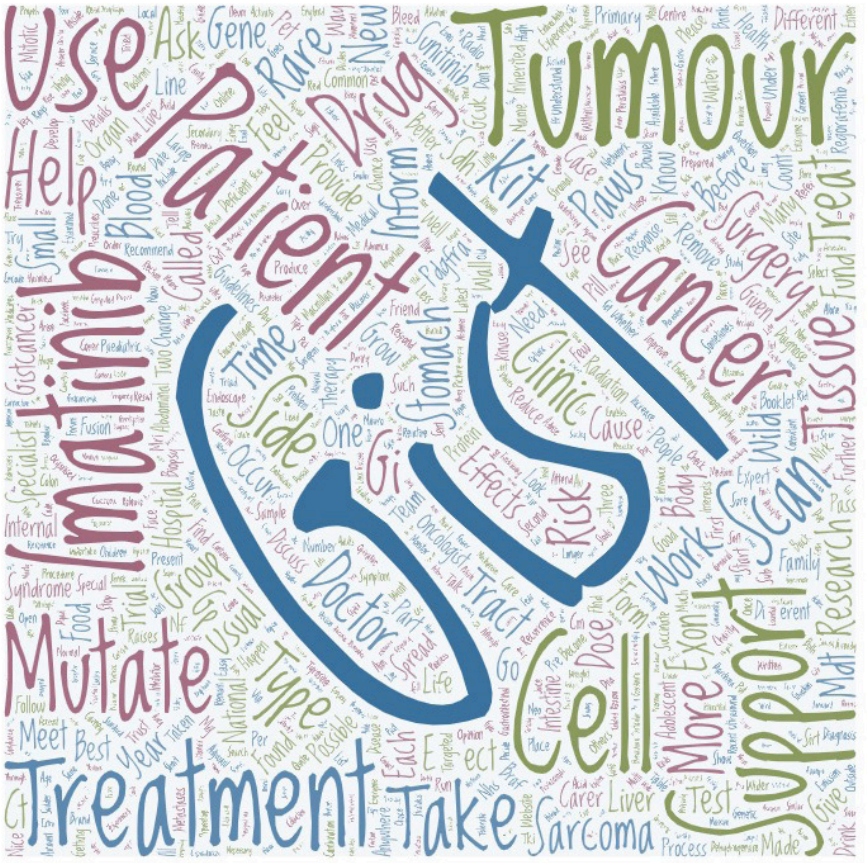
GIST for Beginners

a guide for patients by patients



gist cancer uk

GIST for Beginners

Gastrointestinal Stromal Tumour (GIST) is the name of a rare form of cancer. This booklet provides a short explanation of GIST cancer and how it is typically managed, for patients, their relatives, friends and others who may be interested.

About GIST Cancer UK (GCUK)

GIST Cancer UK is a patient support group and charity, started and run by patients and their carers. It provides information, support networks, promotes awareness of GISTs and their treatment amongst patients and medical professionals and raises funds for GIST research.

Since GISTs are rare, with about 800 new cases each year in UK, the likelihood of meeting another GIST patient by chance is small. Our online community and patient meetings provide the opportunity to share experiences.

For further details about what we do how to join the networks and for other information and support go to **www.gistcancer.org.uk**

DISCLAIMER

This booklet has been written by patients with input from healthcare practitioners. This edition has been further reviewed, revised and extended by a group of GIST patients. We have tried to ensure that the information is accessible, accurate and up-to-date but the treatment of GISTs is constantly changing and everyone's circumstances are different. **Any decisions about your treatment should be made after discussion with your consultant, preferably a GIST expert.** The booklet aims to make you better prepared to have these discussions.

Contents

Introducing GISTs

GastroIntestinal Stromal Tumour, or GIST for short, is a very rare cancer which is classified as a sarcoma (cancer of the soft/connective tissues) rather than a carcinoma (a cancer in the skin or in tissues that line or cover an internal organ). So, people who get this diagnosis not only face the shock and fear experienced by all patients who are told they have cancer, but also feel isolated, as not many people will have heard of GIST.

Over recent years massive strides have been made in the understanding and treatment of GIST, and the future for GIST patients is much brighter now than previously. This booklet will introduce you to what we currently know about the cancer and its treatment.

What is cancer?

The human body is made up of countless cells. Each cell contains information which is copied during cell division. Most organs remain healthy by getting rid of old cells that no longer work. These are replaced by new cells and this process takes place in the body all the time.

Cancer occurs when there is a breakdown in this process. If a cell grows and divides when it is not supposed to, it becomes a cancer cell and when a mass of these cells develops, a tumour forms. Some tumours are harmless because they cannot spread to other parts of the body. These are called benign tumours. However, others can spread and these are called malignant tumours.

What is a GIST cancer?

GIST was only recognised as a disease and given its name in the late 1990's, when it became possible to diagnose it reliably. In the past, GIST would often have been classified as another cancer.

GISTs arise from the precursors of the interstitial cells of Cajal which form a network of cells in the wall of the Gastro-intestinal (GI) tract and coordinate peristalsis (the movement that propels food along the GI tract). GISTs can grow from this wall into the abdominal cavity, and sometimes grow very large before causing any problems and being discovered.

Most GISTs are caused by alterations in either the KIT or the PDGFRA genes present on chromosome 4. These alterations or mutations can activate cell division. Usually, it is the KIT gene that mutates. In about 10%-15% of cases it is the PDGFRA gene that mutates. In a further 10% -15% of cases, neither of these genes has mutated and a different mechanism is responsible. These are called Wild-type GISTs (Page 4).

GISTs usually occur in people above the age of 50. They are rare under the age of 40 and very rare in adolescents and children. GISTs occurring in children, adolescents and young adults behave differently from the more common GISTs occurring in older adults. GISTs occurring in families are extremely rare and there is very little chance of passing the GIST on to your children.

