



CML Advocates - Best of ASH Abstracts 2009

WARNING - Please note: This is a subjective collection of ASH abstracts I found most interesting. The abstracts have been copied from the ASH website, but many of them have been simplified/modified by me, reducing complexity and removing details which are medically interesting but not relevant for patient advocates to understand the basic conclusions. They also have a headline summarizing my conclusion from it. Those who want to know the exact details, please see the originals on the ASH website at <http://ash.confex.com/ash/2009/webprogram/start.html>

Jan Geissler, 15 Dec 2009

Nilotinib Study ENACT (Expanding Nilotinib Access in Clinical Trials) with Update on Side Effects

The ENACT study is a Phase IIIb, open-label, multicenter study that evaluated the efficacy and safety of nilotinib in adult patients with imatinib-resistant or intolerant CML in a clinical practice setting outside of a registration program. Data from ENACT are used to characterize the patterns and management of adverse events (AEs) in nilotinib patients with imatinib-resistant or -intolerant CML in chronic or accelerated phase.

1603 patients received nilotinib 400 mg twice daily. The adverse events experienced by 1,603 patients (1,422 chronic and 181 accelerated phase) were generally identified during nilotinib treatment and lasted for short durations. The number of the grade 3 and 4 adverse events in CP and AP, median time from start of treatment and median duration are reported in Table. For all included adverse events, the overall most common action taken for the first occurrence was dose adjustment or temporary interruption with the exception of hyperglycaemia which was most often managed by treatment with concomitant medications (8/11 of hyperglycaemia adverse events in CP and 1/2 in AP). In the majority of the biochemical abnormalities other than hyperglycaemia there was no additional action taken. 49/308 (16%) events of thrombocytopenia in CP patients (9 in AP) were managed by non-drug therapy. 31/204 (15%) events of neutropenia in CP patients were managed by concomitant medication (6/33 events in AP). Permanent discontinuation of study drug was infrequently observed (number of patients in CP; AP): thrombocytopenia (25; 7), neutropenia (15; 2), hyperglycaemia (1; 0), elevated lipase (3; 0), hyperbilirubinaemia (2; 0), elevated ALT (3; 0), and elevated AST (1; 0).

Conclusions: Based on a large cohort of 1,603 nilotinib patients with CML-CP and CML-AP, nilotinib is well-tolerated. Most study drug-related grade 3/4 adverse events could be managed by temporary treatment interruption or dose adjustment, such that permanent discontinuation of study drug due to AEs was infrequent. The only events requiring concomitant medication administration or non-drug therapy were thrombocytopenia, neutropenia, hyperglycaemia and hyperbilirubinaemia. The adverse event profile observed was predictable and similar to that seen in registration trial.

Source: ASH-Abstract 1115: Philipp D. le Coutre, MD

Old age affects survival but not response: Trials with Imatinib, Nilotinib and Dasatinib

The median age of CML patients is close to 60 years. In the prognostic classifications (Sokal, Hasford) that were elaborated before the introduction of Imatinib, age was a significant and important prognostic factor. The most recent Imatinib studies have not clarified the prognostic importance of age and therapy with Imatinib, Dasatinib and Nilotinib is still denied to several elderly patients. A number of studies presented at the ASH conference assessed the use of Imatinib, Dasatinib and Nilotinib in elderly patients.

Imatinib



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A GIMEMA Study assessed the relationship between age (less and more than 65 years) and outcome, in CML patients treated front-line with Imatinib in early chronic phase (ECP). Data of 559 previously untreated ECP patients who received IM 400 mg daily (76%) or 800 mg daily (24%) was analyzed. The median follow-up is currently 42 months. There were 115 patients more than 65 years old (median age 71 years), while 444 (79%) were less than 65 years (median age 46 years). The proportion of patients who were treated with IM 800 mg daily was the same in both age groups.

The cumulative complete cytogenetic and major molecular response rates were identical in the two age groups (88% vs 88% and 82% vs 83%, respectively). However, overall survival (86% vs 93%), failure-free survival (72% vs 81%) and particularly event-free survival were significantly inferior in the older age group. All these differences were mainly due to comorbidities leading to more deaths in CP.

These data show that response to IM was not affected by old age. Survival curves were affected because of age-related complications and comorbidities. Age should never be a contraindication to IM treatment.

Nilotinib

ENACT is a Phase IIIb study that evaluates the efficacy and safety of nilotinib in adult patients with imatinib-resistant or intolerant CML in a clinical practice setting outside of a registration program. It is the largest single source of efficacy and safety information of any available tyrosine kinase inhibitor (TKI) in CML, particularly among the elderly. This sub-analysis of the ENACT study assessed the efficacy and safety of 400 mg twice daily nilotinib in elderly patients initiating treatment in CML-CP who were resistant and/or intolerant to imatinib.

Of the 1,422 CML-CP patients enrolled in the ENACT study between January 2006 and October 2008, 452 (32%) were elderly (minimum 60 years) at study initiation and 165 (37%) of these patients were minimum 70 years, 10 were minimum 80 years. Countries that enrolled min 20 elderly patients include France, Italy, USA, Germany, UK, Spain, Canada, and Brazil.

In ENACT, patients aged over 60 years at study initiation appear to have longer durations of CML, be more heavily pre-treated and more intolerant to imatinib than the younger cohort. Nonetheless, nilotinib induced comparable clinical responses in CML-CP patients regardless of age. Importantly, the safety profile of nilotinib is maintained in elderly pts.

Dasatinib

At present there is no data on toxicity and efficacy of Dasatinib in unselected elderly patients. To highlight this issue, 97 patients treated with Dasatinib aged over 60 years were retrospectively evaluated from 16 Italian Centers on a "real-life" basis.

There were 52 males and 45 females, median age at Dasatinib start was 69.5 years (65-73). All patients were in CP when Dasatinib was started. Starting dose of Dasatinib was 140 mg/day in 47 patients, 100 mg/day in 44 patients and ≥ 50 mg/day in 6 patients, respectively.

Overall, 11/97 patients (7 treated with 140 mg, 3 with 100 mg and 1 with below 100 mg) permanently discontinued Dasatinib due to toxicity; a dose reduction was needed in 56/97 patients (91% treated with 140 mg and 27% with 100 mg). The mean overall survival was 45 months, the Event-Free Survival 25 months.

The analysis showed that Dasatinib could have a major role in the treatment of unselected patients aged > 60 years resistant/intolerant to Imatinib; in particular, when employed at the current recommended dose of 100 mg/day, it is very effective and has a favourable safety profile also in heavily pretreated elderly subjects.

Sources:

- **ASH-Abstract 1118: Old Age Affects Survival but Not Response in CML: GIMEMA Study; Gabriele Gugliotta**



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- **ASH-Abstract 3286: Efficacy and Safety of Nilotinib in Elderly Patients with Imatinib-Resistant or -Intolerant CML-CP: A Sub-Analysis of the ENACT Study; Philipp D. le Coutre**
- **ASH-Abstract 2211: Real-Life Analysis of Dasatinib in CMP-CP Patients Aged >60 Years Resistant/Intolerant to Imatinib; Roberto Latagliata**

Stopping Imatinib Therapy in Molecular Remission: More than half of CML patients relapse

Imatinib (IM) has greatly improved survival rates in CML. However, all patients must continue treatment for an unknown period of time. A pilot study of the first patients who discontinued IM therapy was previously reported (Rousselot). The multicentre study "Stop Imatinib" (STIM) was initiated in July 2007 in order to evaluate the persistence of complete molecular remission (CMR) after stopping IM, and to determine the factors that could be associated with CMR persistence

Inclusion criteria were IM treatment duration of at least 3 years and sustained CMR. Sustained CMR was defined as BCR-ABL/ABL levels below a detection threshold corresponding to a 5-log reduction (undetectable signal using RQ-PCR) for at least 2 years. Molecular relapse, defined as RQ-PCR positivity, was taken into account if confirmed in two successive assessments. In cases of molecular relapse, patients were re-challenged with IM at 400 mg daily.

From the pilot study, 8 among 15 patients are still in CMR with a median follow up of 42 months (range 37-49). The number of patients enrolled in the STIM study was 69. 34 patients had received interferon alpha (IFNa) prior to IM and 35 patients were previously untreated. Median follow-up (range) was 17 months (6-24). 37 patients relapsed (loss of CMR) within the first 6 months, and two patient relapsed after more than 6 months (month 7 and 18). At month 12, the probability of remaining in CMR was 45% (44% for those previously treated with IFN, 46% for previously untreated patients).

