Imatinib Dose Interruption in GIST: High Progression Risk for 3-Year Responders

Interrupting imatinib therapy among advanced gastrointestinal stromal tumor (GIST) patients who have had a long lasting response results in a high risk of rapid progression, according to results of a recent clinical trial (BFR14). That risk, said Axel Le Cesne, MD, speaking for the French Sarcoma Group, persists regardless of the quality of prior response to therapy.

"The optimal duration of imatinib therapy in responding patients with advanced GIST is unknown," Dr. Le Cesne said, pointing out that in earlier results among 58 advanced GIST patients who had imatinib dose interruptions after 1-year of response, median progression-free survival (PFS) was 6.1 months among those whose imatinib dose was interrupted as compared with 28.3 months for those who had continued imatinib therapy ($p<0.0001$). Overall survival (OS) was similar between the groups.

The current trial examined the effects of dose interruption in patients whose response (stable disease, partial response, or complete response) to 400 mg of imatinib had been sustained for 3 years. Included individuals with advanced metastatic GIST were randomized to continued therapy (CONT) with imatinib 400 mg or to therapy interrupted (STOP) until progressive disease followed by resumed dosing at 400 mg. The main endpoint was PFS, with secondary endpoints of OS, and response to imatinib re-start in the STOP arm. BFR14 had initially included 338 patients, among whom 58 had been randomized at 1 year. Another 50 were randomized to CONT or STOP at 3 years. The statistical hypothesis was that at 1-year PFS would be 90% in the CONT arm and >75% in the STOP arm.

Mean age was ~61 years. Primary sites were most commonly gastric or in the small bowel. At 1-year there were 12 events in the 25 STOP patients (PFS 20.2%) and 1 event among 24 CONT patients (PFS 91.7%, $p=0.0013$). Progressive disease rates in the STOP arm were 47%, 64% and 85% at 6 months, 9 months and 1-year, respectively. There were no deaths. Dr. Le Cesne pointed out that the 1-year PFS curves in the STOP arms of the 1- and 3-year analyses were similar at 25.0% (1-year) and 20.2% (3-year).

When Dr. Le Cesne and colleagues asked also whether prolonged responding patients are different from the initial non-randomized population (n=276), they found female gender, small bowel primary site, liver involvement only and smaller tumor size to be more commonly occurring features (only female gender significantly so). In addition, mutational analysis conducted in 49% of patients showed the exon 11 mutation to be present in 83% at randomization. Exon 9 and wild type were each found in 8.5% of patients. In the exon 11 group, 90% of mutations were proximal (10% distal).

Dr. Le Cesne concluded that imatinib interruption in responding patients after 3 years is associated with reduced PFS and cannot be recommended outside of clinical trials. He noted further that the impact of the re-introduction of imatinib at the same dose on tumor control is currently being investigated. The impact of imatinib interruption on OS after 3-years of treatment is yet unknown.

Discussant Peter Reichardt, MD, Bad Saarow, Germany, commenting on the similar PFS pattern in the 1- and 3-year STOP arms, said, "This clearly leads to the question of whether we already need to think about a 3rd generation adjuvant trial with treatment duration beyond 3 years." Dr. Le Cesne, in fact, proposed a new randomization in non-progressing patients at 5-years with the same statistical hypothesis.

Highlights from the
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Longer Progression-Free Survival at Higher-Dose Imatinib in GIST

Results from the two largest clinical trials (combined n=1,640) ever conducted in gastrointestinal stromal tumors (GIST) show longer progression-free survival (PFS) with high-dose imatinib (800 mg daily) compared with standard dose (400 mg daily). They suggest also, stated Martine Van Glabbeke, PhD, speaking for the GIST Meta-analysis Group, that high-dose therapy benefits depend on mutation type.

The two randomized, intergroup phase 3 trials were conducted among patients with unresectable or metastatic GIST expressing the *KIT* receptor tyrosine kinase (CD117). One, conducted in the US and Canada (US-CDN, n=694) had overall survival (OS) as its primary endpoint, and the other, conducted in Europe, Australia and Asia (EU-AUS, n=946) had PFS as its primary endpoint. The trials, planned together, had wide entry criteria, including performance status up to 3, with no upper age limit and prior therapy permitted. In both trials patients received either imatinib 400 mg daily or 800 mg daily until progression, with crossover to the higher dose allowed after progression in the 400 mg group. Mutation data were gathered in a total of 772 cases.

The meta-analysis aims were to compare results between the two trials, to build prognostic models for PFS and OS, and to characterize patients who may benefit from the high-dose therapy. Median follow-up was 55/42 months in the US-CDN/EU-AUS trials.

PFS and OS were consistent between the two trials, Dr. Van Glabbeke said. In the combined trials, median PFS was 19/23 months in the 400 mg/800 mg groups, respectively, a small but significant increase for the higher dose (HR 0.89, p=0.04). Median OS was identical (49 months, HR 1.00).

Multivariate prognostic analysis revealed four factors adversely affecting both PFS and OS: poor performance status, high neutrophil count at trial entry, absence of *KIT* exon 11 mutations and male gender. Small bowel origin and low hemoglobin at trial entry adversely affected PFS. OS was adversely affected significantly by advanced age, low albumin at trial entry and large lesions.

Median PFS and median OS (months) for *KIT* exon 11 mutants/*KIT* exon 9 mutants/wild types/other were 26/60, 13/31, 16/43 and 11/34, respectively. Dr. Van Glabbeke noted that cases with *KIT* exon 11 mutants had doubled PFS and nearly doubled OS as compared with those with *KIT* exon 9 mutants.