We do not know why some people get a GIST. There is no obvious cause such as smoking, drinking or a particular life-style which makes people pre-disposed to getting a GIST. More research is needed to explore this although their very rarity makes study difficult.

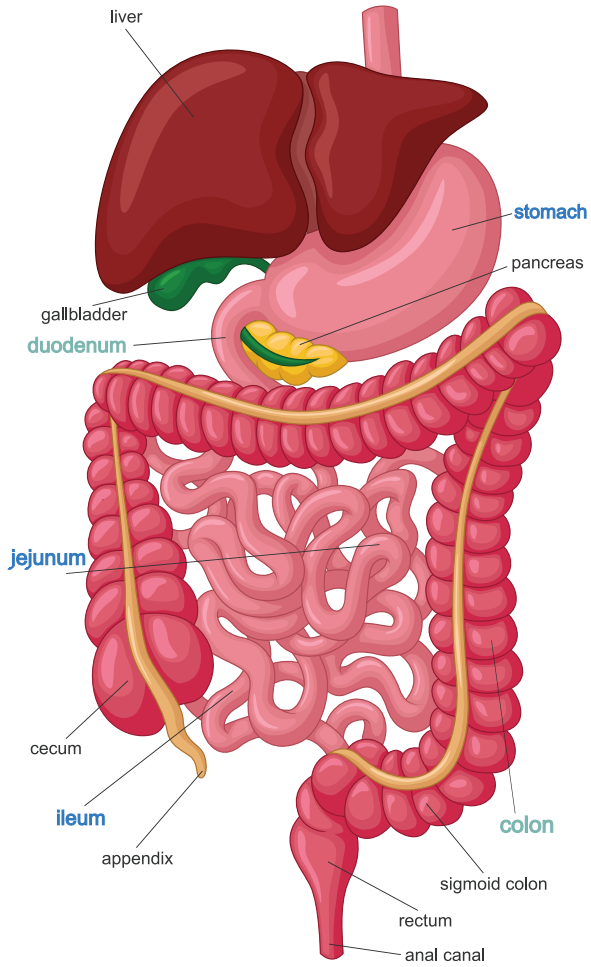
GISTs are classified as stromal tumours because the cancer starts in the stroma, which is a tissue in the walls of the stomach or intestine, rather than in the cells that line them. GISTs are most commonly found in the stomach (60-65%), in the small bowel (25-30%), in the colon and rectum (5%), and rarely in the oesophagus. Very rarely, GISTs are found outside the GI tract. These E-GISTS (Extra-gastrointestinal GISTs) usually carry mutations that are found in common GISTs and are treated in the same way.

GISTs can vary greatly in size and in the ease with which they can be treated. They may be very small, 1-2 cm in diameter, or they can be large, up to 20 cm or more in diameter. They may be easily removable or be wrapped round other organs making surgery more difficult.

If GIST cancer cells enter the blood stream this can result in new tumours forming in other organs of the body. These tumours are called metastases or secondary tumours and can develop either in the liver or elsewhere within the abdominal cavity because blood goes directly from the stomach and intestines to the liver, and cells may have escaped from the outside of the GIST and spread within the abdominal fluid. It is important that the primary GIST is found and treated early to reduce the risk of it spreading. Although large, fast-growing GISTs are the most likely to return, even small tumours may metastasize eventually.

If the tumour bleeds into the abdomen or ruptures during surgery, cells are likely to spill into the abdominal cavity giving rise to secondary tumours later. This situation is sometimes treated as if spreading has already occurred.

The Gastrointestinal Tract (GI Tract) and what happens where



Stomach

- Mixing of food
- Release of digestive enzymes
- Some mineral absorption

Duodenum

- Food sensing
- Release of hormones
- Release of digestive enzymes
- Some mineral absorption

Jejunum & Ileum

Absorption of:

- Sugars
- Fats
- Amino acids *(The building blocks of proteins)*
- Vitamins
- Minerals

Colon

Absorption of:

- Salt
- Water

Possible symptoms

GISTs often show no symptoms for a long time and the first signs are often as a result of the tumour pressing on some other organ. Sometimes the GIST may bleed into the abdominal cavity or the GI tract. This causes anaemia (iron deficiency). If the GIST is large, the doctor may be able to feel a swelling in the abdomen.

Location	Possible symptom
Oesophagus	Can cause difficulty with swallowing (dysphagia).
Stomach	Can cause pain or discomfort, indigestion, nausea, vomiting, feeling of fullness, bleeding into the GI tract causing black-coloured stools, or any combination of these.
Intestine	Can cause bleeding, constipation, diarrhoea, or just vague abdominal discomfort.

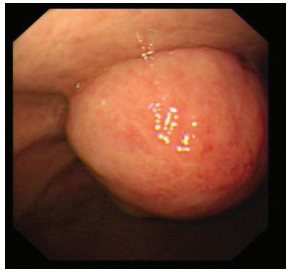
All these symptoms can be caused by other common problems. If they don't respond to simple treatment, and haven't got better on their own after some time, your GP should refer you to a gastroenterologist for investigation.

Diagnosing GIST

Tests which may be done

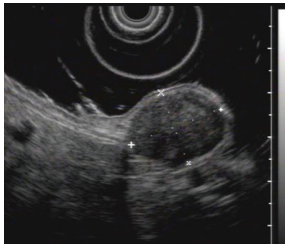
Endoscopy

In endoscopy a tube with a tiny camera is passed into the stomach. You can ask to be sedated for this procedure. During the process small pieces of the tumour tissue can be removed for examination. This is called an endoscopic biopsy and the samples can be sent to the pathology laboratory to confirm a GIST diagnosis.