All patients in molecular relapse were sensitive again after imatinib re-challenge (decreasing BCR-ABL level, achievement CMR again). Male patients had a better probability of survival without molecular relapse, and a trend was observed for the low Sokal risk group.

Peripheral natural killer cell counts prior to IM discontinuation were significantly lower in relapse patients (mainly cytotoxic cells CD56dim) as compared to the non relapse pts.

Conclusions: The investigators have confirmed that CMR can be sustained after discontinuation of imatinib with a long follow-up, particularly in male patients and in patients with cytotoxic natural killer cells in their peripheral blood. Using stringent criteria, it is possible to stop treatment in patients with sustained CMR, even in those treated with IM as a single agent.

Source: ASH-Abstract 859: Francois-Xavier Mahon

Optimization of Imatinib Therapy: 5 Year Results of the German CML Study IV

Rapid relapse after discontinuation of imatinib, the need for indefinite therapy and residual disease in most patients are the major challenges in management of CML. Combinations of imatinib with IFN simultaneously, or consecutively preceding imatinib, or with araC may improve treatment outcome. The German CML Study Group therefore designed a randomized trial to compare standard imatinib vs. imatinib + interferon alpha (IFN) vs. imatinib + low dose araC vs. imatinib after IFN failure. The current evaluation represents the prefinal results of the pilot phase of the trial.

Included were newly diagnosed CML patients in chronic phase. By the end of 2005, 657 patients were included. Patient characteristics of treatment arms were similar for age, sex, and risk score (low 35%,



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intermediate 54%, high 10%). The median dose of imatinib was 400mg/day in all arms, of araC 10 mg per treatment day and of IFN 4.2 Mio I.U./day in the imatinib-after-IFN arm and 1.8 Mio I.U./day in the imatinib+IFN arm. Median observation time was 57 months. 55 patients died, 73 patients were transplanted in first CP, 81 patients progressed, 59 patients were switched to second generation TKIs. After 3 years 126 patients (72%) of the imatinib 400mg arm still received the initial therapy as well as 60 patients (30%) of the imatinib+IFN arm and 53 patients (34%) of the imatinib+araC arm. 9 patients (7%) of the imatinib after IFN arm are still on IFN only. 5-year overall survival of all patients is 91%. 5-year PFS of all patients (no death, patient still in first chronic phase) is 87%.

Type and severity of adverse events (AE) over a 5-years period did not differ from those reported previously. Hematologic AEs grade III/IV were similar in all therapy arms except leukopenia grade III/IV, which was more frequently observed in the imatinib after IFN arm (14%). Non hematologic AEs were mainly fluid retention, neurological and gastrointestinal symptoms and fatigue. Neurologic symptoms and fatigue were more often reported for the therapy arms with IFN.

	Imatinib 400mg	Imatinib+IFN	Imatinib+AraC	Imatinib after IFN
5-Year Survival and Response Rates				
OS	87%	93%	92%	92%
PFS	84%	91%	88%	84%
CCR	92%	92 %	89%	83%
MMR	83%	78%	80%	70%
Adverse Events, WHO Grade III/IV				
Anemia	7%	1%	3%	3%
Leukopenia	4%	5%	2%	14%
Thrombocytopenia	5%	6%	6%	6%
WHO Grade I-IV				
Edema	15%	13%	5%	0%
Neurological	5%	15%	5%	22%
Gastrointestinal	17%	27%	21%	15%
Fatigue	8%	13%	9%	23%

This analysis shows excellent survival and durable response rates in all arms. Currently, survival in all treatment arms is equal to, or better than in IRIS. To verify possible differences in survival, e.g. imatinib 400 mg vs. imatinib + IFN, longer observation is planned. Although cytogenetic and molecular responses in the imatinib after IFN failure arm at 5 years are inferior to that in the other treatment arms, the question of whether the consecutive therapy with IFN first and imatinib after IFN-failure provides a survival advantage requires long term follow-up. Imatinib in combination with, or after IFN, or with low dose araC are feasible and safe treatment modalities.

Source: ASH-Abstract 862: Nadine Pletsch

ENESTnd trial: First line Nilotinib shows lower rate of progression and higher response rates than Imatinib

The ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) is a phase III, randomized, open-label, multicenter study comparing the efficacy and safety of 300 or 400 mg twice daily nilotinib with 400 mg/day in patients (pts) with newly diagnosed Ph+ CML in chronic phase.

846 patients with newly diagnosed CML in chronic phase were randomized to nilotinib 2x300 mg/day, nilotinib 2x400/day, and imatinib 400 mg/day arms. All patients had a minimum of 12 mos of treatment or discontinued early; median follow-up was 14 mos. MMR was defined as a value of $\leq 0.1\%$ of BCR-ABL/ABL.



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Median dose intensities of nilotinib delivered were 592 mg/day for 2x300/day and 779 mg/day for 2x400/day; imatinib dose intensity was 400 mg/day. Overall, 84% patients remained on the study for 2x 300 mg/day nilotinib, 82% on 2x400 mg/day nilotinib, and 79% on 400 mg/day imatinib,

Rates of MMR at 12 mos were superior for nilotinib 2x300mg (44%) and nilotinib 2x400mg (43%), compared with imatinib 400 mg (22%). Median time to MMR was faster for the nilotinib arms (less than 6 months) compared with imatinib (8 months). 80%/76% of nilotinib patients achieved CcyR within 12 months, compared to 65% of imatinib patients.

The rate of progression to advanced disease was significantly lower for nilotinib 2x300mg (2 pts) and nilotinib 2x400mg (1 pt) compared with imatinib 400mg (11 pts, 4%).

Overall, both drugs were well-tolerated. Rates of discontinuation due to adverse events or laboratory abnormalities were 7% for nilotinib 2x300 mg, 11% for nilotinib 2x400mg, and 9% for imatinib 400mg. Patients were monitored for QT prolongation and LVEF. No patients in any treatment arm showed a QTcF interval > 500 msec. There was no decrease from baseline in mean LVEF anytime during treatment in any arm. The study is ongoing.

Conclusions: Nilotinib at both 2x300 mg and 2x400mg induced significantly higher and faster rates of MMR and CCyR compared with imatinib 400mg, the current standard of care in patients with newly diagnosed CML. Nilotinib was effective across all Sokal scores. After only one year of treatment, both nilotinib arms resulted in a meaningful clinical benefit compared to imatinib, with reduction of transformation to AP/BC. Nilotinib exhibited a favorable safety and tolerability profile. The superior efficacy and favorable tolerability profile of nilotinib compared with imatinib suggests that nilotinib may become the standard of care in newly diagnosed CML.

Source: *ASH-Abstract LBA-1: Nilotinib Demonstrates Superior Efficacy Compared with Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: Results From the International Randomized Phase III ENESTnd Trial: Saglio et al*

IRIS-Study: Sustained Survival and Low Risk for Progression after 8 years

Already in previous years, the IRIS study demonstrated superior safety and efficacy of imatinib (IM) relative to Interferon-Alpha + Cytarabine. Based on results from this trial, IM is currently recommended as front-line therapy for CML-CP patients (pts). Now the 8-yr follow-up data of IRIS was reported at ASH 2009, evaluating long-term efficacy and safety of IM.

At the 8-year data cut-off, 304 (55%) of the 553 patients remained on IM study treatment, and 45% had discontinued treatment due to adverse events (AEs)/safety (6%), unsatisfactory therapeutic outcome (16%), SCT (3%), death (3%) or other reasons (17% for withdrawal or lack of renewal of consent and miscellaneous). No new safety issues were identified in a long-term analysis of serious adverse events.

Estimated EFS at 8 years was 81% and freedom from progression to AP/BC was 92%. Estimated OS was 85% at 8yr, and 93% when only CML-related deaths and those prior to SCT were considered.

Three events occurred in year 8: 1 progression to AP/BC and 2 deaths unrelated to CML (chronic obstructive pulmonary disease; pneumonia aspiration). The annual rates of progression to AP/BC in yr 4 to 8 after initiation of therapy were 0.9%, 0.5%, 0%, 0%, & 0.4%, respectively. Only 15 (3%) patients who achieved complete cytogenetic response (CCyR) progressed to AP/BC, all but 1 within 2 yr of achieving CCyR.

BCR-ABL transcript numbers were monitored sequentially in 98 pts. Among these, the rate of major molecular responses (MMR, < 0.1% BCR-ABL/ABL ratio on international scale) increased from 24% at



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6 months, and 39% at 12 months, to a best observed MMR rate of 86% in year 8. None of the patients with documented MMR at 12 month progressed to AP/BC.

