these two cell types in those contexts. It will also be essential to extend that study to other antigens that have been described as potential targets for allo-reactive $CD4^+$ T cells to have a clearer picture of the role of this co-ordinated response post HSCT. Moreover, additional studies will also be needed to understand how this co-ordinated response between T cells and B cells is initiated in transplanted patients.

In summary, Kremer *et al*. reported for the first time a co-ordinated response between allogeneic T cells and autologous B cells against a specific antigen, PTK2B, following DLI after allogeneic HSCT in a patient relapsing from CML. As we gain a better understanding of the key roles of T cells in immunity after allogeneic HSCT, further studies aiming to evaluate the role of reactive antibodies in the immune response in patients post HSCT or post DLI will be key. Such studies will provide a better understanding of the roles of $CD4^+$ helper T cells and how different cell types co-operate in this immune response.

Aurore Saudemont is a Senior Research Assistant at the Anthony Nolan Research Institute and University College London. Her main field of interest is immunotherapy, cord blood and hematopoietic stem cell transplantation. Alejandro Madrigal is the Scientific Director at the Anthony Nolan Research Institute and University College London. His main field of interest is hematopoietic stem cell transplantation, cord blood, immunotherapy, HLA and immunogenetics.

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Moving towards patient-centered decision-making in chronic myeloid leukemia: assessment of quality of life and symptom burden

Michele Baccarani,[1] Fabio Efficace,[2]* and Gianantonio Rosti[1]

[1]Department of Specialistic, Diagnostic and Experimental Medicine, S.Orsola-Malpighi Hospital, University of Bologna, Bologna; and [2]Data Center and Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA), Rome, Italy

E-mail: f.efficace@gimema.it *doi:10.3324/haematol.2013.094045*

Chronic myeloid leukemia (CML) was a fatal disease for almost all patients until the introduction of allogeneic stem cell transplantation (SCT) and of interferon-alfa (IFNα). However, these were of benefit only for a minority of patients.[1] The targeted therapies, first imatinib, then the other tyrosine kinase inhibitors (TKIs), have dramatically changed the scenario. The scientific community enjoyed the expected normal life span for most TKI-treated CML patients, considering the extrapolation of the survival curves.[2,3] More recently, the scientific community is focusing on the importance of achieving a deeper and deeper response that can only be measured through molecular methods.[4-7] It is expected and predicted that the deeper the response the better the outcomes, where, today, outcome is considered in terms of overall survival, while tomorrow it is likely to be treatment-free survival.[8,9] Accordingly, the choice of treatment has traditionally been based on efficacy criteria including rate, time and depth of response.[8,9] This policy has sound clinical bases because CML is a cancer, and the ultimate objective is to provide a cure. Consequently, outcome assessment in CML has, till now, been heavily disease oriented. While this policy must be implemented, we should also bear in mind the fact that the disease course and treatment approaches have radically changed over the last decade. Currently, based on at least ten years of experience with imatinib and on the availability of other TKIs, less than 20% of patients are still at risk of dying of leukemia, less than 20% can achieve a treatment-free remission, and more than 60% are facing a situation of chronic, life-long treatment.[9]

For many years, we have dedicated our efforts and resources to the evaluation of the response, achieving remarkable success in the standardization of the methods used to assess minimal residual disease (MRD), and widespread agreement on the evaluation of treatment

response and on treatment recommendations.[7-9] While biochemical or laboratory abnormalities can be recorded objectively, clinical side-effects, for example, are typically recorded and collected by health care professionals (HCPs) who interpret and evaluate reports from the patients themselves. Probably only a few side-effects, like skin rash, alopecia, edema and fluid retention, can really be evaluated directly and, to a certain extent, objectively by the investigators. All available TKIs for first-line therapy, that is imatinib (i.e. 1st-generation TKIs) and dasatinib or nilotinib (i.e. 2nd-generation TKIs), have side-effects that one should consider when deciding which therapy is best for the individual patient. However, some side-effects can be more frequent with a given TKI. As an example, while fatigue has been reported to be similar amongst the three TKIs,[10] others, such as rash, have been reported to be worse with both 2nd-generation TKIs.[11,12] In any case, in most studies, recording and assessing the type, the intensity and the duration of the side-effects are not planned, apart from formal reference to some internationally recognized scoring systems (e.g. NCI, SWOG). The data obtained with this methodology can be very different, even in company-sponsored, registrative studies.