Endoscopic picture of a stomach GIST

Conventional endoscopic biopsies may not pick up GIST cells which lie underneath or on the outside of the inner lining of the stomach. Endoscopic guided ultrasound (EUS) from the inside of the stomach gives a clearer picture and shows tumours both in and outside of the stomach. This enables a deeper biopsy of the tumour under ultrasound guidance.



Endoscopic Ultra-sound image of a GIST on the stomach wall

Colonoscopy

If there is fresh blood in your stools, you may need a colonoscopy. The endoscope is passed via the anus into the large bowel (rectum & colon). For GISTs in the small bowel (jejunum and ileum) biopsies using endoscopy may not be possible.

Blood tests

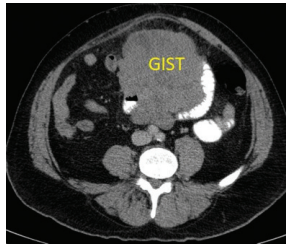
Your blood will be tested to see whether you are anaemic, and to check that your liver and kidneys are working well.

Ultrasound

This is a painless and harmless procedure using no X-rays. It is used all the time for looking at unborn babies, but it is also good for finding tumours.

CT scan (Computed Tomography)

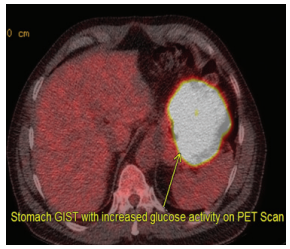
This is the most common diagnostic study. It uses X-rays to build up a three-dimensional picture of your insides. It is painless and uses a small amount of radiation. You will usually be asked to drink lots of water before the scan and be given an injection of a contrast medium during the procedure. If for some reason you cannot tolerate the contrast medium, you will be given a special liquid to drink before you have the scan.



CT scan of a GIST on the stomach wall

Positron Emission Tomography (PET)

A PET scan (Positron Emission Tomography) is rather like a CT scan but you are given an injection of special glucose containing a small amount of radioactivity. Very actively growing cells will absorb more of this glucose than other cells and are then highlighted on the scan. A PET scan is usually used either before surgery if the doctor thinks there may be more than one tumour, or to see how your tumour is responding to treatment.



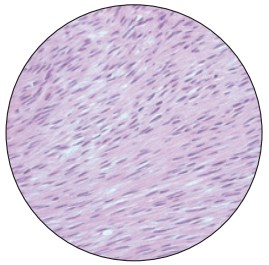
PET scan of a stomach GIST

MRI-scan (Magnetic Resonance Imaging)

This is an alternative to CT scanning that uses no radiation, is painless but noisy, and takes quite a long time. It is most useful in assessing GISTs in the rectum and for secondary liver tumours.

Histology

This means looking at the cells from your tumour under a microscope. If a biopsy is taken before you have surgery, this biopsy sample will be examined to confirm the diagnosis. If your tumour has been removed, it will then be looked at by a pathologist. The diagnosis of GIST can then be confirmed. The edges of the tissues removed will be very carefully examined to make sure that none of the tumour has been left behind.



This is what spindle cells from a stomach GIST look like under the microscope

Mitotic Count

The pathologist will also estimate the rate at which the tumour was growing. This is done by counting the number of cells which are in the process of dividing, (undergoing mitosis), in a 5-millimeter square of the tumour. This is called the mitotic count per 5mm square. GISTs with a higher mitotic count tend to have a more aggressive behaviour. However, this does not apply to the wild-type GISTs.

GISTs and Risk

The risk of a GIST coming back after surgery depends mainly on three things:

- How big the tumour was
- What the mitotic count was
- Where the tumour was

The relative risks of recurrence for non PAWS-GIST patients are set out in the following table.

Risk	Size (cms)	Mitotic count per 50 HPFs	Tumour site
Very low	<2	<5	Anywhere
Low	2.1 – 5.0	<5	Anywhere
Intermediate risk	<5	6 – 10	Anywhere
	5 - 10	<5	Anywhere
High Risk	Any	Any	Tumour rupture
	>10	Any	Anywhere
	Any	>10	Anywhere
	5.0	>5	Anywhere
	<5.0	>5	Non-gastric
	5.1 - 10	<5	Non-gastric

Risk table as recommended by a group of UK GIST experts, adapted from a table produced by H Joensuu in 2008.

Mutations and GIST-types

We strongly recommend that all patients with GISTs, except those with very small stomach GISTs, should ask to have mutational testing performed. Mutational analysis is probably a key predictor for the course of the disease and will determine treatment options after the primary GIST has been removed or a biopsy has been taken.

It is particularly important in the case of tumours with a high risk of recurrence and is essential before considering adjuvant (preventive) treatment with imatinib after surgery and if the GIST has spread to other parts of the body. It will also tell doctors whether newer drugs are likely to be more beneficial, for example, PDGFRA D842V mutant GISTs do not respond to imatinib.

Most GISTs have mutations in either the KIT or PDGFRA genes in parts called 'exons' (similar to a compartment in a train) which are pieces of DNA that encode proteins.