Conclusions: CML-CP patients responding to IM had a low overall risk of progression to AP/BC. Most AP/BC events occurred early, with minimal risk after yr 3 and no evidence for an increase over time. Minor CyR at 3, PCyR at 6 and 12, and CCyR at 18 months were associated with stable CCyR over the observation period. The safety profile of IM remains unchanged after 8 yr, with no previously unreported AEs identified over the past 36 months. These data suggest that patients responding to IM are likely to maintain their responses on long-term therapy and confirm a favorable risk-benefit ratio in CML-CP patients.

Source: *ASH-Abstract 1126: International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up; Deininger et al*

Combining Interferon and Imatinib: significant molecular responses, but also adherence challenges

Imatinib (IM) is the current standard of therapy in chronic myeloid leukemia (CML). However, Interferon-alpha (IFN-alpha) has induced a low but reproducible curative effect in some CML patients, inducing durable remissions lasting even after therapy discontinuation. For this reason, the interest on the possible use of IFN-alpha in the treatment of CML is still substantial, and very recently some newer prospective studies from the French and the German Groups have proposed the re-introduction of IFN-alpha in the front-line treatment of early chronic phase CML, in association with IM.

The GIMEMA Working Party compared the response of 495 CML patients in early chronic phase, enrolled into three different prospective studies. 419 patients were treated with imatinib 400mg and 76 with imatinib 400mg plus IFN-alpha. Patients were equally distributed by Sokal risk in the two groups. Median follow-up was 43 months in the IM group and 54 mos in the IM+IFN-alpha group. Compliance to IM was excellent in both groups, with 90 to 95% of patients receiving IM 400 mg/daily throughout the follow-up. Conversely, the proportion of patients continuing IFN-alpha dropped from 41% at 12 mos to 18% at 18 months, 13% at 24 months, 3% at 36 months; by the end of the fourth year, all patients were off IFN-alpha.

The number of patients in CCgR was higher in the IM+IFN-alpha than in the IM group at 6 months (60% vs 42%) but not from 12 months on. The number of patients in MMolR was higher in the IM+IFN-alpha than in the IM group at 6, 12 and 24 mos, but not later on. Also the number of patients with undetectable Bcr-Abl transcript levels was higher in the IM+IFN-alpha group at 12 months (15% vs 5%) but not later on (19% vs 18% at 48 months).

These data support the preliminary analysis of the French SPIRIT group, reporting a higher rate of MMolR after initial treatment with IM and IFN-alpha as compared to IM alone. The loss of the difference from 24 months on could be explained by the fact that almost all patients had discontinued IFN-alpha during the first two years, pointing out that the low compliance to the combination may limit its utility in practice.

Source: *ASH-Abstract 2192: The Combination of Interferon-Alpha with Imatinib in Early Chronic Phase CML Patients Induces a Significant Improvement of the Molecular Responses in the First Two Years of Treatment: Results From Three Studies From the GIMEMA CML Working Party. Francesca Palandri*

Study on Imatinib long term side effects: No surprises (= no news is good news)

Imatinib is an effective first line therapy for CML and has substantially changed its biological and clinical behavior. Durable responses were reported in the majority of patients, with a rather benign side



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effect profile, despite the 'off target' inhibition of several other kinases, including Kit, PDGFR and Lck. Since available information is largely based on sponsored trials and long-term field studies are lacking, the ILTE study was conceived as an independent, academic, multicenter trial supported by Italian health authorities.

ILTE is an international study on a retrospective cohort and includes 31 centers in Europe, North/South America, Africa, Middle East and Asia. Patients with CML who started imatinib between 1999 and 2004 were eligible if they were in CCyR after two years of imatinib treatment. Study endpoints were (a) survival, (b), serious adverse events (including second cancers), (c) toxicities not qualifying as serious adverse events but judged by the referring physician as substantially impacting quality of life, (d) loss of CCyR, and (e) development of PCR negativity.

A total of 948 patients were enrolled, 88% of which met eligibility criteria after centers were visited and monitored. The median age of eligible patients was 51 (range 18-92) years; 59% of patients were males and the median follow-up was 4.0 years (excluding the first 2 years of treatment).

As of 31 Dec 2008, 3255 person years were available for analysis. 21 deaths were observed (only 6 of them caused by relapsed CML). A total of 138 serious adverse events were recorded (most frequent type "heart failure"), with 20% being considered related to imatinib. Second cancers were documented in 29 patients, which is in line with expectations in the general population. Among the 761 other substantial toxicities were recorded: the most frequent types were cramps, asthenia, edema, skin fragility, diarrhea; 69% of them were considered related to imatinib. A total of 18 patients (2%) discontinued imatinib because of toxicities during the period of observation. 40 patients lost CCyR, with stable or increasing rates over time. Finally, 256 patients (36%) developed durable (longer than 1 year) PCR negativity.

In conclusion, this report from ILTE shows that CML patients on imatinib die infrequently of CML related causes, do not appear to have substantially higher second cancer rates than the general population, have mortality rates similar to an age/sex matched population and do not show new types of imatinib-related adverse events. They also experience a low but steady rate of loss of CCyR and develop PCR negativity in approximately 1/3 of cases. Follow-up and further analyses are ongoing.

Source: ASH-Abstract 2199: Imatinib Long Term Effects (ILTE) Study: An International Study to Evaluate Long-Term Effects in CML Patients, Carlo Gambacorti-Passerini

SPiRiT study now focuses on comparing Imatinib+Peg-IFN with Imatinib-400

The purpose of the SPiRiT Study was to first determine whether higher doses of IM or combining IM with interferon or Ara-C would result in higher rates of molecular responses and if so, in better survival.

A French study group designed a phase III randomized multicenter open-label prospective trial comparing Imatinib 400 mg/d (n=159) with 3 experimental arms: Imatinib 600 mg/day (n=160), Imatinib 400 mg/day combined to s/c cytarabine (Ara-C, n=158) and Imatinib 400 mg/d combined to Peg-IFN2a (90 µg/week)

Thus the trial was designed to be conducted according to 2 parts. During the part 1, the increased dose of Imatinib or a combination regimen would be considered as promising at 1 year, if it increased the 4 log reduction response rate by at least 20 percentage points, e.g. from 15% to 35%, with an acceptable tolerability. A planned interim analysis of 636 patients based on an optimal molecular response (OMR = BCR-ABL/ABL ratio \leq 0.01) at 1 year has suggested the superiority of the combination of Peg-IFN2a and imatinib (ASH 2008).

The group now reports the 18 months update of this planned interim analysis of part 1 of the trial. Patients of part 1 were recruited between 2003 and 2007, median age 51 yrs (18-82), 62% males;



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Social risk scores: low 37%, intermediate 39%, high risk 24% of patients. Median follow-up was 42 months (range 18-73)

During the first year of treatment the median dose of IM was 400 mg/day for the 3 arms including Imatinib 400, 590 mg/day for IM 600; the median dose for Peg IFN2a was 54 µg/week (range 11-166) and for AraC was 24mg per day (range 10-40). Overall, 45% of the patients discontinued Peg-IFN2a during the first 12 months.

Of interest, duration of treatment with Peg-IFN2a had an impact on responses. In patients who have been treated less than 4 months as compare to more than 12 months, rate of MMR, OMR and UMRD increased from 48% to 82%, 23% to 49% and 8% to 20% respectively.

Grade 3/4 neutropenia and/or thrombocytopenia occurred during the first year in 8% IM Imatinib 400, in 14% Imatinib -600, in 41% Imatinib -Ara-C and in 40% Imatinib -PegIFN arms respectively. No significant infection rates were observed between the 4 arms. Grade 3/4 non-haematological toxicities occurred in 19% Imatinib -400 (oedemas, muscle cramps), in 30% Imatinib -600, in 27% Imatinib -Ara-C (diarrhoea) and in 31% Imatinib -PegIFN patients (skin rashes, asthenia).

Based on these results, the CML French Group (FI-LMC) stopped accrual into the Imatinib 600mg and Imatinib 400mg + Ara-C arms and is currently continuing with Imatinib 400 mg as control arm and the combination Imatinib 400mg + Peg-IFN2a as best experimental arm. This second part of the trial aims to confirm if achieving significant higher molecular responses will translate into a better event free and overall survival.

Source: ASH-Abstract 340; Significant Higher Rates of Undetectable Molecular Residual Disease and Molecular Responses with Peg-Interferon a2a in Combination with Imatinib (IM) for the Treatment of newly diagnosed CML Patients: Confirmatory Results at 18 Months of Part 1 of the Spirit Phase III Randomized Trial of the French CML Group; François Guilhot

Interferon maintenance might be an effective alternative after molecular Imatinib remission

Imatinib is a selective and very potent inhibitor of the BCR/ABL kinase. However, BCR/ABL persistence is the rule despite ongoing imatinib therapy. This suggests that imatinib will not cure CML and raises concerns about emerging imatinib resistance, long-term imatinib tolerability and compliance to therapy.