Just to illustrate how challenging it is to draw conclusions with regards to toxicity data, we report (for descriptive purposes only) five studies,[12-16] all in newly diagnosed, chronic phase, CML patients treated with imatinib 400 mg once daily (Table 1). Interestingly, the reported proportion of patients with any grade fatigue and muscle pain ranged from 8% and 34% (ENESTnd)[14] to 50% and 95% (IRIS),[13] respectively. Similarly, marked differences were also reported for all the other major groups of side-effects (Table 1). The purpose of these studies, that tested imatinib *versus* other drugs, was to compare the type and

Table 1. Percentage of newly diagnosed, chronic phase, CML patients who were reported to complain of the listed side-effects with imatinib.

Side-effects (all grades)	Pivotal trials comparing imatinib (400 mg once daily) *versus* IFNα or 2nd-generation TKI				
	IRIS	ENESTnd	DASISION	SWOG	BELA
FATIGUE (including asthenia, depression)	50	8	10	54	12
MUSCLE PAIN (including cramps, inflammation, spasm, myalgia)	95	34	43	44	50
JOINT/BONE PAIN (including arthralgia)	28	0	0	0	26
EDEMA (including peripheral edema, superficial edema, eyelid edema, periorbital edema, face edema, fluid retention, weight gain)	68	39	86	50	38
NAUSEA and VOMITING (including dyspepsia)	77	45	30	71	68
DIARRHEA	33	21	17	41	21
ABDOMINAL PAIN	27	0	0	0	5
SKIN RASH (including pruritus)	41	16	17	28	15
HEADACHE	31	8	10	19	8
SUM	**450**	**171**	**213**	**307**	**243**

The data are from five prospective, company-sponsored, GCP, CRO-monitored studies testing imatinib versus *IFNα plus low-dose arabinosyl cytosine (IRIS)*[13] versus *nilotinib (ENESTnd)*[14] versus *dasatinib (DASISION and SWOG)*[12,15] and versus *bosutinib (BELA).*[16] *In the original reports, the figures represented the proportion or percent of patients complaining of each side-effect. Of course, in all studies, the sum of the figures was higher than 100% because many patients complained of more than one side-effect. The differences among the totals, and among each side-effect, underscore the variability in collecting and reporting the side-effects, although all patients were treated frontline with the same dose (400 mg once daily) of imatinib. The differences among studies are quite impressive. The difference is also impressive for grade 3/4 side-effects: from a total of 18.1% in IRIS*[13] *to a total of 3.6% in ENESTnd*[14] *(data not shown in the Table).*

Table 2. Summary of basic characteristics for the EORTC QLQ CML-24 and the MDASI CML questionnaires.

Questionnaire	Main purpose	N. items	Time recall	Domains/scales measured	Scoring and Interpretation
E ORTC QLQ CML-24*					
Website for requesting permission to use: *http://groups.eortc.be/qol/modules-development-and-available-use*	Assess Quality of Life in CML Patients	24	Patients are asked to evaluate their Quality of Life during the last week	*-Impact on daily life;* *-Impact on worry/mood;* *-Body image problems;* *-Symptom burden;* *-Satisfaction with care and information;* *-Satisfaction with social life*	Score ranges between 0 and 100 for all scales (except for two†) with higher scores indicating worse outcomes.
MDASI CML					
Website for requesting permission to use: *http://www3.mdanderson.org/depts/symptomresearch/*	Assess the severity of symptoms and the impact of these on daily functioning in CML patients	26	Patients are asked to evaluate their symptoms during the last 24 hours	*-Symptom severity* *-Impact of symptoms on daily functioning*	Score ranges between 0 and 10; higher scores indicate increased symptom burden

**This questionnaire should be used in conjunction with the EORTC QLQ-C30 to comprehensively assess HRQOL in CML patients. †For the following two scales:* satisfaction with care and information *and* satisfaction with social life. *Higher score indicates better outcomes.*

severity of the side-effects, but not the duration, between two different drugs. However, the reported data in the imatinib arm differed so greatly that it was difficult to assess the imatinib-related burden of symptoms, and can raise doubts as to the value of the comparison. Limitations of standard physician-reported toxicity with regards to the documentation of drug safety have been acknowledged[17] and have prompted the National Cancer Institute (NCI) to create a version of the NCI's Common Terminology Criteria for Adverse Events (PRO-CTCAE) that can be completed by patients themselves, providing direct patient feedback on their experience of their symptoms during treatment.[18]

In the context of CML treated with long-term TKI therapy, it has been shown that even low-grade side-effects can substantially impact quality of life (QoL).[19] Also, a recent CML study has shown that physicians tend to under-estimate symptom severity and over-estimate the overall health status of their patients.[20] This evidence underscores the need for directly asking patients themselves about their disease and treatment burden, and also confirms, with empirical data, the previously raised concerns about the current practice of assessing intolerance to TKIs (i.e. not patient-reported).[21]

