Adherence in Chronic Myeloid Leukemia: Results of a Patient-driven Pilot Survey

Optimal adherence to oral cancer therapy is of key importance to maximise treatment effectiveness in patients. With the advance of molecular target therapies, cancer treatment in more and more indications is transforming from in-hospital care towards oral treatment in an outpatient setting. With cancer becoming a chronic disease, patients are often required to take the drug indefinitely on a daily basis. Ensuring an optimal adherence to treatment over the long-term period could be a challenge. As data on the driving factors of non-adherence in oncology is scarce, a pan-European workgroup of the CML Advocates Network has conducted a pilot study which has unveiled differences of non-adherence between countries, administration types and use of adherence tools in Chronic Myeloid Leukemia. This pilot study has provided the groundwork for a larger global adherence study that is currently ongoing in 12 languages.

Background
Chronic Myeloid Leukemia (CML) has been pioneering targeted therapies in cancer, and since Imatinib’s broad availability in 2001, the effect of intentional and non-intentional non-adherence has been observed. Noens et al. (2009) first demonstrated that non-adherence to Imatinib is very common and associated with poorer response to treatment. More recently, Marin et al. (2010) found a correlation between low adherence rate (less than 90%) and the six-year probability of achieving a major molecular response (MMR). In addition, non-adherence was found to be the main reason for losing response to CML treatment. These studies emphasise that strict adherence to the prescribed Imatinib dose is key to ensuring treatment effectiveness in patients with CML.

There is not much literature on potential reasons for non-adherence to oral anti-cancer treatments (Ruddy, 2009). Even less data is available on reasons why CML patients might be non-adherent to Imatinib therapy (Breccia, 2011; Eliasson, 2011). A number of factors may influence compliance to oral medication regimens (Partridge et al., 2002). These not only include treatment-related aspects but also individual patient characteristics and personal factors (Ruddy et al., 2009) as well as patient education, supporting self-management of patients and engaging their social network (EBMT Nurses Group, 2011). A recent study has also revealed that only 53% of CML patients reported strict adherence, with adherence being influenced by the availability of patient information, social support and concomitant drug burden (Efficace et al., 2012).

Both intentional and non-intentional non-adherence in CML are very common, but so far, the reasons, as well as the feasibility of supportive adherence tools, have not been investigated in depth.

For this reason, the CML Advocates Network, a global network of 68 leukemia patient advocacy groups in 55 countries, has run a pilot survey to gain greater understanding of CML patients’ attitudes and behaviours surrounding adherence, and to develop the questionnaire for a larger study to ultimately support physicians and patients to improve compliance and to develop adherence tools. Given the limitations of a pilot survey with small participant numbers, the primary objective was to confirm the accessibility and usability of the questionnaire in anticipation of a broader, global survey.

Methodology
The pilot survey was provided in eight languages: Czech, Dutch, English, French, German, Hebrew, Italian and Polish. The questionnaire was developed by patient advocates and CML experts with in-kind logistical support from Bristol-Myers Squibb. Local CML patient advocacy groups disseminated the online questionnaire, based on a SNAP Surveys technical survey platform, to 10-20 CML patients per country. The survey data was compiled and analysed by an independent statistician. To determine whether the pilot survey measures are reliable, Cronbach’s alpha was employed to assess the consistency and reliability of the data results across the survey. A Cronbach’s alpha of 0.81 was produced, indicating an expectation of CML duration to be strongly associated with CML medication duration. This suggests that there is some level of reliability and consistency within the survey. Given the pilot survey’s design and distribution methods, the results are biased as the recruitment addressed rather educated, informed, younger, active patients who are online.

Demographics
In total 150 total online responses from 10 different countries were received over a period of two weeks. Austria (n=1), Czech Republic (24), France (21), Germany (25), Israel (25), Italy (19), Netherlands (18), Poland (11), Switzerland (1) and United Kingdom (5). The responses reflect the general CML patient demographics, with the majority (96%) of patients having CML in chronic phase, a relatively even split between male (46.3%) and female (53.7%). The average age of respondents was 51 years.

Results
Of note is that the pilot survey was not powered to be statistically significant. The pilot was designed to confirm the usefulness of the questionnaire and to develop indicators for an upcoming broader, statistically significant research work. However, the pilot survey already indicates that there might be substantial differences in adherence across countries. When asked whether patients missed at least one dose within the past month, non-adherence rates varied from...
18% (Poland) to 33% (Netherlands). Self-reported overall adherence in general was even lower in most countries, with 8% (Germany) to 36% (Poland) of patients claiming to take their medicines strictly as prescribed (see Figure 1). Interestingly, patients tend to wrongly estimate their own adherence, as evidenced in the difference between patients’ reported perception of their own adherence behaviour and the reported instances of actual missed doses.