It was previously suggested that a combination of imatinib and immunotherapy by IFN may additionally control CML via induction of autologous cytotoxic T-cell (CTL) responses, such as those directed against the leukemia-associated antigen proteinase 3 (PR3). For example, induction of PR1-CTL which recognize PR3 on CML blasts was previously shown to be associated with IFN-, but not imatinib response.

Indeed, the German investigators presented at ASH 2007 about a cohort of 20 newly diagnosed CML patients that low dose of IFN maintenance therapy alone was able to maintain or improve remissions obtained by a prior imatinib/IFN combination treatment. After a median time of IFN maintenance therapy of 1.2 years, 80% of the patients remained or improved molecular remission.

These patients were further followed up, and additional translational studies to examine markers of IFN response were started.

20 patients (14 male, 6 female; median age 45) with low (n=13), intermediate (n=6), and high risk (n=1) according to the Hasford score risk calculation have been investigated. Imatinib therapy had been administered for 2.4 yrs (0.2-4.9), combined with PEG-IFNa2a (Pegasys, n=17) or IFN a2a (Roferon, n=3). Maintenance therapy consisted of PEG-IFN (n=16) or IFN (n=4). Dose was adjusted according to response and tolerability and ranged between 135 µg PEG-IFN every 3 weeks to 180 µg



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PEG-IFN every week, or alternatively 2 to 5 times 3 Million Units IFN/week. Imatinib was terminated due to side effects (n=5) or upon personal request of the patients after informed consent (n=15). At the time of imatinib withdrawal, two patients were in complete molecular remission (CMR) and 15 patients in major molecular remission (MMR).

After a median observation time of 2.8 years (range 6 months to 4.5 years), 15 patients were in MMR, 5 of them in CMR. Thus, the number of MMR patients increased from 2 at baseline to 5 after two years. Five patients relapsed within 4 months (range 2-10 months) after imatinib discontinuation, but were imatinib then re-established molecular remission. Side effects to maintenance IFN were minor.

The group also studied putative markers of IFN response. IFN therapy was associated with an increase in the expression of PR3, and in the presence of auto-reactive PR1-CTL. In one of five assessable patients PR1-CTL were detected prior to imatinib withdrawal, but in four of seven assessable patients during IFN maintenance therapy. Longitudinal measurements of PR-1 CTL counts suggested an inhibition of the expansion of PR1-CTL by imatinib, implying that an optimal CTL expansion may occur preferentially in the absence of imatinib. This would explain the conversion to a CMR status in some patients only after imatinib withdrawal.

In summary, IFN maintenance after a prior imatinib/IFN induction therapy may be an effective alternative to permanent imatinib therapy, because it enables to safely discontinue imatinib even in those patients that have not achieved a CMR at the time of pausing imatinib. Induction of a PR1-specific CTL response by IFN may contribute to the particular efficacy of IFN after CML-debulking by imatinib.

Source: ASH-Abstract 647 - IFN- α 2a Maintenance Therapy After Imatinib Plus IFN Induction Therapy in CML Induces Stable Long-Term Molecular Remissions and Is Associated with Increased Proteinase 3 (PR3) Expression and the Presence of PR1-Specific T-Cells, Andreas Burchert

Nordic Study Group: Imatinib+PegIFN shows major advantage over Imatinib monotherapy

Imatinib mesylate 400 mg once daily is the current standard first-line therapy for CML. Several biological and clinical observations suggest that combining IM with interferon alpha (IFN α) may improve the outcome of treatment. To compare the effects of standard-dose IM to combination of Imatinib and IFN α in newly diagnosed chronic phase CML patients with an intermediate or low Sokal risk score. The primary end point was to compare the major molecular response (MMR) rate after 12 months between the treatment arms (intention-to-treat analysis).

In a Nordic CML Study Group (Denmark, Finland, Norway and Sweden) and Israel multicenter study we randomized 112 newly diagnosed CML patients in complete hematological remission following 3 months of Imatinib-400 mg induction therapy. The study arms were Imatinib and the combination of Imatinib and IFN α 2b (PegIntron, Schering-Plough). Imatinib dose was fixed at 400 mg. IFN α was started at 30 μ g/week but could be escalated to 50 μ g/week or reduced down to 15 μ g/week depending on tolerability.

Poster summary: 130 patients were registered by study closure in March 2008. Rate of Major Molecular Response at 52 weeks was significantly higher in the Imatinib+PegIFN arm (82%) compared to the Imatinib-only arm (54%). No unpredictable complications or adverse events were reported. Neutropenia, rash and fatigue were more common in the combination arm, whilst edema and muscle cramps were more frequent in the monotherapy.

Source: ASH-Abstract 3280 & Poster, updated with content of poster at ASH 2009: A Randomized Phase II Study Comparing Imatinib and the Combination of Imatinib and Pegylated Interferon Alpha-2b in Newly Diagnosed Non-High Risk Chronic Myeloid Leukemia (CML) Patients in Complete Hematological Remission After Imatinib Induction Therapy Bengt Simonsson, MD



First-line therapy with Dasatinib continuing only with once daily dosages

A phase II trial was set up to study efficacy and safety of dasatinib in patients with previously untreated CML-CP. The aim is to investigate the efficacy and safety of dasatinib as initial therapy for CML patients in chronic phase.

Pts with previously untreated CML-CP were randomized to either 50 mg-twice-daily or a 100 mg-once-daily. 62 patients have been enrolled, 31 each on daily and twice daily schedule. Median follow-up is 24 months. Among 50 patients followed for at least 3 months, 49 (98%) achieved complete cytogenetic response (CCyR). Major molecular response has been achieved in 35 (70%), including 5 (10%) with complete molecular response.

Major molecular response by 24 months was achieved by 71% on dasatinib, 55% on imatinib 400mg, 66% on imatinib 800mg. There was a trend for higher MMR rate with the daily schedule of dasatinib: by 12 months 52%. Grade 3-4 non-hematologic toxicity included fatigue (6%), pain (muscle or joint) (6%), dyspnea, neuropathy and memory impairment (5% each). Pleural effusion occurred in 13% evaluable patients (grade 3-4 in 2%). Grade 3-4 hematologic toxicity (transient) included thrombocytopenia 10%, neutropenia 21%, and anemia 6%. Thirty (48%) of 62 patients required transient treatment interruptions.

The actual median daily dose for all patients was 100mg. There is no significant difference in grade 3-4 toxicity by treatment schedule, but there was a trend for less pleural effusion with daily (3%) vs twice-daily (10%). Three patients lost CCyR: 2 because of non-compliance, 1 due to treatment interruption because of pleural effusion. 24 month EFS (event = loss of CHR, loss of MCyR, AP/BP, death, or off because of toxicity) is 88%. All patients are alive.

Rapid CCyR occurs in nearly all patients with previously untreated CML in chronic phase, treated with frontline dasatinib therapy; the MMR rate at 18 months was 71%, with a favorable toxicity profile. Because of favorable trends in response and toxicity, only once-daily arm will continue accrual.

ASH-Abstract 338: Efficacy of Dasatinib in Patients (pts) with Previously Untreated CML in Early Chronic Phase (CML-CP): Jorge Cortes

Imatinib in Children: CML-PAED II and French Phase-IV Study, Transplantation becoming second line therapy

CML is a rare malignancy in pediatrics. Imatinib has been established also as first line treatment for children with CML while allogeneic stem cell transplantation as treatment option is postponed for those cases becoming intolerant or refractory to tyrosine kinase inhibitor treatment. The CML-PAED II study reports an analysis of pediatric data from patients with newly diagnosed Ph-positive CML on up-front treatment with imatinib.

According to protocol CML-PAED II pediatric patients with confirmed diagnosis of Ph+ CML were treated in CP with Imatinib 300 mg/sqm once daily, while in accelerated phase (AP) or in blastic phase (BC) the dose was increased to 400 mg/sqm and 500 mg/sqm daily, respectively.

From 2004 until March 2009 a total of 51 patients (21 female, 30 male; median age: 10.6 yrs (range 1-20 yrs) were registered: 10 patients with ongoing Imatinib treatment were recruited and analyzed retrospectively while 41 patients were enrolled prospectively. Stages of disease were: CP n=47; AP n=1; BC n=3. Those four patients diagnosed in AP and BC underwent early stem cell transplant. Observed side effects in the whole group included: nausea (n=9), muscle pain (n=7), edema (n=3), rhabdomyolysis (n=1, short interruption of Imatinib), reduced blood cell count (n=2, short interruption of IMA in one pt), biochemical alterations in bone metabolism (n = 8), impaired longitudinal growth (n=1). Two patients experienced intolerance (muscle pain) or toxicity (hepatic), respectively, therefore stopped imatinib and were put on dasatinib after 4 and 10 months, respectively.