Because of the modest 11% benefit in PFS, investigators looked for subpopulations with higher potential benefit from high-dose therapy. They found that only the presence or absence of *KIT* exon 9 mutations significantly affected the relative PFS (p=0.015) benefit of high-dose therapy. The interaction was not significant for OS (p=0.071). PFS with *KIT* exon 9 mutants was 6 months at 400 mg and 19 months at 800 mg (p=0.017); OS was 28/35 months (p=0.15).

Dr. Van Glabbeke concluded, "Treatment with high-dose imatinib compared with standard dose results in a small but statistically significant PFS advantage, but this does not affect OS. …There is statistically significant evidence that the relative benefit of high-dose therapy depends on the mutation type." She added that starting imatinib therapy at a daily dose of 800 mg in *KIT* exon 9 mutants will improve PFS, but there is no evidence that it will prolong survival.

Imatinib Increases Recurrence-Free Survival in Completely Resected GIST

Among patients with resectable gastrointestinal stromal tumors (GIST), adjuvant imatinib mesylate at 400 mg/day for a year increases recurrence-free survival (RFS) and is safe and well-tolerated. The finding emerged from the North American Intergroup phase 3 trial ACOSOG Z9001, which included patients with completely resected, localized primary GIST.

Ronald DeMatteo, MD, Memorial Sloan-Kettering Cancer Center, New York, noted that GIST is the most common sarcoma of the intestinal tract, and further that more than 90% of GIST tumors have a *KIT* or *PDGFRa* mutation. Clinical trial experience has shown imatinib mesylate to provide benefit in more than 80% of patients with metastatic GIST. For patients with localized primary GIST, surgery has been the gold standard, Dr. DeMatteo said, and currently among patients with unresectable tumors, imatinib is the standard of care.

The question naturally arose whether imatinib would be beneficial given to patients with primary GIST just after surgery. Before the development of imatinib, when there were no therapies available, 5-year survival was

Continued on page 34

Continued from page 10

Despite the success of UCBT in children, this strategy does not work as well for adults due to low cell doses and mismatches. A new strategy of using a double UCB platform seems to markedly increase the eligibility of adults for UCBT and appears to positively impact survival. Additionally, nonmyeloablative therapy clearly extends the eligibility with a low incidence of transplant-related mortality. Finally, a new approach that is being developed is to reduce non specific SC losses and optimize homing by direct injection into the pelvis (the BM microenvironment).

In conclusion, allogenic SCT is a viable option for patients without an exact match. Alternatively, recent data has shown that unmatched CB has greater success than either BM or PBSCs that are unmatched. Furthermore, UCBT is the standard of care in children, but the double UCB platform and nonmyeloablative therapy has markedly extended the use of UCBs in adults. It seems that interest in UCB will not wane in the near future as more benefits and applications are being realized.

Continued from page 31

only 54%, according to Dr. DeMatteo's earlier research (*Ann Surg* 2000). DeMatteo and colleagues hypothesized that adjuvant imatinib would prolong RFS following the complete resection of primary GIST.

The main entry criterion was primary GIST size of ≥3 cm. All patients had complete gross resection of KIT+ tumors and were randomized to a year of either placebo or of 400 mg daily of imatinib. The endpoints were recurrence-free survival (RFS, primary), overall survival (OS, secondary) and safety. Progressing patients were unblinded and switched from placebo to imatinib 400 mg or from 400 imatinib to 800 mg/day.

After the third scheduled 6-month analysis, with 644 of a planned 732 patients enrolled, the trial was stopped prematurely. Similar percentages of the prescribed dose were delivered to both groups (placebo 71%, imatinib 67%), with tumor recurrence (38% placebo, 1% imatinib) and toxicity (7% placebo, 50% imatinib) the main causes, respectively, of dose alterations. Grade 3-4 toxicities with imatinib were mainly neutropenia, liver function test elevations, skin rash and edema.

OS was similar in both groups, with a surprisingly small number of events (4 deaths placebo, 3 deaths imatinib, p=0.72), Dr. DeMatteo said. Six (6) were attributed to disease recurrence. For the primary PFS endpoint at 1-year, there were 62 events in the placebo arm and 21 in the imatinib arm (83% vs 97%, p=0.001). Dr. DeMatteo pointed out that at about 6 months after the completion of treatment the RFS slope began to turn downward.

Subgroup analysis showed stronger imatinib effects in patients with the largest tumors (≥10 cm), with RFS of 67% in the placebo arm and 96% in the imatinib arm (p=0.001), and a descending PFS slope at about a year and one-half.

Dr. DeMatteo concluded, "One-year of 400 mg/day imatinib mesylate is safe and well-tolerated after the complete resection of a primary gastrointestinal stromal tumor. Recurrence-free survival is increased. Overall survival has not been altered at this time with these preliminary data."

Continued from page 33

There were 3 toxic deaths in Head Start I and 1 in Head Start II. Five (5) patients relapsed in Head Start I, whereas only 2 patients did so in Head Start II; all relapses developed within 25 months and the majority occurred locally. Overall quality of life (QoL) was within the average range at both times of assessment (70 months and 124 months); younger patients displayed fewer behavioral problems and higher adaptive function at both time points.

In conclusion, EFS in this study mirrors those reported in the German HIT study [Rutkowski et al. *New Eng J Med* 2005]. Incomplete resection and absence of desmoplasia trend toward inferior EFS, but not OS. These results show that, despite administering the myeloablative chemotherapy, these patients can be retrieved with either more chemotherapy or irradiation. Although the number of patients is limited in these studies, the QoL was within the normal range in the Head Start I study and it was improved in 3 out of 4 patients in the Head Start II study.

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