Introduction

GIST is a rare cancer, but may nevertheless be the commonest histologic subtype of soft tissue sarcoma. It is estimated that the annual incidence is approximately 1.5/100,000/year (1). A study in the Rhône-Alpes region of France indicated an annual incidence of 11 per million (2). This is predominantly a disease of middle age, with a peak incidence between 60–65 years. However, it does occur in younger people, including children, in whom it is usually gastric in origin, often multifocal at presentation, may involve lymph nodes and is usually driven not by a mutation in KIT or the platelet derived growth factor alpha gene (PDGFRA) but most commonly involving loss of SDH (3). GIST is usually driven by an activating mutation in either the KIT or PDGFRA gene, most commonly in exon 11 of KIT. However, other mutations have been identified including in NF1 (neurofibromatosis type 1) and BRAF. Tumours lacking mutations in KIT or PDGFRA used to be referred to as “wild-type” (WT), but it is more appropriate to specify those genes that have been tested, e.g., WT for KIT, PDGFRA, NF1 and BRAF (4). In the majority of such patients, these tumours are associated with loss of function in one of the SDH genes, either due to a mutation, or an
epigenetic switch.

If a diagnosis of GIST is suspected, and the immunohistochemistry is inconclusive, molecular analysis for activating mutations in KIT or PDGFRA may be informative. Mutational analysis is always recommended as part of the diagnostic work-up, since it may predict for response to receptor tyrosine kinase inhibitors. For those GISTs that do not respond to imatinib, such as those driven by the PDGFRA exon 18 mutation D842V, this is important information, especially if adjuvant therapy is being considered. One exception to this recommendation might be those small <2 cm GISTs, which virtually never recur or metastasise. In the absence of activating mutations, studies to look for loss of SDH, usually using immunohistochemistry, may be carried out, since if confirmed this will inform prognosis and may help guide therapy, although specific treatments for SDH-deficient GIST are currently lacking. In addition to BRAF mutations, important because this can be targeted, TRK inhibitors are now available for tumours with an NTRK fusion, including GIST. Those GISTs with no known driver mutation and no evidence of SDH deficiency should probably be investigated for NTRK fusion, albeit such patients are exceedingly rare. Patients with a germline mutation in NF1, have a lifelong increased risk of GIST as well as malignant peripheral nerve sheath tumour. Currently there is no specific treatment recommendation for NF1 mutant GIST.

**Initial management**

Prior to the year 2000 surgery was the only effective treatment, since GIST does not respond to cytotoxic chemotherapy. Surgery remains the only curative modality and is recommended for all resectable GIST larger than 2 cm in size, with no dissection of clinically negative lymph nodes, since metastasis to nodes is very rare. When adjacent organs are involved these need to be removed en bloc with the tumour in order to achieve negative margins whenever possible. In the case of laparoscopic surgery, the same principles apply (5).

Imatinib is a receptor tyrosine kinase inhibitor (TKI) that inhibits KIT, platelet derived growth factor receptors A,B,C and ABL. It first entered clinical trials in GIST in 2000. It proved highly effective and was registered for the treatment of unresectable or metastatic disease in 2002 (6). It has become the standard therapy for such patients and also has a role in some patients before or following surgery, as will be discussed.

If immediate surgery is likely to lead to serious functional loss, as in the case of total gastrectomy or an abdomino-perineal resection of rectum, it is appropriate to initiate therapy with imatinib, provided an imatinib-resistant mutation has not been identified (7-10). This is a situation where mutational analysis is essential to exclude those patients with a PDGFRA D842V mutation and potentially permit dose escalation for those with KIT exon 9 mutant disease, which is likely to respond better to a higher dose of imatinib (11-13). Treatment is usually administered for 6–12 months in order to shrink the tumour, facilitate subsequent surgery, and improve outcomes, for example by converting a total gastrectomy to a partial gastrectomy, with important symptomatic benefits. There may also be advantages in terms of reducing the risk of bleeding and tumour rupture at the time of surgery. Early imaging is essential, in order not to delay surgery in those patients that do not respond to neo-adjuvant therapy. Research has shown that gross tumour size is not a reliable guide to imatinib response, since tumours may become hypo-attenuating on computed tomography (CT), indicating a loss of vascularity, and nevertheless initially increase in size. This lead to the use of Hounsfield Units to measure changes in the level of contrast enhancement in response to imatinib therapy and the development of specific CT criteria, Choi criteria, for response evaluation in GIST (14). In addition to CT, 18F-PET-CT, may be useful in this setting, since GISTs responding to imatinib may rapidly become negative on 18F-PET-CT as glucose uptake is switched off (15).