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Keeping in mind that the number of pediatric patients is still small, imatinib treatment for children and adolescents with CML in CP is associated - like in adults - with high treatment response rates. Refractoriness to imatinib is uncommon and side effects seem tolerable, as only 10% of the total cohort stopped imatinib and were put on 2nd generation TKI. However, disturbances of bone metabolism and longitudinal growth impairment may be of special concern in this not yet outgrown cohort.

Only 3/47 patients not diagnosed in advanced phases of CML so far underwent stem cell transplant thus underlining that also in pediatrics stem cell transplant has been shifted to a second-line strategy for high-risk patients and those who failed therapy with imatinib.

Source: ASH-Abstract 342: CML in Pediatrics - First Results From Study CML-PAED II, Meinolf Suttorp, MD, PhD

In another study in France, 44 children with a median age of 11.5 yrs (range 10 months-17 years) have been enrolled. The rate of complete cytogenetic response was 62% at 12 months. The rate of major molecular response (MMR) defined as a BCR-ABL/ABL ratio \leq 0.1% was 34% at 12 months.

In this study, change of body height was observed during the first year of treatment with imatinib in the 22 patients with a sufficient follow-up: a significant decrease of height standard deviation scores was observed between the start of the treatment and 12 months later.

Conclusion: Imatinib is efficient in children and adolescent with previously untreated CML in early chronic phase. However, a negative impact of imatinib on the growth in a cohort of children and adolescents treated with imatinib was observed.

ASH-Abstract 863: Imatinib Is Efficient but Has a Negative Impact On Growth in Children with Previously Untreated chronic Myelogenous Leukaemia (CML) in Early Chronic Phase (CP): Results of the French National Phase IV Trial; Frédéric Millot

Adherence to Imatinib Therapy Is Critical Factor for Achieving Molecular Responses

There is a great variability in the degree of molecular responses achieved by CML patients treated with imatinib. These different levels of molecular response could reflect different degrees of adherence to therapy. We measured the adherence to imatinib therapy in 87 consecutive CML chronic phase patients who had received imatinib 400 mg day as first line therapy for a median of 60 months before enrolment and therefore all them were in complete cytogenetic response.

Adherence levels were monitored during a 3-month period using microelectronic monitoring devices (MEMS) and were related to levels of molecular response. MEMS consist of an electronic device fitted in the cap of a normal looking medication bottle that automatically records each time the bottle is opened. MEMS are considered as the 'gold standard' for measuring adherence. We also measured the imatinib plasma level, the presence of TKD mutations and the other prognostic factors.

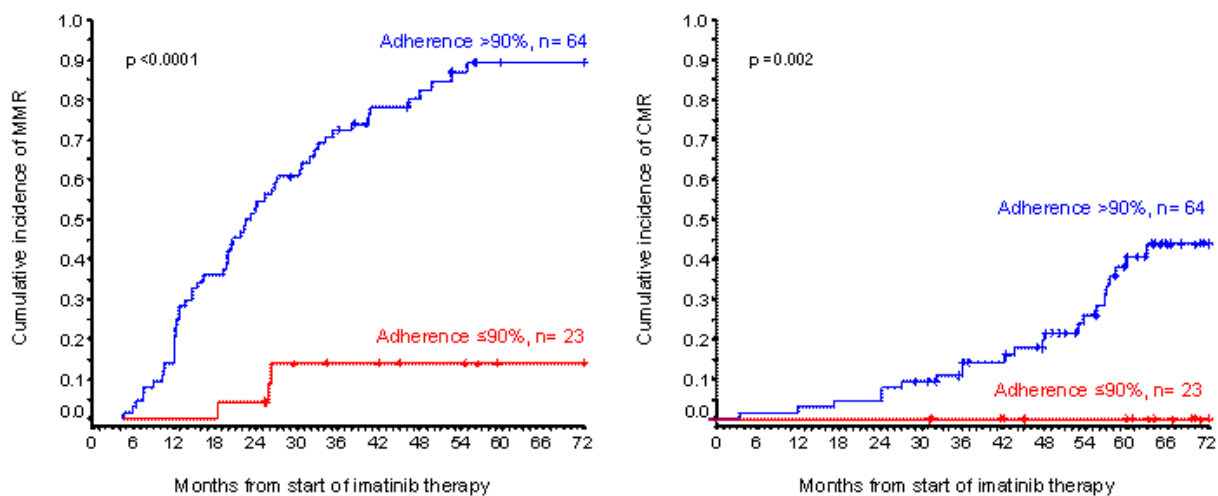
The median adherence rate was 97.6% (range 22.6-103.8%). In 27% patients adherence was below 90% (median 76%) and in 14% below 80% (median 63%). We found a strong association between adherence rate (below 90% or over 90%) and the 6-year probability of major molecular response (MMR) (28% vs 95%) and complete molecular response (0% vs 43.8%).

Adherence was the sole independent predictor for CMR. No molecular responses were observed when the adherence was below 20%. In patients whose imatinib dose had been increased (n=32) the adherence was poor (median 86%). Adherence was the only independent predictor for failure to achieve a 3-log transcript reduction in this subgroup of patients.

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Patients with CML vary greatly in their response, as demonstrated originally by Sokal et al. in 1984, and the same variation is seen in patients treated with imatinib in the modern era. The basis for this variation is unknown but it has been attributed to the intrinsic biological heterogeneity of the leukemia. In contrast we show here that adherence to therapy is the major factor determining the degree of response that a CML patient treated with imatinib will achieve.

Figure



Source: ASH Abstract 3290: Long Term Adherence to Imatinib Therapy Is the Critical Factor for Achieving Molecular Responses in Chronic Myeloid Leukemia Patients, Alex Bazeos

Influenza and Pneumococcus Vaccination and CML treatments

Imatinib, nilotinib and dasatinib are remarkably effective for CML in chronic phase. However little is known on their potential impact on the immune system and to date no human *in vivo* data are available. An understanding of the effects of different TKIs on the immune response will have implications for the development of immunotherapeutic strategies. The aim of this study was to prospectively analyze humoral and cellular immune responses to vaccination against influenza virus (Flu) and Pneumococcus in CML patients treated with IM, dasatinib or nilotinib compared to healthy controls.

Data from *in vitro* and animal studies on the effects of Imatinib on the immune response have been contradictory ranging from impaired antigen-specific T-cell response to enhanced stimulation of tolerant T cells. In addition few data are available to assess potential immunomodulatory effects of the second-generation tyrosine kinase inhibitors nilotinib and dasatinib. Dasatinib has inhibitory activity against a broader range of protein kinases than imatinib including the Src family kinases Lck and Fyn, both of which are associated with T-cell activation. Dasatinib may also inhibit B cell signaling through the Lyn pathway which may have potential implications for immunotherapeutic strategies.

50 CP-CML patients on standard dose TKIs (IM, n=22; dasatinib, n=15; nilotinib, n=13) and 15 healthy controls were vaccinated against Flu (Inflenza vaccine Ph. Eur. 2008/2009, CSL biotherapies) and pneumococcus (Pneumovax II, Sanofi Pasteur MSD). Samples were taken pre and at 1 and 3 months post-vaccination.



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The preliminary results suggest that in patients with CML on TKIs the B cell response to vaccination with Pneumovax is significantly impaired compared to healthy controls. The authors have as yet not detected a significant difference in T-cell response following vaccination with Flu in CML patients on TKIs compared to healthy controls.

Source: ASH-Abstract 2214: "Influenza Virus and Pneumococcus in Chronic Phase CML Patients Treated with Tyrosine Kinase Inhibitors", Hugues de Lavallade

Weekend Drug Holiday of Dasatinib in CML Patients Not Tolerating Standard Dosing Regimens

Dasatinib (DA) is a multitargeted tyrosine kinase inhibitor (TKI) approved for 2nd line treatment of CML patients after imatinib failure. D-related toxicity mandates dose reduction in selected patients beyond the labelled reduced continuous dosing. In chronic phase (CP) patients, intermittent targeting of BCR-ABL by a once daily regimen reduces side effects with equal efficacy compared to the initially explored twice daily regimen. Thus, considering the short half-life of DA (3-5 hours) additional treatment interruptions to reduce the total weekly dose may not negatively affect treatment outcome while allowing continued treatment with an effective drug.

