present in semen or vaginal fluids. It is safest to either avoid sex or use a barrier form of contraception for about 48 hours after having a dose of the drug.

Breast feeding

Bevacizumab may enter breast milk, so it is advised that you do not breast feed while taking this drug.

Fertility

It is possible that bevacizumab will affect a woman's ability to have children, so talk with your doctor before taking the drug if you think you may wish to have children in the future. In particular, taking bevacizumab in combination with chemotherapy can cause ovarian failure.

Effects of bevacizumab on men's fertility are not documented. If you are concerned you may wish to discuss the possibility of sperm banking with your health team.

Other medicines

Some medicines, including those that you can buy in a shop or chemist, complementary therapies, vitamins and herbal drugs, can be harmful to take when you are having bevacizumab. Tell your specialist about any medicines you are taking.

What if I have further questions?

If you require further information, any clarification of information, or wish to discuss any concerns, please contact our Support and Information Team:

Call: 0808 800 0004

(free from landlines and most mobiles:
3, O2, Orange, T-mobile, EE, Virgin and Vodafone)

Email: support@thebraintumourcharity.org

**Join our closed Facebook group:
bit.ly/supportonfacebook**

About us

The Brain Tumour Charity makes every effort to ensure that we provide accurate, up-to-date and unbiased facts about brain tumours. We hope that these will add to the medical advice you have already been given. Please do continue to talk to your health team if you are worried about any medical issues.

The Brain Tumour Charity is at the forefront of the fight to defeat brain tumours and is the only national charity making a difference every day to the lives of people with a brain tumour and their families. We fund pioneering research to increase survival, raise awareness of the symptoms and effects of brain tumours and provide support for everyone affected to improve quality of life.

We rely 100% on charitable donations to fund our vital work. If you would like to make a donation, or want to find out about other ways to support us including fundraising, leaving a gift in your will or giving in memory, please visit us at thebraintumourcharity.org, call us on 01252 749043 or email fundraising@thebraintumourcharity.org

About this fact sheet

This fact sheet has been written and edited by The Brain Tumour Charity's Support and Information Team. The accuracy of medical information has been verified by leading neuro-oncology health professionals. Our fact sheets have been produced with the assistance of patient and carer representatives and up-to-date, reliable sources of evidence. If you would like a list of references for any of the fact sheets, or would like more information about how we produce them, please contact us.

The **BRAIN** **TUMOUR** **CHARITY**

Bevacizumab (Avastin®)

Your notes



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