LONDON CANCER NEW DRUGS GROUP RAPID REVIEW

Update on high dose imatinib for gastrointestinal stromal tumour (GIST)
harbouring KIT exon 9 mutations

Date prepared: May 2012

Summary

Imatinib was the first licensed treatment in the UK for KIT positive unresectable and/or metastatic GIST at an initial recommended dose of 400mg/day. It was approved by NICE for use as first line treatment in 2004, but use of an increased dose for those who developed progressive disease after initially responding to treatment was not recommended as this was not a licensed dose at the time of the guidance. Following the incorporation of data into the SPC on dose escalation in patients progressing at the lower dose, NICE issued a partial update of its guidance in 2010 to address this area. Data from the EORTC-62005 and S0033 trials (n= 1640) comparing 400mg and 800mg doses of imatinib were reviewed by NICE, who concluded that the current available clinical and cost-effectiveness evidence did not justify a positive recommendation for the use of imatinib at increased doses of 600mg and 800mg/day as an appropriate use of NHS resources. Although a meta-analysis of data from these two studies (MetaGIST) confirmed a small progression free survival (PFS) advantage of high dose imatinib, essentially amongst KIT exon 9 mutants (HR 0.58; 0.38 to 0.91, p=0.0115), the Committee considered that the clinical evidence supporting this practice is based on the experience of a small number of people and the metaGIST data showed no statistically significant difference in overall survival between people with exon 9 mutations treated with 400mg/day compared with 800mg/day, therefore, it concluded that there was not sufficient evidence to justify a separate recommendation for the use of higher doses imatinib for people with exon 9 mutations whose disease had progressed on standard dose imatinib.

The Appraisal Committee had also been informed that clinicians might choose to begin treatment with 800mg/day without having tried lower doses in patients with the KIT exon 9 genotype. However, this is outside the current marketing authorisation and was thus not considered further by NICE. European and US guidelines published around the same time, supported the use of the higher dose of imatinib in patients with KIT exon 9 mutations based on the PFS benefit observed in MetaGIST, though there is currently no evidence that this will improve overall survival (OS).

Background

Epidemiology

Approximately 900 people are newly diagnosed with gastrointestinal stromal tumours (GIST) in the UK each year. Although GISTs can occur at any age, the usual age of presentation is between 50 and 70 years. Diagnosis of GIST is confirmed by clinical presentation and tissue biopsy to determine the histological characteristics of the tumour, including expression of the KIT (CD117) protein. Approximately 4% of GISTs have characteristic clinical and morphological features, but do not express the KIT (CD117) protein.1 Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation, the prognosis of which is poor with few, if any, people surviving beyond 5 years, in the absence of effective treatment.2

Imatinib

Imatinib was the first licensed treatment in the UK for KIT positive unresectable and/or metastatic GIST at an initial recommended dose of 400mg/day.3 It was approved by NICE for use as first line treatment in 2004, but use of an increased dose for those who
developed progressive disease after initially responding to treatment was not recommended as this was not a licensed dose at the time of the guidance. Following the incorporation of data into the SPC on dose escalation in patients progressing at the lower dose, NICE issued a partial update of its guidance in 2010 to address dose escalation and recommended against use of imatinib at 600 or 800mg/day in this setting.

**EORTC and SOO33 studies**

The data assessed by NICE included two RCTs of similar design which compared the effects of two doses of imatinib (400mg OD vs. 400mg BD) on overall and disease specific survival in patients with metastatic or unresectable disease who had not previously been treated with imatinib. Crossover to the higher dose was allowed in cases of disease progression in those taking the lower dose.

The EORTC study reported that both regimens of imatinib were associated with similar response rates but statistically significantly better PFS was reported for the BD regimen (disease progressed in 263 (56%) on OD vs 235 (50%) on BD regimen; estimated HR; 0.82; 95% CI, 0.69- 0.98; p = 0.026). The presence of KIT exon 9 mutations was the strongest prognostic factor of risk for progression and death. PFS (but not OS) for the exon 9 genotypes in this trial was statistically significantly better in the high-dose imatinib arm (400 mg, twice daily) compared with the standard-dose arm (400 mg, daily), with a 61% reduction in relative risk ($p = 0.0013$). In addition, the response rate after crossover from 400 mg of imatinib daily to 400 mg twice daily was higher among patients with KIT exon 9 mutations (57%) than among those with KIT exon 11 mutations (7%).

The phase III S0033 trial confirmed that the KIT exon 11 genotype is associated with favourable outcome in patients with advanced GIST compared with KIT exon 9 genotype or wild-type GIST. However, the PFS advantage in patients with KIT exon 9 mutations treated with high-dose imatinib observed in the EORTC study was not confirmed in this trial, although evidence showed improved response rates in these patients compared with those treated with a standard dose of imatinib (67% vs. 17%, respectively).