In a retrospective analysis 33 CML patients with intolerance (n=11) or resistance (n=22) to imatinib were investigated. Patients were selected based on the toxicity-guided administration of a dose reduced dasatinib regimen and were treated with an on/off regimen (3 to 5 days on, 4 to 2 days off) expecting a reduction of DA dependent off-target toxicity. Patients were followed by routine hematologic and cytogenetic assessment, and molecular monitoring (quantitative reverse transcriptase polymerase chain reaction, PCR) to safeguard clinical response to the altered drug schedule. Further, resistant patients were regularly screened for BCR-ABL mutations.

Non-exclusive reasons for dose reduction were hematologic toxicity (51%), and fluid retention (55%), including 17 patients with pleural effusions. 27 patients (82%) suffered from grade III/IV side effects. The median weekly dose of the DA weekend holiday schedule was 500mg (320-500). During interval treatment, mean CTC grade for hematologic toxicity improved from grade 3.2 to 1.5, and for fluid retention from grade 2.9 to 1.6. All but 2 patients (89%) affected by fluid retention, and all but one patient suffering from hematologic toxicity (94%) achieved a lower CTC toxicity level by allowing drug holiday.

For response analysis, 2 patients were excluded due to early stem cell transplantation or loss of follow up. 13/31 (42%) did either show transient improved molecular response or remained on stable BCR-ABL load over time. 3/31 progressed to advanced phase CML. 18/31 (58%) patients showed the desired disease control according to established criteria despite reduced total weekly DA doses. Of note, 10/12 patients with improved response have been treated for a minimum of 6 mo with continuous dosing DA regimens without having achieved the response level observed after allowing drug holiday.

We conclude that weekend treatment interruption allows continuation of DA treatment for patients suffering from side effects. This retrospective analysis in patients resistant or intolerant to imatinib with up to 5 preceding treatment modalities suggests good and in many cases even improved efficacy of interval treatment compared to continuous dosing. These data mandate the initiation of clinical trials to investigate alternative intermittent targeting regimens

Source: ASH-Abstract 1119: Paul La Rosee

Hypophosphatemia During Imatinib Treatment of Newly Diagnosed Chronic Myeloid Leukemia Patients Is Associated with Better Response



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The Spanish Registry on CML (RELMC) is a multicentric, hospital-based cancer registry whose aim is to describe what is the actual treatment received by patients with CML in Spain, its outcome, and the variables which influence it.

Aim: To study the variables which could influence the outcome in newly diagnosed CML patients treated with Imatinib, including classic and new variables, such as phosphate serum levels, which are diminished in a substantial number of patients (Osorio et al ,2007)

Patients: 207 CP-CML patients, newly diagnosed, were included in 17 Spanish hospitals. Sex: 131 M,76F(63%,37%). Age: Median: 51,5 (18,7-87,5).The risk group distribution was as follows: Sokal L/I/H: ((47%;35%;18%). Hasford (44%,49%,7%). The variables studied at diagnosis were sex, Sokal and Hasford group. During the treatment: dose of Imatinib, anemia, neutropenia, thrombocytopenia and hypophosphatemia.

Results: Median follow up of the series have been 19,1 months. Among 207 patients, frequency values for anemia, neutropenia, and thrombocytopenia were 21%, 29% and 11%, respectively. Ninety-one patients had serum phosphate measured during the treatment. Among them, 49 (54%) had hypophosphatemia . Complete hematologic response (CHR) was obtained in 94,6% .No significant association was found between Sokal or Hasford group and the achievement of complete HR.

Complete cytogenetic response (CCR) was obtained in 73%. A significant association was found between obtaining CCR and Low or intermediate Hasford group or having hypophosphatemia during the treatment . The probability of obtaining CCR was higher in patients having hypophosphatemia in the 9th month of therapy. Patients who had hypophosphatemia during the treatment also showed a trend for higher probability of CCR.

Major and complete molecular response (MMR, CMR) were obtained in 71% and 48%, respectively. MMR was significant worse in Hasford high-risk patients, and the probability of MMR was higher in patients developing hypophosphatemia.

Regarding CMR, Hasford high risk had a significant association with worse rate of CMR. Also, the probability of CMR was significantly higher in patients having hypophosphatemia.

Conclusion: In our series, Hasford risk system has a stronger predictive value than the Sokal classification. It is interesting to note that half of our patients had hypophosphatemia during the treatment with Imatinib. Intriguingly, having low serum levels of phosphate during treatment is associated with better response, and it invites to further study of the biological basis of this finding and its relevance as prognostic variable.

ASH-Abstract 1121: Luis Felipe Casado, MD,

Resistance, Outcome and the Development of Mutations with Dasatinib in Patients with Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

Dasatinib is an FDA approved tyrosine kinase inhibitor (TKI) targeted at BCR-ABL for the treatment of CML after imatinib resistance or intolerance. A phase III dose-optimization study of dasatinib in CML-CP, where patients received either 100 mg or 140 mg of dasatinib on a once- or twice-daily schedule, indicated that 100 mg once daily dasatinib provided durable disease control with an estimated progression-free survival (PFS) of 73% at 36 months.

We conducted a retrospective analysis to expand on these results to determine if earlier cytogenetic response (CyR) predicts superior outcomes within this dosing arm and also to quantify progression to advanced-phase CML and characterize the quality of BCR-ABL mutations associated with loss of response to dasatinib. Our landmark analysis demonstrated that 90% of patients receiving dasatinib 100 mg once daily who achieved complete cytogenetic response (CCyR) at 12 months were progression-free at 36 months, a considerable improvement over those without CCyR at 12 months



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(Table 1). Of the 164 patients receiving dasatinib 100 mg once daily, 59 had attained CCyR at 6 months of therapy. The rate of PFS after 36 months within this cohort was 93%, whereas those with partial CyR or those without major cytogenetic response (MCyR) at 6 months had 36-month PFS rates of 76% and 54%, respectively. A total of 36 subjects experienced progression events while receiving dasatinib 100 mg once daily: 8 due to death, 5 due to development of advanced phases of CML, 3 due to increases $\geq 30\%$ in Ph+ metaphases, 9 due to increasing white blood-cell count, 4 due to loss of complete hematologic response, 4 due to loss of MCyR, and 3 for unknown reason. The majority (86%) of patients who do progress while receiving dasatinib remain in CP at 36 months.

The development of mutations in BCR-ABL is a known mechanism of loss of response to dasatinib. In participants with loss of response to dasatinib who have available mutation data (n=61), the incidence of developing mutations during dasatinib therapy (at any dose) is 19% (5/27) in patients without baseline mutations, and 47% (16/34) in those with mutations at initiation of dasatinib. Of the patients who lost response to dasatinib and developed new mutations during therapy, 13 patients harbored T315I, 6 possessed F317L, 3 had V299L, and 1 acquired E255K. Three other patients developed mutations not associated with resistance to dasatinib (Table 2). New mutations that emerged in the 100 mg once daily arm and 70 mg twice daily arm were of similar frequency. In conclusion, patients who achieve early and complete CyRs to second-line dasatinib exhibit reduced rates of long-term progression versus those without CCyR at 6 months. Of the patients who do progress while receiving dasatinib, the majority remain in CP at 36 months. Of patients treated with 100 mg once daily, only 3% progressed to accelerated or blast phase with 36 months of follow-up.

This transformation-free survival rate favors the use of dasatinib following imatinib failure in patients who have the option of pursuing allogeneic stem cell transplantation. Finally, the development of new mutations leading to resistance during dasatinib therapy is uncommon, and the lower total daily dose employed by the 100 mg once daily regimen does not appear to select for a greater variety of mutations than have been previously identified in patients treated with 70 mg twice daily. In patients who lose response to dasatinib and develop new mutations, a switch to an alternate TKI or stem-cell transplantation may be appropriate.

ASH-Abstract 1122: Neil Shah

Update On Imatinib-Resistant Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) On Nilotinib Therapy at 24 Months: Clinical Response, Safety, and Long-Term Outcomes

Background: Nilotinib is a selective and potent BCR-ABL inhibitor, developed through structure-based drug design, indicated for the treatment of Philadelphia chromosome positive (Ph+) CML patients in CP or accelerated phase (AP) resistant or intolerant to prior therapy including imatinib. Recently, 24-month follow-up data from the pivotal nilotinib 2101 study demonstrated achievement of rapid and durable cytogenetic responses in the majority of patients and an excellent overall survival (OS) rate of 87%. The current update focuses on the major molecular response (BCR-ABL transcript levels $\leq 0.1\%$ according to the international scale; MMR) of patients treated with nilotinib.