In 2009, three tyrosine kinase inhibitors were approved therapies: Imatinib, which was the gold standard for first-line CML treatment and is usually administered once daily without having any food effects. So-called approved second-generation drugs were Nilotinib, which is taken twice daily with two hours fasting before and one hour after, and Dasatinib, a once-daily oral drug without food effects. By the time of the survey, the second-generation drugs Nilotinib and Dasatinib were usually administered as a second-line treatment after Imatinib failure or intolerance, but not as a first-line treatment. Given administration regimen, side-effect profiles and the psychological impact of first-line failure may both be interesting influence factors of adherence, so the survey looked at differences in adherence between these types of treatments.

The majority of respondents were taking Imatinib (72%), while fewer were taking a second-generation tyrosine kinase inhibitor (26%). There was no difference in overall adherence between the medications (25% adherence on Imatinib, 23% on second-generation treatment). However, the reasons for missing doses appear to vary by treatment and intention: 24% of Imatinib patients missed the doses accidentally, while only 15% of patients treated with second-generation drugs forget to take their pills. In contrast, only 7% of Imatinib patients but 21% of patients with second-generation drugs consciously decided not to take their drug as prescribed. As forgetting to take the medication is the most common reason for non-intentional non-adherence, a large proportion of patients is interested in tools to improve their adherence. Patients were asked whether they use, or would use if available, alarm clock reminders, mobile phone-based reminders, reminder phone calls, email reminders, reminders from doctors during appointments, reminders from family members, magnets at refrigerators or medication dispensers.

As Figure 2 reveals, family members reminding patients to take their medicine (41%), medication dispenser boxes (36%) and SMS reminders (19%) are the most frequently used tools today. An additional 11-20% of patients would want to use these reminder tools if they were available to them. At the same time, there is a large proportion of patients that reject these tools, with email reminders (92%), phone calls (83%), health professionals and alarm clocks (76%) being least popular. This may indicate that a significant proportion of patients do not want to be reminded in their daily life that they have cancer.

### Discussion

The pilot survey indicates that a significant proportion of patients tend to overestimate their own adherence to therapy. In other words, their perceived adherence differs from how often they report missing or skipping doses. Also, the difference on intentional and non-intentional non-adherence between first- and second-generation CML drugs, and subsequently the different motivation for adherence between first- and second-line treatment, prove the need for further needs for research on the drivers of non-adherence. A significant proportion of patients use tools to increase their adherence, but there is a large group that feels these tools intrusive.
tools are not yet available to them. However, there is no single adherence tool for everyone, which is demonstrated by a large rejection rate of all tools in some groups. A more statistically significant survey may provide insights into which tools might work best for certain subpopulations within the patient community.

Overall, the pilot survey has strengthened our thinking that there are certain country-specific characteristics, drug- and disease-phase-related factors, as well as different drivers and tools influencing intentional and non-intentional non-adherence.

The next phase of this research work, run by a workgroup of eight European CML patient advocates and two CML experts from European countries, is currently underway. The survey is conducted online and offline and intends to have at least 2000 respondents. The questionnaire was deployed on 22 September 2012 in 12 languages (English, Spanish, German, French, Italian, Portuguese, Finnish, Dutch, Czech, Hebrew, Polish and Russian), with more than 1600 patients from 73 countries having responded in the first eight weeks. To minimise the online recruitment bias, clinicians in three national CML research groups - GIMEMA in Italy, FI LMC in France and the German CML Study Group - are cooperating with the CML Advocates Network to distribute hard-copy questionnaires to CML patients in addition to the online survey. Results of the study are expected to become available in spring 2013.

References
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Acknowledgements
The pilot survey on CML Adherence was developed and run by a workgroup of the following CML patients and experts:

- Giora Sharf, Chair of the Adherence Workgroup / CML Advocates Network / Leukemia Patient Advocates Foundation, Switzerland / Israeli CML Patients Organisation
- Jan Geissler, CML Advocates Network / Leukemia Patient Advocates Foundation, Switzerland / LeukaNET, Germany
- Felice Bombaci, Gruppo AIL Pazienti Leucemia Mieloide Cronica (Italy)
- Mina Daban, President, Leucèmie Myéloïde Chronique France (France)
- Anna Span, Editor LeukoNiews, Stichting Contactgroep Leukemie (Netherlands)
- Audrey Denis, Secretary, Vivre Avec La LMC (France)
- Tony Gavin, Director of Campaigning and Advocacy, Leukaemia CARE (UK)
- Dr Lina Eliasson, Research Associate, Centre for Haematology, Division of Experimental Medicine, Imperial College London (UK)
- Dr Fabio Efficace, Chairman GIMEMA Working Party on Quality of Life (Italy)
- Dr Joëlle Guilhot, Biostatistics, INSERM CIC 802, University Hospital of Pottiers (France)

The workgroup received in-kind logistical support from Bristol-Myers Squibb.

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The patient-run CML Advocates Network connects 68 leukemia patient organisations in 55 countries on all continents. The network facilitates the sharing of best practice in CML patient advocacy, organizes an annual Global CML Advocacy Summit, and collaborates with researchers and clinicians.