While major stakeholders are pointing out the importance of patient-centered outcome research (PCOR) in medicine,[22] evidence-based data in CML are lacking.[23] This is striking considering the great potential that patient-reported data could have to facilitate clinical decision-making in the current CML arena, where treatment decisions are often highly challenging. We believe that the lack of CML-specific instruments for patient-reported outcome (PRO) is the major cause of the lack of PCOR in CML. The development of methodologically sound PRO instruments requires major financial investment and research efforts as it has to comply with several and rigorous methodological criteria. The patient's unique viewpoint on the burden of disease and the effect of treatment on his/her life can only be known through the use of such instruments and cannot be otherwise inferred from other indirect measures (e.g. physician-reported toxicity).[24]

Use and area of applications of PRO instruments in CML

The good news for the CML community is that two CML-specific instruments, the EORTC QLQ CML-24 and the MDASI-CML, have recently been developed and published in full. Both questionnaires have followed high-quality methodological criteria recommended for the development of PRO measures. The EORTC QLQ CML-24 was developed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group.[25] This questionnaire has been devised to supplement the EORTC QLQ-C30 to comprehensively assess QoL in CML patients. The development of the EORTC QLQ CML-24 involved overall 655 CML patients on treatment with various TKIs from 10 different countries (in Europe, the USA and Asia).[25] A major strength of this tool was its international development, which ensured satisfactory validity and applicability across multiple languages and cultures. Questionnaire items were tested in a pilot study, and debriefing cognitive interviews were held simultaneously in different cultural contexts. This has important implications for using this tool in CML international studies.

The MDASI-CML was developed at the MD Anderson Cancer Center (Houston, TX, USA) and involved 187 patients on treatment with different TKIs.[26] Unlike the EORTC QLQ CML-24, this questionnaire has been devised to evaluate symptom burden (rather than QoL). The strength of this tool was the longitudinal analysis performed in the development process, which further supported validity data. Basic information on scoring and interpretation of both questionnaires are summarized in Table 2.

Two broad areas can be identified for the implementation of these measures: clinical research and routine clinical practice. With regard to clinical research, the introduction of such measures would be of particular value in observational studies and randomized clinical trials (RCTs). Just to illustrate this, in this latter case, it would be used as a study end point to weigh the potential clinical benefit of a new therapeutic approach against risk and toxicities from the patient's perspective. If PRO is to be used in an RCT setting, this assessment should be carefully planned *a priori* in the research protocol and a number of issues should be examined in detail. Typically, these issues would be addressed in a dedicated PRO chapter in the protocol. The selection of the most appropriate PRO questionnaire/s to be used is an important issue and should always be guided by a specific rationale. However, this is just one of several other issues that should be considered in the protocol. Other topics include: i) stating the specific PRO hypothesis being tested; ii) the methods for data collection; iii) management of missing data; and iv) a statistical analysis plan. A naïve approach to PRO implementation in RCTs is unlikely to generate solid data that could be used to facilitate clinical decision making therefore methodological rigor is essential.[27] To date, several guidelines are available to assist investigators in the planning, conducting and reporting of PRO in RCTs, including the recently issued PRO-specific CONSORT standards.[27]

Another important area of application of PRO instruments would be their implementation in routine practice. Previous research has shown that the use of PRO instruments in clinical practice is feasible and can facilitate discussion of health problems between patients and physicians.[28] Systematic use of these questionnaires in follow-up visits might help physicians in the early identification of those CML patients for whom the given therapy is particularly burdensome, and this would enable the timely consideration of alternative treatments. Guidelines and suggestions for implementing PRO instruments in clinical practice are available.[29]

To conclude, while continued efforts towards the definitive cure of CML are necessary, integration of PRO data with clinical and laboratory information (e.g. MRD) is also now needed to capture the real patient burden of treatment and to facilitate a transition to a more patient-centered decision-making approach.

Michele Baccarani is Professor of Hematology (retired) at the Universities of Trieste, Udine, and Bologna, Italy, and is Chairman of the ELN and GIMEMA Working Parties on chronic myeloid leukemia. His main field of interest is leukemia

and stem cell transplantation. Fabio Efficace is Head of the Health Outcomes Research Unit of the GIMEMA Data Center, Rome, Italy, and Chairman of the GIMEMA Quality of Life Working Party. His main field of interest is health outcomes research in oncology. Gianantonio Rosti is a hematologist at the Department of Hematology and Oncology of St. Orsola University Hospital, Bologna, Italy, and is Scientific Secretary of the GIMEMA Working Party on chronic myeloid leukemia. His main field of interest is leukemia and stem cell transplantation.

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