Methods: Imatinib-resistant and -intolerant CML-CP patients (n=321) were treated with nilotinib 400 mg twice daily and followed for at least 24 months. In this report, the efficacy parameters studied were: rate of MMR, rate of major and complete cytogenetic response (MCyR, CCyR), time to and duration of response, time to progression (TTP), and OS. Efficacy parameters were also analyzed based on the presence or absence of a CHR at study entry.

Results: The median duration of exposure to nilotinib was 18.7 months (< 1.0–36.5), with 62% of patients on therapy for at least 12 months and 42% on therapy for ≥ 24 months. Median dose intensity of nilotinib was 788.5 mg/day, very close to planned dosing. Overall, 58% of patients required dose interruption (defined conservatively ≥ 1 day of interruption regardless of reason) with a median cumulative duration of interruption of 20 days (4% of days of exposure). Importantly, 73% of patients that required treatment interruptions resumed treatment after interruption at the planned dose. The



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achievement of MMR in imatinib-resistant and -intolerant CML-CP patients who had BCR-ABL transcript levels available post-baseline (n=294) were included in this efficacy analysis. Of these patients, 105/294 (36%) entered the study with a CHR and 189/294 (64%) did not have a CHR at study entry. The overall MMR rate was 28%; MMR was higher in patients with CHR at study entry (38% vs. 22%). Overall, CCyR was achieved in 46% of patients, among whom 56% achieved MMR. Median time to MMR was 5.6 months. Overall, 77% and 84% of responding patients maintained MCyR and CCyR at 24 months, respectively. Overall (n=321), the estimated rate of progression-free survival (PFS), defined as progression to AP/BC or discontinuation due to progression or death, at 24 months was 64%, however, only 9 patients (3%) progressed to AP/BC based on actual laboratory values. PFS rate at 24 months was higher for patients with baseline CHR (77%) compared with patients without CHR at study entry (56%). OS at 24 months is 87% for the entire patient population. The safety profile of nilotinib remains unchanged at 24 months of follow-up. The majority of first episodes of grade 3/4 bilirubin and lipase elevations occurred within the first month of therapy and were brief in duration (median duration 15 days). The incidences of hepatic and pancreatic disorders on nilotinib were 1.3 and 1.7 per 100-patient years of therapy and no cumulative risk of hepatic and pancreatic events was observed in this population with longer follow-up. Importantly, discontinuations due to hepatobiliary adverse events were uncommon (n=2; < 1.0%).

Conclusions: Nilotinib therapy led to the achievement of MMR in a majority of patients with CCyR, and in 38% of patients with CHR at study entry. Furthermore, the response and outcomes of patients treated with nilotinib was higher in patients with CHR at baseline suggesting that patients with imatinib resistance and intolerance who lost cytogenetic response but not hematologic response have a more favorable response compared to those patients who have lost hematologic response when switched to nilotinib. Overall, the safety profile of nilotinib remains well-tolerated with long-term follow-up. At 24 months, nilotinib therapy remains an effective and tolerable therapy for patients with imatinib-resistant or -intolerant CML.

ASH-Abstract 1129: Hagop M. Kantarjian

Nilotinib 800 Mg Daily as Frontline Therapy of Ph + Chronic Myeloid Leukemia: Dose Delivered and Safety Profile for the GIMEMA CML Working Party

Nilotinib is an effective and registered treatment of chronic myeloid leukemia (CML) after imatinib failure. Its efficacy as frontline treatment has been explored in phase 2 trials from MDACC and Italian GIMEMA, whose results have been presented recently (Cortes ASH Rosti, EHA). Here we present a detailed analysis of the safety profile of nilotinib 800 mg daily in the CML early chronic phase (ECP) setting.

Briefly, 73 ECP patients (median age 51 yrs, range 18-83 yrs, 21/73 – 29% - ≥ 65 yrs at enrolment) received nilotinib at a dose of 400 mg BID. With a median follow-up of 15 months (range 12-24 months), the CCyR rate at 1 yr was 96%, and the major molecular response (MMoR) rate 85%. During the first 365 days, the treatment was interrupted at least once in 38 patients (52%; overall, 86 interruptions), with a median cumulative duration of drug interruption of 19 days (5.2% of 365 days) per patient (range 3-169 days); 35 patients (48%) received the full prescribed dose. The proportion of patients with ≥ 1 interruption decreased during the first and second quarter and second half (37%, 25% and 22% respectively). The mean daily dose was 600-800 mg, 400-599 mg, and less than 400 mg in 74%, 18% and 8% of patients, respectively. Four AEs (≥ grade 2) accounted for the great majority of dose interruptions: bilirubin increase (38%, no gr. 4), skin rash and/or pruritus (37%, no gr. 4), asymptomatic amylase and/or lipase increase (16%, gr. 4: 4%) (no pancreatitis), transaminases increase (19%, no gr. 4). Notably, only 3 events of peripheral edema/fluid retention have been recorded so far (2 gr 1, 1 gr. 2). No pleural or pericardial effusion. Only one pt permanently discontinued nilotinib for recurrent amylase and lipase increase gr. 3-4 after 7 months on nilotinib, without pancreatitis (normal ECO scan and MRI): the pt. is on imatinib 400 mg daily from 12 months, maintaining the CCyR but losing MMoR on imatinib. The transient hyperglycemia (gr. 2 and 3: 6%)



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did not lead to any treatment discontinuation. The hematopoietic toxicity (grade 3-4) was negligible: only 5 events (3 neutropenias and 2 thrombocytopenias) in 5 patients (7%) (all within 3 months from treatment start: 431/438 q2weeks scheduled blood counts evaluable).

Nilotinib 800 mg daily is feasible, safe and very effective in ECP CML (ClinicalTrials Gov.NCT00481052).

ASH-Abstract 2205: Gianantonio Rosti

Comparative *in Vitro* Cellular Data Alone Is Insufficient to Predict Clinical Responses and Guide Choice of BCR-ABL Inhibitor to Treat Imatinib-Resistant Chronic Myeloid Leukemia

Background: Recently, Redaelli et al (*J Clin Oncol.* 2009;27:469) compared the *in vitro* inhibitory activity of imatinib, dasatinib, nilotinib, and bosutinib against 18 mutant forms of BCR-ABL (expressed in transfected Ba/F3 cells) associated with imatinib resistance and proposed a chart to assist in the selection of second-generation tyrosine kinase inhibitors (2TKIs) for the treatment of imatinib-resistant CML associated with mutations. However, the predictability of this chart has neither been clinically evaluated nor does it take into account other important clinical factors (e.g. pharmacokinetics (PK)/pharmacodynamics) that may impact response rates to 2TKIs in the presence of mutations. The purpose was to assess the impact of 2TKIs' *in vivo* plasma levels on the *in vitro* GI₅₀ data, and to determine if *in vitro* GI₅₀ data with or without plasma levels correlates with observed clinical responses in imatinib-resistant patients (pts) with mutations.

Methods: To enable appropriate comparison of the activity of 2TKIs against specific mutations we modified the original *in vitro* GI₅₀ data by adjusting it to include an estimate of *in vivo* C_{max} exposure data for each 2TKI. Further refinement was achieved by calculating the C_{max}/GI₅₀ values for each agent and normalizing these against imatinib vs *wild-type* BCR-ABL. To assess the correlation between patient response and *in vitro* GI₅₀ data, the previously published CCyR rates for patients with specific mutations were plotted according to *in vitro* GI₅₀ values alone and against the adjusted C_{max}/GI₅₀ values.

Results: The adjusted C_{max}/GI₅₀ data suggest that nilotinib delivers the most potent inhibition of most BCR-ABL mutations *in vivo*, with dasatinib being the next most potent. However, when either *in vitro* GI₅₀ data alone or the modified C_{max}/GI₅₀ data are considered, there is poor correlation of clinical responses to both nilotinib and dasatinib against several of the mutations *in vivo* (Figure). Overall, activity of 2TKIs against all mutations was less than expected based on original *in vitro* GI₅₀ or C_{max}/GI₅₀ calculations of systemic exposure. For example, the G250E mutation has similar systemic exposure to nilotinib as the F359V mutation as indicated by C_{max}/GI₅₀, but substantial differences are observed in the CCyR rate (60% vs 0%). For dasatinib, the same was observed for the F317L and L248V mutations which have similar exposures to dasatinib but have different CCyR rates (7% vs 41%). Similarly, several mutations with comparable exposure to nilotinib and dasatinib had substantial differences in CCyR rates, suggesting that other factors were influencing responses. For example, the G250E mutation was considered moderately sensitive to both nilotinib and dasatinib based on the adjusted C_{max}/GI₅₀; however, CCyR rates on nilotinib were much higher (60%) compared with dasatinib (34%). Similarly, the E255K mutation was considered moderately sensitive to both agents based on the adjusted C_{max}/GI₅₀; however, CCyR rates on dasatinib were much higher (38%) compared with nilotinib (13%).