KIT mutations

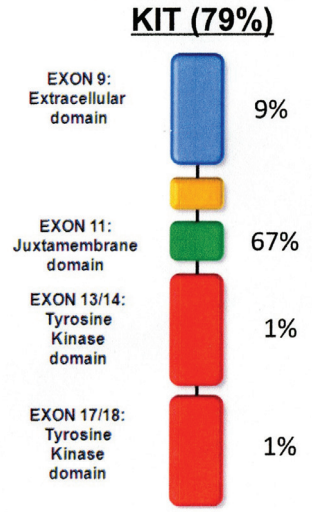
KIT mutations occur in about 80% of GISTs:

Exon 9: (9%) mostly in the small intestine

Exon 11: (67%) which can occur anywhere in the GI tract

Exon 13: (1%)

Exon 17: (1%)



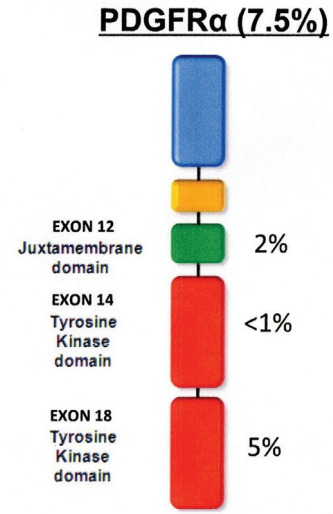
PDGFRA

PDGFRA mutations occur in about 7.5% of GISTs and are almost exclusively found in the stomach:

Exon 12: (2%)

Exon 14: (<1%)

Exon 18: (5%)



Inherited KIT mutated GISTs

These are inherited forms of GIST where KIT mutations are present in every cell of the body and are inherited. These are extremely rare and only a small number of families have been identified worldwide.

BRAF Mutated & NTRK fusion

There are some extremely rare GIST sub-types that can be found using the latest genomic sequencing techniques. These include BRAF mutated GIST (<1%) and NTRK fusion GIST (0.5%). There are targeted therapies available for these rare sub-types of GIST.

PAWS-GIST (Paediatric, Adolescent, Wild-type, Syndromic)

PAWS-GIST is the collective name given to different sub-groups of GISTs which do not have the KIT and PDGFRA mutations. This occurs in 10-15% of GISTs and some of these types can be associated with certain syndromes.

Succinate Dehydrogenase (SDH) Deficient Gist

The largest group of PAWS GISTs are related to a deficiency of the Krebs' Cycle enzyme, SDH (succinate dehydrogenase). These are caused either by a mutation in the SDH gene, or by the silencing of this gene by other mechanisms.

Carney's Triad Syndrome

This is a combination of SDH deficient GIST and two other types of tumour, lung chondroma and paraganglioma. GISTs in this syndrome are due to mutations in the SDH gene and are not due to an inherited mutation in the germline (cells that pass on their genetic material to the offspring).

Quadruple Wild-type GIST

Quadruple Wild-type GISTs have no mutations in the four genes KIT, PDGFRA, SDH or BRAF. At present we do not know much about these GISTs and more research is needed.

Carney-Stratakis Dyad Syndrome

A rare and distinct combination of inherited familial paraganglioma tumours and GIST. This is associated with germline mutations in the succinate dehydrogenase genes SDHB, SDHC, and SDHD.

Neuro-fibromatosis-1 (NF1) and GISTs

NF1 is a rare genetic condition characterized by multiple neuro-fibromas, (tumours formed on nerve cell sheaths) and café au lait pigmentation. Some NF1 patients develop GISTs, most commonly in the small bowel and less frequently in the stomach and large bowel.

Treatment

What are the treatment options?

Guidelines produced by the NHS say that all sarcoma patients, including GIST patients, should have a multi-disciplinary team (MDT) of expert doctors and other health professionals to treat them. Sarcomas are rare, so there are relatively few doctors who specialise in treating them. There are a number of hospitals in the UK which have a specialist GIST MDT and these change from time to time as specialists move and priorities alter. Some smaller hospitals have links with MDTs in larger hospitals to support their care of GIST patients. If your GIST is small, and easy to remove, you may get perfectly good care in a less-specialist hospital, but if things are more complicated, it is certainly best to be in the hands of a team that treats many GIST patients. For the latest list of approved centres see the GIST Cancer UK web site.

The MDT will meet and discuss your case and decide on the best way forward for you. The MDT normally consists of:

- A specialist surgeon (with experience of GIST surgery)
- A gastroenterologist (a specialist in the GI tract)
- A GIST oncologist (a doctor who specializes in diagnosing and treating GIST cancer)
- A pathologist (a doctor who specializes in examining tissue samples to make a diagnosis)
- A radiologist (a doctor who specializes in diagnosing and identifying cancers using imaging techniques)
- A Clinical Nurse Specialist (a CNS)

Second opinions

It is really important that a relationship of trust is established between you and your doctors and if for any reason you would like reassurance from another source about a proposed course of action you can ask for a second opinion to help clarify your position.

This is particularly important if you are facing major surgery. Your GP can arrange a second opinion with a GIST specialist who may be found at one of the hospitals designated as an extension to a Sarcoma Centre MDT, or at one of the designated Sarcoma centers listed on the National Sarcoma Service specification.

Guidelines for treating GISTs

Teams of doctors have prepared guidelines for the best way of treating GISTs. They have looked at all the known evidence from clinical trials. For example, there are the European Society for Medical Oncology (ESMO) guidelines, which are brought up to date as new evidence becomes available.

There are also guidelines for use in the UK called The National GIST Guidelines which forms part of the National Sarcoma Service Specification and takes into account the UK health system and the treatments permitted by NICE. These are up-dated regularly, and the latest version can be accessed via the GIST Cancer UK website.

These Guidelines also recommend the best follow-up regime for patients with different risks of recurrence. They are referenced in the NHS England National Sarcoma Service Specification.

Sometimes, there is no clear answer about how you should be treated in a particular situation. The way forward should then be a matter for you and your close family to discuss with the oncologist and surgeon looking after you.

Surgery

If there is one GIST and it is easy to remove, surgery and the removal (resection) of the primary tumour is usually the best choice. The surgeon may use key-hole surgery or open surgery. This depends on the size and position of the GIST, and whether you have had any previous abdominal operations. Open surgery will lead to a longer recovery time but may be necessary to remove all of the tumour(s).