If neoadjuvant medical treatment is not feasible it may sometimes be acceptable to perform an R1 resection, i.e., with microscopically positive margins. This may be more appropriate for low-risk lesions, since it has not been proven that R1 surgery is associated with worse overall survival (16). If an unplanned R1 excision has occurred, re-excision may be possible, if major functional sequelae are unlikely. Smaller tumours, i.e., <2 cm in diameter, may never display malignant behaviour and they can be managed with surveillance but a diagnosis is nevertheless required since the differential diagnosis includes diseases such as lymphoma and paraganglioma. For gastric lesions the recommendation is to use endoscopic ultrasound-guided core needle biopsy, for more inaccessible tumours excision is necessary for tumours that are growing or symptomatic. For tumours in the rectum surgery is advisable earlier since local recurrence is more difficult to manage.
Adjuvant therapy

Adjuvant therapy trials in patients with resected GIST using imatinib began early in the development process. What we have learnt is that for patients at the highest risk of relapse, adjuvant therapy prolongs relapse-free survival and may actually improve survival. Risk is determined by tumour size, mitotic rate (index) and location (17). Tumour rupture is also a significant risk factor (see Table 1) (18).

In acknowledgement of the fact that criteria such as size and mitotic index are continuous variables prognostic maps have been developed taking this into account, also considering tumour rupture and primary site. These have been extensively validated in thousands of patients from a number of series (19). The impact of tumour site is partly determined by the ease of diagnosis and type of presentation, likely to be easier in the case of gastric GIST, and the impact of mutation type. Exon 18 PDGFRA mutations occur almost exclusively in the stomach and are associated with a slower pace of disease whereas KIT exon 9 mutations generally occur in the small bowel and are less favourable.

The benefit of adjuvant treatment with imatinib was first demonstrated by a placebo-controlled trial of 12 months imatinib in patients with resected GIST >3 cm in size which demonstrated prolonged relapse-free survival (20). A study carried out by the Scandinavian Sarcoma Group in collaboration with centres in Germany compared 1 versus 3 years of treatment in high-risk patients (21). The study showed not only improved relapse-free survival, but also overall survival for 3 years compared with 1 year of treatment. A recent update presented at the American Society of Clinical Oncology meeting 2020 has confirmed the benefit of 3 years of treatment with a hazard ratio of 0.5 compared with 1 year and, at a median follow-up of 10 years, an estimated survival for 3 years therapy of 79% compared with 65% for 1 year. Adjuvant therapy with imatinib continued for 3 years is generally acknowledged to be standard treatment for patients at significant risk of relapse and studies continue to determine whether more prolonged therapy would improve prognosis still further. It is obviously necessary to perform mutational analysis before commencing adjuvant therapy since those tumours driven by a PDGFRA D842V-mutation will not benefit. As discussed below in the metastatic disease section there may be categories of KIT exon 11 mutant disease with a much more favourable prognosis who do not require adjuvant therapy (11). While some oncologists might consider using an 800 mg daily dose of adjuvant imatinib in patients with an exon 9 KIT mutation, since the higher dose is more active in such patients with advanced GIST (12,13,22,23) there are no randomised studies using the higher dose in the adjuvant setting and this cannot be recommended. Adjuvant treatment should probably not be given in NF-1 related GISTs, since they are resistant to imatinib in the advanced setting. However, there is no consensus concerning whether KIT/PDGFRA wild-type SDH-negative GIST should be treated with adjuvant therapy, although there is no evidence of benefit from clinical trials. This reflects on the one hand their lack of responsiveness to imatinib, on the other their

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumour size (cm)</th>
<th>Mitotic index (per 50 HPFs)</th>
<th>Primary tumour site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1–5.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1–5.0</td>
<td>&gt;5</td>
<td>Gastric</td>
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<td></td>
<td>&lt;5.0</td>
<td>6–10</td>
<td>Any</td>
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<tr>
<td></td>
<td>5.1–10.0</td>
<td>≤5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any</td>
<td>Any</td>
<td>Tumour rupture</td>
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<td>&gt;10</td>
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<td>2.1–5.0</td>
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<td>5.1–10.0</td>
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<td>Non gastric</td>
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Tumour rupture before or during surgery almost certainly means that peritoneal spread will have occurred, even if this is undetectable at the time of surgery. Such patients should be considered for adjuvant imatinib therapy, which might need to be continued indefinitely, as for patients with metastatic disease.