Conclusions: This analysis illustrates the limitations of *in vitro* inhibition data alone or in combination with PK exposure data in the selection of 2TKI therapy for imatinib-resistant patients with mutations. The current analysis still does not consider parameters such as protein binding and intracellular influx/efflux, among a variety of other clinical factors that could further influence response rates. This tool is also not useful for patients with mutations of unknown *in vitro* sensitivity, which may represent 15% of all patients with mutations. Currently, clinical responses remain the best approach for selection of 2TKIs in patients with mutations, with only a small subset of mutations having low sensitivity



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mutations existing for each 2TKI. Other factors, such as patient medical history, comorbidities, and the agents' safety profiles, are also important in selection of 2TKIs.

ASH-Abstract 510: Pierre Laneuville

Impact of Allogeneic Stem Cell Transplantation as Salvage Therapy After T315I Mutation Detection in CML and Ph+ALL

Background: The development of a BCR-ABL T315I mutation is associated with a poor prognosis and limited therapeutic options. The impact of the mutation on the outcome of stem cell transplantation (SCT) is unknown.

Aim: To describe the overall survival (OS) of CML patients in any phase and Ph+ ALL patients who received an allogeneic SCT after developing a T315I mutation after exposure to tyrosine kinase inhibitors (TKI).

Methods: We conducted a retrospective, multi-center observational study of 222 CML and *de novo* Ph+ ALL patients who developed a T315I mutation between 1999 and 2008. Data from the medical records of 33 patients (15% of all patients in the registry) from 9 countries (USA, France, Italy, Germany, Denmark, Singapore, and the UK) who received an allogeneic SCT after T315I mutation detection were included in this study.

Results: At the time of diagnosis, the median age was 39 years (range, 16-67); 70% were male; 26 patients were in CML CP, 1 in CML AP, 2 in CML BC, and 4 had Ph+ ALL. The median time between diagnosis and TKI treatment start was 3 months (range, 0-125), between diagnosis and T315I mutation detection was 28 months (range, 3-131), and between TKI treatment start and T315I mutation detection was 19 months (range, 2-64). Five (15%) patients had TKIs as frontline therapy. At the time of T315I detection, 10 patients were in CML CP, 7 in CML AP, 12 in CML BC, and 4 had Ph+ ALL. Hydroxyurea (alone or combined with other treatments) was the most common 1st line treatment (55%) after T315I mutation detection. The median time from T315I mutation detection to SCT was 3 months (range, 0.3-28). At the time of transplant, the median age was 42 years (range, 22-68); 8 patients were in CML CP, 7 in CML AP, 14 in CML BC and 4 had Ph+ ALL; 32 patients received 1 SCT and 1 received 2 SCTs after T315I mutation detection. The source of stem cells was peripheral blood (53%), bone marrow (35%), cord blood (6%), and unknown (6%). 82% were matched donor and 18% were unmatched. The median follow-up time from SCT was 7 months and 15 (55%) patients had died by their last follow-up. The OS of CML CP and CML AP patients was much better than CML BP and Ph+ ALL patients (Fig. 1; logrank, $p=0.050$). The 1-yr OS rates (95% CI) from SCT were 69% (21-91%) for CML CP, 71% (26-92%) for CML AP, 16% (3-39%) for CML BC, and 33% (1-77%) for Ph+ ALL; and the 3-yr OS rates (range) was 69% (21-91%) for CML CP, 71% (26-92%) for CML AP, 0 for CML BC, and 0 for Ph+ ALL.

Conclusion: These results suggest that the survival of patients harboring a T315I mutation and treated with allogeneic SCT is dependent on the disease phase at the time of SCT. SCT is the treatment of choice for these CML patients, particularly those in CP and AP.

ASH-Abstract 645: Franck Emmanuel Nicolini

BCR-ABL Derived Peptide Vaccine in Chronic Myeloid Leukemia Patients with Molecular Minimal Residual Disease During Imatinib: Interim Analysis of a Phase 2 Multicenter GIMEMA CML Working Party Trial



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Introduction: Imatinib (IM) 400mg daily is the standard treatment for chronic myeloid leukemia (CML) patients and a complete cytogenetic response (CCyR) is achieved in the majority of patients within one year of treatment. In addition, a considerable number of patients reach a major molecular response (i.e BCR-ABL/ABL ratio <0.1%) but BCR-ABL transcript is still measurable in most of treated patients revealing the persistence of a minimal residual disease (MRD). In a previous small pilot study, vaccinations with p210 b3a2-derived fusion peptides in IM treated CML patients appeared to induce both a peptide specific immune response and a reduction of residual disease surviving IM.

Methods: To investigate the efficacy of this immune based targeted approach in a larger cohort of patients we designed a phase 2 multicenter study (GIMEMA CML0206) employing 5 p210 b3a2-derived peptides (CMLVAX100 vaccine) in CML patients with at least 18 months of IM treatment and persistence of molecular residual disease. Each vaccination consisted of CMLVAX100 plus 2 doses of GM-CSF as immunological adjuvant. Treatment schedule included 6 biweekly vaccinations (immunization phase) followed by 3 monthly boosts (reinforcement phase) and 2 tri-monthly boosts (maintenance phase). The primary endpoint of the trial was to assess the rate of response (patients showing a reduction by at least 50% of peripheral blood BCR-ABL/ABL ratio compared to the individual prevaccine level) evaluated after immunization and reinforcement boosts (evaluation after 6 months,) and persisting at the 9th month (after 10th vaccination). Secondary endpoints included the rate of undetectable transcript at any time after immunization and the rate of peptide-specific immune response induced by the vaccinations.

Patients population: At present 57/69 planned patients have been enrolled and 43/57 are evaluable for response. Twentyseven are males and 16 are females with a median age of 56.5ys (range 29-78). At diagnosis, 25/43 (58%) patients presented with low, 15/43 (35%) with intermediate and 3/43(7%) with a high Sokal risk. Twenty-one out of 43 patients (49%) started standard IM treatment while in late chronic phase (CP) after a median time from diagnosis of 29 months during which they mainly received alpha interferon therapy. On the contrary 22/43(51%) patients started IM immediately after diagnosis. All patients entered the vaccination protocol after at least 18 months of IM treatment and the median time of exposure to this tyrosin kynase inhibitor before peptide vaccination was 54 months (range 23-100). All patients had obtained a CCyR before entering the study (after a median time of 6 months of IM treatment) and were still in CCyR at enrollment with a median duration of CCyR of 47 months. All patients started vaccination with persisting measurable molecular disease in peripheral blood (any level of BCR/ABL transcript).

Results: Current interim analysis shows that vaccinations (a total of over 400 shots) were very well tolerated, with CMLVAX100-GMCSF toxicity consisting exclusively of some redness and itching at the site of injection and with only 4/43 patients (9%) experiencing a mild fever. Regarding immune response induced by vaccination, 29/43 patients (67%) showed a significant in vitro b3a2-peptide-specific CD4+ T cell proliferation. With respect to MRD response, we observed a reduction of at least 50% of pre-vaccine BCR-ABL/ABL values after 6 months of treatment (i.e. after 9 vaccinations) in 22/43 (51%) patients and the reduction was confirmed in 14/29 (48%) patients who reached the 9th month evaluation (i.e. after 10 vaccinations); 14/43(32%) patients had at least one documented undetectable transcript during this time period. In 2/43 patients we observed a significant raise of BCR-ABL transcript level, after 3 and 18 months from starting vaccinations with subsequent loss of CCyR.

Conclusions: CMLVAX100 vaccine appears to induce a reduction of long lasting molecular MRD surviving IM in about half of vaccinated CML patients, thus confirming preliminary results. If this BCR-ABL-specific immune control of MRD will have a substantial impact on the rate of BCR-ABL mutations, disease evolution and ultimately survival needs longer observation time to be determined.

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Glossary

AE = Adverse Events
CP = Chronic Phase
AP = Accelerated Phase
PFS = Progression Free Survival
CyR = Cytogenetic Response
CCyR, CCgR = Complete Cytogenetic Response
MMoIR = Major molecular response
CMR = complete molecular remission
UMRD = Undetectable minimal residual disease
IFN = Interferon
IM = Imatinib
Pts = Patients