The most common type of GIST has an Exon 11 mutation. If you have any other type of GIST, please tell your surgeon if you wish to consent for your tissue samples to be sent to the National GIST Biobank at the Royal Marsden hospital in London (we already have sufficient Exon 11 samples). The Biobank provides important samples for researchers exploring GISTs and their treatment. The consent is separate from the standard consent that you will be asked to sign at your hospital. Collection must be organised and agreed with the National GIST Biobank well in advance of your surgery in order to make the necessary arrangements for transport and storage. Further details of how to arrange this and what is involved can be found on the GIST Cancer UK website.

PAWS-GIST Clinics

PAWS-GIST clinics provide specialist support and advice for Paediatric, Adolescent, Wild-type & Syndromic (PAWS) GIST patients in the UK. The clinic is the second of its type in the world, the first being at the National Institutes of Health in the USA. It takes place at Addenbrookes Hospital in Cambridge two or three times each year. Each clinic brings together up to 10 patients who meet with GIST specialists from a variety of disciplines. The clinic reviews each patient's:

- medical history
- previous treatment and response to treatment
- scans
- tumour histopathology results (where it exists)
- genetic/molecular analyses

The clinic may undertake further tests, where appropriate, to understand each patient's unique situation and will make recommendations for treatment specifically tailored to each patient's needs.

Attending the clinic allows patients and their families to meet others living with this ultra rare cancer which in itself is an invaluable experience and collectively generates a wealth of information that is assisting the PAWS-GIST multi-disciplinary team to discover the underlying mechanisms behind paediatric, adolescent, wild-type and syndromic GIST.

If you have been diagnosed with one of the GISTs in the PAWS GIST group, we strongly recommend that you attend one of these clinics. You can do this by going to **www.pawsclinic.org.uk**

Patients and their carers are offered help with transport and accommodation costs to attend the clinic by GIST Cancer UK.

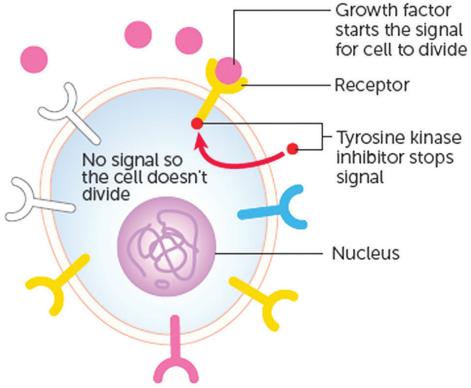
How targeted drugs work

The first, second and third line targeted drugs available in the UK are imatinib, sunitinib and regorafenib whilst clinical trials are being performed across the world investigating other new targeted drugs and combinations. Tumours form when a cell starts to grow in an uncontrolled way. It does this because there has been a change in the genes in the cell. We do not know why this happens in GISTs. The genetic change means that the very complex system, which should tell the cell when to grow and when not to grow, stops working. The cell just goes on dividing, and a tumour grows.

What the targeted drugs do is block one of the essential steps in the growth-signalling system in these particular cancer cells involving the

enzyme Tyrosine Kinase. Hence their name Tyrosine Kinase Inhibitors or TKIs. They do this without affecting the normal cells of the body. Imatinib was the first targeted drug used to successfully treat GIST, and it is still the first choice because it is usually easy for patients to take and gives fewer side-effects.

At the moment we don't have a specific treatment to deal with the loss of the enzyme succinate dehydrogenase, which is found in a large proportion of Wild-type GIST's, although this does result in some responsiveness to sunitinib and regorafenib, both of which inhibit the blood vessel growth (angiogenesis) pathway.



Unfortunately, we now know that GIST cells quite often mutate again and find a way round the block in the signalling pathway. This means that the tumour can start to grow again. In some patients this happens in a few months, but we know of others who have been taking imatinib for 10 + years, and for whom it is still working. Why there is this difference is as yet unknown as is why there is a small percentage of patients who do not respond to imatinib at all. Wild-type and paediatric GISTs respond less well than other GISTs to imatinib, but there is much more we need to know about this. Research in these areas continues.

Drug treatment

Imatinib

The drug imatinib was first made by Novartis, under the name Glivec (UK) or Gleevec (US). It is now out of patent and is made by about five different companies and sold under different names such as Accord, Amarox, Sandoz and Teva.

Imatinib does not have the same side-effects as the chemotherapy used for many other cancers. Imatinib is one of a group of drugs called a Tyrosine Kinase Inhibitor (TKI) which is a targeted therapy acting mainly on the GIST and taken daily as a pill.

While you are taking imatinib you should have regular blood tests to make sure that you are not anaemic and that your liver and kidneys are working well. Typically you will have regular CT or MRI scans to monitor its effectiveness.

There are some drugs which interact with imatinib and should not be taken. Always inform your doctor or oncologist if you are taking any other medication.

Note: Grapefruit juice in combination with imatinib, sunitinib and regorafenib, is strongly discouraged as grapefruit will interfere with the way the liver eliminates the drugs from the body, leading to much more severe side-effects. There are other side-effects that may show up when you have your blood tests at your hospital checks, and the hospital doctors will advise you about these.

Treatment with imatinib before surgery

If your GIST is big, or if other organs would be damaged by removing it, the MDT may want to treat you with the drug imatinib before you have surgery to shrink the tumour. This is called Neo-adjuvant or pre-operative imatinib treatment. Your doctors will first need to check that your GIST has a mutation which will respond to imatinib. If it will, then

the imatinib is given to shrink the GIST and make the operation easier and less damaging. When the GIST stops getting smaller, usually after about 6 months, the MDT will consider surgery again.

Treatment with imatinib following surgery

Imatinib after surgery has been licensed and approved by NICE (The National Institute for Health and Care Excellence) for those GIST patients who have had their primary GIST resected and who are at significant risk of the tumour recurring. A Scandinavian/German research study has shown that taking imatinib for three years after surgery decreases the risk of the tumour coming back (recurrence) and also improves overall survival. This process is called adjuvant imatinib.