The risk of metastatic disease was discussed in relation to adjuvant therapy. In addition to size and mitotic index there are other biological factors that have a major impact on the aggressiveness of the disease. Although the majority of GISTs harbour a KIT exon 11 mutation, within that group there is heterogeneity in relation to the outcome as discussed above. Joensuu et al. reported in 2015 that patients with duplication mutations in exon 11 had a very favourable prognosis, that single codon deletions were more favourable than more extensive mutations and some specific mutations were also associated with less aggressive behaviour (11). Although mostly resistant to therapy with TKIs, patients with PDGFRA mutations have prolonged relapse free survival compared with those with KIT mutations. In terms of patients treated with imatinib, KIT exon 9 mutations are unfavourable, requiring higher doses of imatinib for control and generally having worse progression-free survival. Patients with no mutations in KIT and PDGFRA usually have a slower pace disease, although there are exceptions.

Management of metastatic disease—systemic treatment

Imatinib

Imatinib is standard treatment for patients with advanced disease (24,25), including those patients who received prior adjuvant therapy without relapse. The standard dose of imatinib is 400 mg daily. However, data have shown that patients with KIT exon 9 mutations have improved progression-free survival (PFS) on the higher dose of 800 mg daily, which may be considered the standard treatment in this subgroup. A meta-analysis of both the European-Australasian and North American phase III trials, each of which compared 400 and 800 mg doses, was published in 2010 (23). Across both studies the median progression-free survival was 1.58 years for 400 mg, and 1.95 years for 800 mg. However, the only significant predictive factor for the benefit of the higher dose was the presence of a KIT exon 9 mutation, which clearly requires more intensive treatment. Overall survival was unaffected by dose with a median of just over 4 years. Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have previously been surgically excised (26). Research studies have shown that suboptimal plasma levels of imatinib are associated with a worse outcome, as yet not proven prospectively, although studies are underway (27). Patients with imatinib trough levels of less than 760 ng/mL at 3 months or later (28), had worse progression-free survival (29). Dose escalation of imatinib to 800 mg in the case of a GIST with a KIT exon 9 mutation showing disease progression could be considered if the higher dose was not used initially, since the higher dose is significantly more effective in this setting (23). Higher doses, though not necessarily 800 mg, could be useful if satisfactory plasma levels of imatinib are not being achieved, but this remains experimental. However, increasing the dose of imatinib empirically in the event of disease progression on 400 mg daily is recommended in certain treatment guidelines and may be an option prior to considering a change of drug. As discussed above, the diagnosis of disease progression should be made by experienced radiologists and clinicians since the use of tumour size criteria alone e.g., RECIST, can be misleading (15). Other possible causes of progression included poor compliance with medication and drug-drug interactions.

Sunitinib

Currently the standard second-line treatment for advanced GIST after imatinib is sunitinib, a multi-targeted receptor tyrosine kinase inhibitor (30). In the randomised trial median time to progression on sunitinib was 27.3 weeks, compared with only 6.4 weeks on placebo. Survival was also improved, using a Kaplan-Meier analysis, with a hazard ratio of 0.49, P=0.007. However, median survival had not been reached at the time of reporting and because of crossover to active treatment at the time the trial was unblinded, once median survival according to initial treatment allocation had been reached the difference was no longer statistically significant. The registered treatment regimen is 50 mg daily for 4 weeks following by a 2-week break. Studies have reported that continuous treatment at a dose of 37.5 mg is well tolerated and effective (31). Whatever regimen is chosen, dose modifications are frequently required because of side effects, including palmar-plantar dyseaesthesia, hypertension and diarrhoea. Certain secondary mutations that confer resistance to imatinib also confer resistance to sunitinib, and tumours driven by the PDGFRA
exon 18 D842V mutation are generally resistant.

**Regorafenib**

Regorafenib, is another multi-targeted TKI which was studied in patients with advanced GIST progressing on imatinib and sunitinib at a dose of 160 mg daily using a 3 weeks on/1 week off regimen compared with placebo and significantly improved PFS (32). Median PFS on regorafenib was 4.8 months compared with only 0.9 months on placebo. Cross-over was mandated early in patients progressing on placebo and they were permitted to do so even if their performance status had deteriorated. There was no statistically significant difference in survival between the two groups. Regorafenib is generally regarded as standard third-line treatment. Some tumours with resistance to imatinib and sunitinib because of secondary mutations in the activation loop of KIT, including exon 17, do respond to regorafenib, which is a key advantage (33,34). Skin toxicity is generally more severe than with sunitinib and weight loss may be a problem. Dose modifications are quite frequently required.