**MetaGIST**

Data from the EORTC-62005 and S0033 trials (n= 1640) were combined in a pre-planned meta-analysis (MetaGIST). This noted that wild type patients, KIT exon 9 mutants, and patients with other mutations had a worse prognosis than KIT exon 11 mutants. It confirmed a small PFS advantage of high dose imatinib (HR; 0.89; 95% CI, 0.79 to 1.00, $p=0.04$) for the group as a whole, and also showed a small, but statistically significant benefit in PFS for patients with KIT exon 9 mutations (HR 0.58; 0.38 to 0.91, $p=0.0115$), treated with 800 mg of imatinib compared with standard-dose imatinib, but no OS advantage. It was noted that the lack of a survival benefit comes as no surprise in view of the crossover design of the studies allowing patients randomised to 400 mg/d to go onto the 800mg dose at progression. Although the authors concluded that initial treatment with a daily dose of imatinib 800mg compared with 400mg does not have any advantage for most patients, as well as concerns about clear dose dependent toxicity, they did acknowledge that the only exception may be patients who harbour KIT exon 9 mutations, for whom high-dose therapy would potentially delay the first occurrence of disease progression and increase objective response rate.
NICE discussion of subgroup data

The presence and status of KIT or PDGFRA mutations are predictive of response to imatinib therapy in advanced or metastatic GISTs. The presence of a KIT exon 11 mutation was associated with better response, PFS, and OS rates than KIT exon 9 mutant GISTs or wild-type GISTs. In its consideration of these subgroup analyses, including data from MetaGIST confirming a small PFS advantage of high dose imatinib, essentially amongst KIT exon 9 mutants, the Committee considered that the clinical evidence supporting use of a higher dose in this group is based on the experience of a small number of people and there was no statistically significant difference in OS between people with KIT exon 9 mutations treated with either dose, therefore it concluded that there was not sufficient evidence to justify a separate recommendation for the use of higher doses of imatinib for people with exon 9 mutations whose disease had progressed on the standard dose. The Appraisal Committee was informed that clinicians might choose to begin treatment with 800mg/day without having tried lower doses in patients with the KIT exon 9 genotype, however, this is outside the current marketing authorisation, and was thus not considered further by NICE.

International guidelines

European and US guidelines issued around the same time as the NICE guidance supports the use of the higher dose in patients with exon 9 KIT mutations.

- **ESMO guideline 2010**
  These clinical practice guidelines noted that as level III,A evidence indicate that patients with exon 9 KIT mutations fare better in terms of PFS on a higher dose level, i.e. 800 mg daily, this should be the standard treatment in this subgroup.

- **National Comprehensive Cancer Network (NCCN) guideline 2010**
  According to these US clinical practice guidelines, statistically significant evidence shows that the relative benefit of high-dose imatinib depends on the mutation type, and that starting imatinib at a daily dose of 800 mg will prolong median PFS in patients with KIT exon 9 mutations, though no evidence shows that this will improve survival.

Cost (incl VAT)

400mg x 30 tablets = £2069

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References


9. MIMS May 2012

Details of search strategy:

NeLM
MIDB
EMC
NICE
NCCN

Embase/Medline: search history:
1. EMBASE; exp IMATINIB/; 20466 results.
2. EMBASE; exp GASTROINTESTINAL STROMAL TUMOR/; 6932 results.
3. EMBASE; 1 AND 2; 3325 results.
4. EMBASE; 3 [Limit to: Publication Year 2010-Current and Human and English Language]; 784 results.
5. EMBASE; *IMATINIB/ [Limit to: Publication Year 2010-Current and Human and English Language]; 970 results.
6. EMBASE; 2 AND 5 [Limit to: Publication Year 2010-Current and Human and English Language]; 180 results.
7. EMBASE; *GASTROINTESTINAL STROMAL TUMOR/; 3917 results.
8. EMBASE; 5 AND 7 [Limit to: Publication Year 2010-Current and Human and English Language]; 142 results.
9. MEDLINE; exp GASTROINTESTINAL STROMAL TUMORS/; 2930 results.
10. MEDLINE; imatinib.ti,ab; 6808 results.
11. MEDLINE; 9 AND 10; 957 results.
12. MEDLINE; 11 [Limit to: Publication Year 2010-Current and Humans and English Language]; 219 results.
13. MEDLINE; *GASTROINTESTINAL STROMAL TUMORS/; 2616 results.
14. MEDLINE; 10 AND 13; 898 results.
15. MEDLINE; 14 [Limit to: Publication Year 2010-Current and Humans and English Language]; 207 results.
16. EMBASE, MEDLINE; Duplicate filtered: [5 AND 7 [Limit to: Publication Year 2010-Current and Human and English Language]], [14 [Limit to: Publication Year 2010-Current and Humans and English Language]]; 349 results.
17. MEDLINE; 12 [Limit to: Publication Year 2010-Current and (Publication Types Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial or Comparative Study or Controlled Clinical Trial or Guideline or Meta Analysis or Multicenter Study or Practice Guideline or Randomized Controlled Trial) and Humans and English Language]; 33 results.
18. EMBASE; exp PHASE 3 CLINICAL TRIAL/ OR exp PHASE 4 CLINICAL TRIAL/ OR exp CONTROLLED CLINICAL TRIAL [+NT]/; 337699 results.
19. EMBASE; exp RANDOMIZED CONTROLLED TRIAL/; 298222 results.
20. EMBASE; 18 OR 19; 337699 results.
21. EMBASE; 4 AND 20 [Limit to: Publication Year 2010-Current and Human and English Language]; 22 results.
22. MEDLINE, EMBASE; Duplicate filtered: [12 [Limit to: Publication Year 2010-Current and (Publication Types Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial or Comparative Study or Controlled Clinical Trial or Guideline or Meta Analysis or Multicenter Study or Practice Guideline or Randomized Controlled Trial) and Humans and English Language]], [4 AND 20 [Limit to: Publication Year 2010-Current and Human and English Language]]; 55 results.

Acknowledgements

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