Presently three years of adjuvant imatinib is the standard length of provision in the UK for patients at high risk of recurrence with an imatinib sensitive mutation. There are currently research trials investigating if 5 years of imatinib treatment improves the situation further.

Side-effects of targeted drugs

If you read the leaflet which is enclosed with the pills of imatinib, sunitinib or regorafenib, you could start feeling ill - before you have even taken a single pill! However, remember that the company which makes the pills has to mention every side-effect known and most of them are very rare. Some are fairly common, but most of these, at least for imatinib, are quite easy to cope with for most people (see table on page 26) although everyone's response is different.

With all these drugs, some patients have virtually no side effects, and many people find that the side-effects they have at first, become less of a problem after time. Targeted drugs act mainly on the GIST cells, so they cause far fewer side-effects than the usual drugs used to treat other cancers. Targeted drugs are taken as a pill. You should always discuss any side-effects that you are experiencing, with your consultant.

Occasionally it is necessary to decrease the dose to reduce the side effects, but problems like diarrhoea and nausea can be reduced by giving drugs such as loperamide and metoclopramide. Imatinib is taken with food, usually with the main meal of the day and with plenty of water although some people find that taking it last thing at night (so that side-effects occur whilst sleeping) or first thing in the morning (when it's more easily remembered) works best for them.

Patients have found that different brands of imatinib seem to have different side-effects. It is not known why this is since the basic drug in each is the same and quality controlled. If the side-effects of your version are really troublesome, do ask your oncologist to insist that the pharmacy prescribes a different brand.

Sunitinib and regorafenib can produce more serious side-effects than imatinib, such as worse fatigue, hoarse voice, severe diarrhoea, high blood pressure and hand/foot syndrome in some patients.

For more details on side-effects see the MacMillan cancer support website **www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs** and search for the drug you have been prescribed.

Tips from Patients Taking Imatinib

Common side-effects of imatinib	Patients' suggestions for dealing with them
Puffy eyelids	Diuretic tablets. Better not to drink alcohol or coffee.
Swollen ankles	Put your feet up when you can.
Indigestion or feeling sick	Take your pills with a main meal and with a large glass of water. Try eating a little food. Try peppermints, or if they don't work try Gaviscon. Take the pills just before bed so you sleep through the side-effects.
Being sick	Ask your GP for help. There are various medicines which can help.
Diarrhoea or abdominal pain	Ask Your GP for help.
Rash	Ask Your GP for help.
Cramp, particularly at night	Make sure your blood chemistry is fine. If it is, some patients find that quinine helps. Tonic water contains small amounts of quinine, but if this is not enough, ask your GP.
Tiredness	Get your blood chemistry checked and try to get more rest and drink water to increase hydration

If you can't maintain a healthy weight, do ask your GP or oncologist to refer you to a consultant nutritionist who will help you to stabilize your weight.

Taking targeted medicines may cause a temporary loss of taste. Food and drink may suddenly taste different. This does usually get better in time. In the meantime, try to keep up a healthy weight by eating all kinds of good food.

There are a few very rare and possibly serious side-effects. These include, chest pain, sudden bleeding in the stomach or intestine producing black or red stools, sudden high fever or very sore throat, rapid swelling and weight gain, and sudden shortness of breath. If you have any of these, go to your nearest A&E department, and make sure the doctors there know that you are a GIST patient and taking imatinib, sunitinib or regorafenib.

If you are one of the very few unlucky people for whom the side-effects become intolerable, and you and your oncologist have tried changing the brand of drug you are taking and still nothing seems to help, it may be possible to lower the dose. This is something you must talk to your GIST specialist about. (We do know of a patient who remained stable on only 100mg imatinib per day.) It is your life, and only you can decide when something is too bad to live with.

What happens if imatinib does not work or stops working?

Some types of GIST are resistant to imatinib and unfortunately, we now know that GIST cells can quite often mutate again, and find a way round the block in the signaling pathway. This means that the tumour can start to grow again. In some patients this happens in a few months, but we also know of some who have been taking imatinib for over 10 years, and it is still working. The average time to progression is two to three years. Why there is this difference is a question we cannot yet answer.

Change to sunitinib (Sutent)

The drug usually prescribed after imatinib, is sunitinib (sutent), which is referred to as a second line drug treatment. This drug binds differently to the KIT or PDGRA protein, sometimes overcoming resistance to imatinib. It also helps to stop new blood vessels from growing. This may help to make it work on the GIST.

Before you start sunitinib, you will be given an information booklet on how to take the tablets, and how to monitor and manage the side effects. Please do not hesitate to phone your nurse specialist if the side effects become troublesome. If the standard dose and schedule of sunitinib do not suit you, it may be possible to reduce the dose, or change the schedule so that you can tolerate it better and stay on the drug for longer without compromising your quality of life.

Sunitinib can also affect your heart. Your oncologist will advise on regular monitoring of your heart with special scans.

Increase the dose of imatinib to 800 mgs a day

If you know you have an exon 9 mutation, this would probably be the best course to take, since it has been proved to work better than 400 mg for exon 9 mutant GISTs. The double dose of imatinib usually has fewer side-effects than sunitinib.

Change to regorafenib (Stivarga)

Regorafenib is approved for patients whose tumours no longer respond to imatinib or sunitinib. The side effects of regorafenib are usually similar to those of sunitinib, and the dose and schedule should be tailored to how well you tolerate the drug. It is the third line treatment for GIST in England, Scotland & Wales. If you live in Northern Ireland your doctor can apply to your local Health and Social Care (HSC) trusts through the Individual Funding Requests (IFR) process.

Have more surgery

This needs to be discussed and agreed with your GIST MDT. It may not be appropriate for every patient.

Enter a clinical trial

Sometimes new drugs become available as part of a clinical trial. Trials are generally run at specialist GIST centres rather than at local hospitals (search for clinical trials on the GIST cancer website).