**Ripretinib**

Ripretinib is a so-called “switch kinase” inhibitor, which acts allosterically by altering the shape of the KIT molecule, specifically by inhibiting movement of the activation loop, rather than by binding at the active ATP-binding site. It was studied in a randomised, placebo-controlled trial in patients with advanced GIST who had had progressed after treatment with 3 or more TKIs. The study showed a significant improvement in progression-free survival (PFS) compared with placebo (HR 0.15; 95% CI: 0.09, 0.25; P<0.0001) (35). The median PFS on ripretinib was 6.3 months (95% CI: 4.6, 6.9) compared with 1.0 month (95% CI: 0.9, 1.7) on placebo. There was also a survival benefit with median OS on ripretinib being 15.1 months (95% CI: 12.3, 15.1) compared with 6.6 months (95% CI: 4.1, 11.6) on placebo (HR 0.36, 95% CI: 0.21, 0.62). Side effects included fatigue, lipase increase, hypertension, and electrolyte disturbances. Ripretinib was approved by the FDA in May 2020.

**Avapritinib**

Avapritinib was developed specifically for patients with GIST harbouring the PDGFRA D842V mutation. It was first studied in a single-arm phase I study in GIST patients with PDGFRA exon 18 mutation, including 38/43 with PDGFRA D842V mutations. The trial concluded that a dose of 300 mg daily was safe and tolerable. In patients with PDGFRA D842V mutations there were 49 of 56 responses, with 44 partial responses (79%) and 5 complete responses (9%) (36). Reported side effects include nausea, fatigue, diarrhoea, oedema, skin rash and neurocognitive disturbances. Avapritinib was approved by the FDA specifically for patients with PDGFRA D842V mutant GIST in January 2020.

**Metastatic disease—local therapy**

**Radiofrequency ablation**

Selected patients with oligometastatic liver disease may be treated by surgery or radiofrequency ablation (RFA) after achieving a maximum response to imatinib, or in the case of focal disease progression. RFA is generally limited to tumours up to 3cm in diameter and may not be a suitable approach for tumours adjacent to large vessels or for superficial lesions under the liver capsule. The best outcomes are reported in patients who exhibited a good response to imatinib and complete ablation of all detectable lesions was obtained (37).

**Liver metastasectomy**

Surgery may have a limited role in the treatment of metastatic disease. Complete excision of residual metastatic disease may improve prognosis in patients who are responding to imatinib (38-40). However, there have been no prospective randomised trials to confirm this view. As in the case of generalised peritoneal disease progression, surgery is not recommended for patients with multifocal progression in the liver, but focal progression can be managed surgically with good results provided disease elsewhere remains under control with imatinib, or other TKI.

A systematic review of surgery for liver metastases from GIST found that 5-year survival rates in selected patients were reported to be as high as 91%, but that best results were obtained in patients treated with a short period of neo-adjuvant therapy. More definitive conclusions were not possible owing to considerable bias in patient selection and reporting (41). A study by Brudvik et al. in 146 patients also reported long term survivors (42). As is the case with other localised therapies it is important to exclude occult active disease.
Radiotherapy

Radiotherapy can be a useful local therapy in GIST in the advanced disease setting for relatively localised, symptomatic disease. Radiotherapy can provide local tumour control, and possibly prolong the use of a TKI (43). Radiotherapy at lower doses may be useful in the palliation of pain or bleeding. Most reports are small series or single cases from single institutions so more definitive conclusions cannot be drawn.

Hepatic embolization and similar approaches

Embolisation of liver metastases has been used for a number of years and different methods are available. A randomised study of two such approaches concluded that Embosphere embolisation was more effective than chemotherapy with lipiodol and ischaemia (44) Selective internal radiotherapy is another approach which is used in the management of patients with liver metastases from colorectal cancer and has recently been applied to patients with metastatic GIST (personal communication). No publications are as yet available.

Conclusions

As is true for all sarcomas, the management of GIST is truly multidisciplinary. An individual patient may benefit from a number of different effective treatment modalities at different points in their disease. Systemic treatment of advanced disease is constantly evolving and the recent approval of 2 new agents is much to be welcomed. The outlook for patients with this disease has steadily improved since the introduction of imatinib in 2000 and median survival for patients with advanced disease is now thought to be around 5 years or more. Mutational analysis is essential if the most effective systemic treatment is to be used, whether prior to surgery in the case of some patients with gastric or rectal tumours, or following surgery in the case of those patients with a high risk of recurrence, for whom 3 years of adjuvant imatinib is currently indicated. While advanced disease can be treated effectively in many cases, we are still lacking effective treatment for SDH deficient GIST and this is one of a number of disease subgroups requiring additional research. This is a constantly evolving field and no doubt the next few years will see further breakthroughs as our understanding of GIST biology improves.

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