Part 1 - Introduction

Interesting article on the use of Imatinib a tyrosine kinase inhibitor (TKI) in Gastrointestinal Stromal Tumours (GIST). TKI’s are an interesting group of drugs (small molecules) because unlike conventional chemotherapy which kills actively dividing cells. The TKI’s blocks cancers cells to grow beyond normal cells by targeting cell receptors, proteins enzymes, controllers of programmed cell death (apoptosis) and formation of new blood vessels (angiogenesis).

Imatinib (ABL-BCR kinase inhibitor) was first used in treatment of 95% of patients with chronic myelogenous leukaemia (CML), 15 – 30% of all patients with acute lymphocytic leukaemia (ALL). Imatinib targets a genetic abnormality arising due to the translocation of the BCR gene on chromosome 22 and the ABL gene on chromosome 9. The fusion of these two genetic mutations results in the formation of the BCR-ABL oncogene. The response rate of Imatinib is about 65% - 90% in CML and about 20 – 40% in ALL.

The problem with Imatinib is resistance can develop in white blood cells allowing the cancer to return. Mutations in the BCR-ABL kinase can be mitigated through use of an alternative TKI, Dasatinib which block 14 out of the 15 mutations.

Part 2

In addition to Imatinib use in CML and ALL it also used in patients GIST, by inhibiting c-KIT and Platelet Derived Growth Factor Receptor (PDGFR). Imatinib has been licenced for treatment of GIST formation in c-KIT positive unresectable tumours and for malignant GIST tumours.

The side effects of Imatinib range from neutropenia, thrombocytopenia, anaemia, tumour lysis syndrome all expected side effects for anti-cancer drugs to some unexpected cardiogenic shock / left ventricular dysfunction.

The results of the survival outcomes associated with 3 Years vs 1 Year Adjuvant Imatinib for patients with high-risk GIST, builds on the results of an earlier study the Scandinavian Sarcoma Group XVIII/German (SSGXVIII/AIO) which compared use of 3 years of adjuvant Imatinib with 1 year of Imatinib over a follow-up period of 4.5 to 7.5 years, and whether Imatinib improves overall survival (OS) over an extended follow-up period of 5 to 10 years.

Part 3

The study population Intention to Treat (ITT) was small 397, but since we are studying a fairly potent target specific drug the effect size would be large enough to provide adequate statistical power for the study. The patients were split equally between the two treatment groups. The age range measured by interquartile range (IQR) was similar in both groups. There were equal numbers of men and women in the trial. Both groups seems well-balanced according to the overall numbers and demographics so one can reasonably conclude the results would generalize well to the general population.

Intention to Treat (ITT) for Recurrence-free survival (RFS) Post-Surgery Primary Endpoint

36 month Imatinib treatment group, 5 year 71.4%; 10 year 52.5%

12 month Imatinib treatment group, 5 year 53.0%; 10year 41.8%;

Hazard Ratio (HR) 0.66 (0.49 – 0.87) p=0.003

The 3 year treatment group gives RFS (1/0.66)=1.55 times that of the 1 year treatment group

Part 4

Intention to Treat (ITT) for Overall Survival (OS) Post-Surgery Secondary Endpoint

36 month Imatinib treatment group, 5 year 92.0%; 10 year 79.0%

12 month Imatinib treatment group, 5 year 85.5%; 10year 65.3%;

Hazard Ratio (HR) 0.55 (0.37 – 0.83) p=0.004

The 3 year treatment group gives OS (1/0.55)=1.81 times that of the 1 year treatment group

Efficacy (Per Protocol), treatment compliant patients only (Secondary Analysis)

15 patients excluded because they did not have GIST, and 24 patients with intra-abdominal metastases removed at surgery

36 month group 10 years OS 81.6%

12 month group 10 years OS 66.8%

Hazard Ratio (HR) 0.50 (0.32 – 0.80) p=0.003

Part 5

The slightly more significant result for OS in the secondary analysis compared with the primary analysis suggests the non-compliant individuals where evenly distributed between the 1 year and 3 year Imatinib treatment groups. There is no difference in compliance between the two groups indicating that Imatinib is well tolerated.

Overall a well-designed study proving that taking Adjuvant Imatinib for 3 years post-surgery increased recurrence free survival (primary endpoint) by over 50% and overall survival (secondary endpoint) by just over 80%. The results of the study adds to the results of the previous Scandinavian Sarcoma Group XVIII/German (SSGXVIII/AIO) study on increased overall survival time for GIST patients post-surgery.