Please ask your oncologist about whether you might be eligible for one. Trials have strict entry criteria which depend on what treatments you have already had, and often on the mutation of your GIST.

Radio Frequency Ablation

With this treatment, the tumour is destroyed by focused microwaves. This may be appropriate for a limited number of tumours in the liver.

Radiotherapy

It had been thought that radiotherapy does not work on GISTs. However, it has been found to be quite successful in shrinking some tumours. More work needs to be done to see how radiation can best be used for GIST patients.

The Cyberknife can irradiate the tumour from many directions by highly focused X-rays. Currently there are very few Cyberknife installations in the world, and the treatment is still experimental.

Embolisation

This technique chokes off the blood supply to the tumour, so that the tumour dies. This is only used for liver tumours, in suitable places.

SIRT (Selective Internal Radio Therapy)

Selective Internal Radiation Therapy (SIRT) or radio-embolisation is a form of radiotherapy that has been developed for the treatment of unresectable primary and secondary liver cancers. SIRT has been used to treat SDH deficient liver tumours on some patients who have attended the PAWS-GIST clinic and is showing early potential as an effective treatment.

Larotrectinib and Entrectinib

For Rare NTRK fusion GISTs, Larotrectinib and Entrectinib are two drugs that have been approved for use in England, Wales & Scotland.

Sterotactic Radiation

Recent reports suggest that stereotactic body radiation therapy (SBRT) can be used to deliver doses of radiation therapy while minimizing the dose to surrounding organs at risk and, therefore, may improve responses of GISTs to radiation therapy.

Advanced Disease (where the GIST has spread to other organs)

If the disease has spread, either to the liver or to other places within the abdomen, then initial treatment is imatinib and research studies are investigating other therapies.

Life with GIST

Preparing for treatment

Make a list of all the medications you use both from the chemist and from the supermarket or other store whether this is regularly or once in a while. Talk with your oncologist and/or your family doctor about these and they should identify any that might conflict with your treatment.

Make written notes of all the questions you want to ask. It is very easy to forget something until you are on the way home. The time with your consultant goes very quickly, but he or she will be happy to answer all your questions. It's a very good idea to take a family member or a friend with you. They will often remember things from the discussion that you don't.

Questions you might like to ask your surgeon or oncologist:

- Where is the primary tumour?
- Are there any metastases (secondary tumours)?
- Do you know the mutation (Kit exon, PDGFRA exon, Wild-type?) If not, please can I have mutational analysis done?
- What experience do you have of treating GISTs?
- What treatments are you proposing?
- What are the possible side-effects and risks?
- What is the chance that the tumour will come back?
- If treatment isn't working, can I participate in a trial, or are there any new approaches to treatment available?
- If you are preparing for or have had surgery for a non-exon 11 GIST: then discuss the possibility of having your tissue stored in the National GIST Biobank.

Compliance

If you've been prescribed drugs then do ensure you take them. If you don't, then the tumour cells have a chance to start growing again. If you happen to miss a dose or two, do tell your oncologist. Your care is a joint venture and you do need to have an oncologist you trust, and who trusts you; he or she can only do their best for you if you are honest with them.

Getting wider support

Hearing the news that you have a rare cancer, and having to face up to all the treatments and hospital appointments, can put a huge strain on the life of a GIST patient. Feelings of panic and fear are almost inevitable. Your family and friends will be scared too. There may well be times when you feel depressed, and this is very understandable. Since it often takes years before a GIST is finally discovered, you may have experienced a long period of unexplained symptoms and the lonely feeling of not being understood. Talking about your feelings helps. You may find it helpful to tell your story to the hospital oncology nurse, who may refer you to a specialist for counselling, or you can go to your GP and ask for support. In any case, do not keep these feelings to yourself, but get help somehow.

GIST Cancer UK has an online forum supporting a community of GIST patients from all over the UK and further afield. GIST patients and their relatives and carers who sign into this group, often find other patients who live near to them and form useful friendships. Some meet up regularly for coffee etc. You may want to contribute with your story, or to ask questions about other patients' experiences or your own treatment. How you use the group is up to you. Many patients get huge support from this new group of friends, who really do understand what you are talking about.

There are other more general cancer support groups available locally. Some towns have Sarcoma groups, and GIST is a sarcoma, so these groups would be open to you. There may be Macmillan cancer support facilities near you, or a Maggie's Centre. These provide general information about living with cancer, eating well, and offer complementary therapies which may make you feel better and can also help with financial advice. They also make a good cup of tea and provide understanding friendship.

GIST is rare, so you are very unlikely to find another patient by chance. You can find out more about GISTs and the latest news by going to our website **www.gistcancer.org.uk** or if you are a PAWS-GIST patient to **www.pawsgistclinic.org.uk**.

Better still, register with us. Once registered you will be invited to the regular patient support meetings and be invited to join GIST Cancer UK's private online patient forum.

GIST Cancer UK

About GCUK

GIST Cancer UK has been a registered charity since 2009 (originally called GIST Support UK), and is run by a team of volunteer trustees, most of whom are GIST patients or their carers. Our primary aims are to offer support and information to patients and their carers, and to foster research to improve patient outcomes.

We have a Medical Advisory Board of expert doctors, who advise the Trustees on medical or research issues.

We provide:

- **web sites**: **www.gistcancer.org.uk** and **www.pawsgistclinic.org.uk**
- **a telephone help line** 0300 4000000
- **a private Email forum**, for GIST patients and carers
- **2 or 3 UK patient and carer conferences each year**, where you can meet others and hear about the latest research and developments from GIST specialists
- **2 or 3 PAWS-GIST clinics a year** where PAWS-GIST patients and their carers meet with world-class experts
- **A dedicated YouTube channel** with a range of videos on GISTs and their treatment from clinicians and patients see https://www.youtube.com/@gistcanceruk4310
- **Facebook, Twitter (X) & Instagram communities** giving you the most up to date information on GIST cancer developments and what GIST Cancer UK is doing to improve services for GIST patients.

