Introducing GIST and Sarcoma Specialist Dr Richard Quek

Dr Richard Quek says he has "the best job in the world".

The Singapore based specialist in both GIST and sarcoma cancers believes it is a great privilege to care for patients during what is often a difficult cancer journey. "I enjoy the deep interactions I have with my patients and I am honored that they come to me and entrust me with their treatment, health and life," he reflects.

As STA prepares to launch a new GIST therapy in South East Asia, Dr Quek generously shared his insights about the disease, which "most people have never heard of" before they are diagnosed. "Patients should ultimately know there are good treatments available for GIST, even for those patients whose disease has spread," Dr Quek said. "The median survival rate is now more than five years and we have several lines of therapy for patients – so when one drug becomes ineffective, there are other options we can turn to. Patients who are diagnosed with GIST should have hope."

Firstly, what is a GIST tumour and who do these tumours affect?

A gastrointestinal stromal tumor – or GIST – is the most common type of soft tissue tumor in the gastrointestinal (GI) tract. GIST is thought to arise from the Interstitial Cells of Cajal (ICC), which are the pacemaker cells of the GI tract.
Within the GI tract, the stomach is the most common primary location for a GIST, followed by the small bowels. GIST is also known to arise in the rectum.
GIST tends to affect adults, and typically, people are diagnosed in their sixties. There are however, some rare and specific forms of GIST that affect young children. A proportion of these are familiar in nature (i.e. heritable diseases).

1. What makes a GIST tumour different to other cancers?

GIST differs from other cancers in several aspects. GIST arises from the mesenchymal layer (connective tissue) of the human body while most other solid tumors arise in the epithelial layer (which lines the internal organs). As such, GIST is usually grouped under the umbrella of sarcoma instead of carcinoma.

GIST is molecularly heterogeneous. Most GISTs are driven by a mutation in either the KIT or PDGFRA gene, resulting in uncontrolled cell growth and metastasis (spread). While the minority of GIST are driven by a whole host of other genes, including NTRK, SDH, BRAF, NF1 etc. In some cases, we do not detect any driver mutations, we call them wild type GIST. But wild type GIST represents fewer than 10% of all GIST cases. Very rarely, GIST can affect young children and in the pediatric population, two cohorts exist. The first is familial GIST where there is a mutation in the blood line and the driver mutation is heritable. Some of these heritable genetic mutations include NF1 and KIT. Other cases of paediatric GISTs involve non-blood line mutations in SDH genes.

2. How common is the incidence of GIST in South East Asia and particularly, in Singapore?

GIST is a rare tumor and most patients have not heard of GIST prior to their own diagnosis. While we do not have exact incidence figures of GIST in Singapore and South East Asia, the incidence is believed to be similar to that in the west, which is approximately 15 cases per million population per year. However, autopsy data of incidentally detected GIST suggest the incidence of GIST to be higher than previously estimated.

3. What are the early symptoms of these tumours?

Symptoms are variable. Some patients may have an asymptomatic lesion that is found by chance, while others might present with massive lesions that are causing significant symptoms.

Symptoms also depend on where in the GI tract the tumor arises from and/or where it has spread to.

Common symptoms include:

- Abdominal bloating,
- Early satiety (feeling full easily after a small meal)
- Symptoms of anemia (low red blood cell count)
- Pain (in cases of tumor perforation)
- Rectal symptoms including feeling of incomplete bowel evacuation, blood in stools
- Urinary symptoms (when the rectal GIST irritates the urinary passage). Symptoms resemble those of an enlarged prostate and include urinary frequency, poor urinary flow, or a sense of incomplete urination

4. What are the next treatment paradigms for GIST?

Treatment of GIST involves a multi-disciplinary approach.

In cases of localised disease, where the disease has not yet spread, treatment will involve surgery with or without adjuvant (preventive) systemic treatment. If the tumor is easily resectable, surgery is advised. Patients are then risk stratified based on tumor size, site, mitosis per 50 high-power field (HPF) and presence/absence of tumor rupture. Patients with low and very low risk GIST are best observed post-surgery. Patients with high-risk GIST are advised to commence on extended adjuvant systemic therapy with imatinib. Currently, the duration of extended adjuvant imatinib is three years. For patients with intermediate risk GIST, the data is less clear and the clinical situation calls for shared decision making with the patient.

In cases of localised GIST where surgery is potentially morbid e.g. rectal GIST involving an abdomino-perineal resection and permanent colostomy, one can consider pre-operative systemic therapy to downsize the tumor prior to surgery.

In cases of metastatic GIST, treatment is palliative. Having said that, the field has made many significant advances since the early 2000s. We now have four lines of approved tyrosine kinase inhibitors (TKIs) for use in advanced GIST including imatinib, sunitinib, regorafenib and now, ripretinib.

Notably, the response to each type of drug also depends on the molecular profile. Some GIST harbour mutations which respond very well to certain drugs while others do not. Making things even more complicated, some specific subtypes of mutations within the same gene respond differently to the same drug. For example, in *KIT*-mutant GISTs, patients with *KIT* exon 11 respond well to imatinib while those with *KIT* exon? respond less well.

5. What is the five-year survival rate for GIST cancers?

With the development of effective drugs, median survival of patients with

advanced/ metastatic GIST is now more than five years.

Most clinicians and pathologists are now familiar with diagnosis and initial management of GISTs. The potential blind spots could be molecular testing at initial diagnosis and potentially at time of resistance. Knowing this information may help tailor our choice of drug use.

6. What could the availability of new drugs mean for advanced GIST patients? Why is there a need for new therapies for these cancers? What would you like patients to know about the available treatments for GIST?

Effective treatment delays cancer worsening, prolongs period of disease control and potentially, survival.

There is clearly a need to discover new therapies because while we have many treatments available, advanced/ metastatic GIST is still considered incurable.

I would like patients to know there are many effective lines of treatment even in the advanced/ metastatic setting.

There is good treatment available for GIST and availability of specialised care for this rare cancer here in Singapore. Patients can be heartened by this.

7. On a personal level, what do you love about your job? What has inspired you to work with GIST cancers and sarcoma in particular?

This is the best job in the world!

I enjoy the deep interactions I have with my patients as they go through their difficult cancer journey. I am honored that they come to me and entrust me with their treatment, health (and life).

Sub-specialsing in GIST and sarcoma is a little serendipitous. Prior to joining the private sector, I had trained and worked at the National Cancer Centre Singapore. At the time of completion of my medical oncology fellowship, I had noticed a service gap in my centre, namely in the area of bone and soft tissue sarcoma and GIST. That got me thinking and before I knew it, I was at the Dana-Faber Cancer Institute in Boston doing a two-year clinical research fellowship in GIST and sarcoma . This has been followed by a wonderful career thus far dedicated to sarcoma, GIST and general oncology. I am very much enjoying what I do!

8. What are the research areas offering hope to patients impacted by these cancers? Do newer immunotherapy agents currently play a role in GIST or would you like to see more research and development in this area?

Isolating the mechanisms of resistance and developing new drugs for resistance offers hope to patients.

The role of immunotherapy is currently more limited in GIST. Cancers which are addicted to specific genetic mutations like GIST may have a lower mutational burden and do not respond well to single agent immunotherapy (check point inhibitors).
Moving forward, we eagerly await new data surrounding novel agents, drug combinations, immunotherapy-TKI combinations in GIST. There is definitely hope for continuing to improve outcomes for these cancers.

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