We can give you:

More copies of, "GIST for Beginners", for you and your family, and your GP. This booklet is also for hospitals to give to newly diagnosed patients.

"Eating after GI Surgery for GIST", includes hints to help you get back to normal.

"No Stomach?" Help and tips for patients after removal of the stomach.

GIST Cancer UK badges and wrist bands so that patients can recognize each other (eg at a hospital clinic).

Information and help with sending GIST tissue samples to the National GIST BioBank – if you are about to have surgery, please let us know.

We also:

- Represent GIST patients' interests at NICE appraisals of new drugs and other treatments.
- Represent GIST patients' interests, nationally and internationally.
- Work to support a research environment which can find new treatments and a cure for GIST.
- Lobby for the rights of GIST patients.
- Work with the pharmaceutical industry to support research and provide good patient information about their drugs.

Funding and fundraising

GCUK are very grateful to receive grants from pharmaceutical companies to help fund our patient meetings and produce information and materials to help patients.

Fund-raising by our supporters is a vital element for the future of our charity to help us continue the work that we undertake on behalf of GIST patients. As we are all volunteers and have no paid staff, every penny raised is used to support patients and further our aim of improving treatments and finding a cure for GIST. Fund-raising has enabled us to fund vital new GIST research projects.

We are very grateful to everyone who organises and participates in fundraising events. We have T-shirts, banners and other items you can use. More information and fundraising packs can be obtained by going to our web site.

How to Give

Cheques made out to GIST Cancer UK, can be sent to our Treasurer. Please contact him via: treasurer@gistcancer.org.uk

Set up a standing order to Account no: 00078670 Sort code: 40-41-57

Donate online using Just Giving

Sign up with the Charities Trust:

www.charitiestrust.org.uk and select GIST Cancer UK as your charity of choice.

If you are a tax payer please complete a gift-aid form, which can be found on our website, and post it to our treasurer above.

Or go to **www.gistcancer.org.uk** and follow the links for donations.

Other useful organisations

UK Clinical Trials The NHS site giving details of UK trials **https://www.nhs.uk/conditions/clinical-trials/**

Sarcoma UK An organisation dedicated to support and research on all kinds of sarcoma **www.sarcoma-uk.org**

Macmillan Cancer Support Macmillan has many leaflets on all aspects of cancer including information on statutory UK benefits **www.macmillan.org.uk**

Pediatric & Wild-type GIST Clinic USA **www.pediatricgist.org**

Maggie's Centres These provide emotional and practical support for all cancer patients **www.maggiescentres.org**

GIST Support International An independent international US-based patient group. **www.gistsupport.org**

SPAGN Sarcoma Patients Global Network A European organization of doctors and patients for support and advocacy of sarcoma patients and their carers. GCUK is a member. **www.sarcoma-patients.eu/index.php**

Life Raft Group U.S.A. A US patient group **www.liferaftgroup.org** dedicated to making a difference in the lives of GIST patients.

Social Media:

Twitter/X: @gistcanceruk
Facebook: @gistcanceruk
Instagram: @gistcanceruk

Twitter/X:@pawsgist
Facebook: @pawsgist
Instagram: @UKgisters

Glossary

Adjuvant	Preventive treatment
Anaemia	A blood disorder in which the blood has a reduced ability to carry oxygen due to a lower than normal number of red blood cells
Benign	A tumour that grows slowly and usually doesn't spread to other parts of the body
BRAF	BRAF is a human gene that encodes a protein called B-Raf
Cajal	A network of cells in the wall of the GI tract coordinate peristalsis
Carcinoma	Cancer in the skin or in tissues that line or cover an internal organ
Computerised Tomography (CT)	A scan that uses X-rays and a computer to create detailed images of the inside of the body
Endoscopy	A test in which a thin tube with a small camera inside, called an endoscope, is passed into your body through a natural opening such as your mouth
Exon	Pieces of coding DNA that encode proteins.
GIST	Gastro-Intestinal Stromal Tumour
KIT gene	Provides instructions for making receptor tyrosine kinases which transmit signals from the cell surface into the cell
Malignant	A tumour that may grow rapidly and spread to other parts of the body
Multi-disciplinary Team (MDT)	Responsible for monitoring your health and treatment plan
Metastases	Secondary tumours arising away from the main tumour
Mutation analysis	The search for mutations in your genomic DNA
Neo-adjuvant	Pre-operative treatment given with the goal of making the main treatment more likely to be successful.
NICE:	National Institute for Health and Clinical Excellence - the government body responsible for deciding which treatments can be paid for by the NHS in England, Wales and Northern Ireland.
NTRK fusion	Clinically actionable tyrosine kinase inhibitors
PAWS GIST	Paediatric, Adolescent, Wild-type, Syndromic GIST
PDGFRA gene	Provides instructions for making a protein called Platelet-Derived Growth Factor Receptor Alpha (PDGFRA)
Peristalsis	The movement that propels food along the GI tract
PET	Positron Emission Tomography
Sarcoma	Cancer of the soft/connective tissues
Stroma	Tissue in the walls of the stomach or intestine,
Succinate dehydrogenase (SDH)	A mitochondrial enzyme which participates in both the citric acid cycle, where it oxidases succinate to fumarate, and the electron transport chain, where it reduces ubiquinone.
Tyrosine Kinase Inhibitor (TKI)	A drug that inhibits tyrosine kinases - enzymes responsible for the activation of many proteins

www.gistcancer.org.uk

Published by GIST Cancer UK
Spring 2024
Charity No: 1129219