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Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia

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Philadelphia chromosome-positive (Ph$^+$) acute lymphoblastic leukemia (ALL) is a relatively uncommon disease. However, it accounts for about one quarter of adult cases of ALL. Due to the paucity of patients, randomized controlled trials of therapy are unusual. This, together with the fact that outcomes for patients with Ph$^+$ ALL treated with standard combination chemotherapy are poor, has led to novel therapies typically being adopted early, in some cases prior to their risks and benefits being completely understood. Indeed, our two front-running therapeutic additions to standard combination chemotherapy – myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) and tyrosine kinase inhibitors (TKI) (principally, at present, imatinib) have never been evaluated in randomized controlled trials. Early inclusion of unrelated donors as a source of stem cells for allogeniec HSCT has largely precluded future donor *versus* no donor analyses, such that the role of sibling donor allogeneic HSCT has only been evaluated formally in a limited fashion. In addition, the great success of imatinib in treating chronic myeloid leukemia was very quickly interpreted as being similarly relevant to Ph$^+$ ALL. Hence, studies in adult patients in which the drug imatinib was not included at all in any treatment arm became impossible to conduct. As a result, data indicating a benefit from imatinib have all been generated from historical comparisons, with not one randomized study of imatinib *versus* no imatinib having ever been conducted in *de novo* Ph$^+$ ALL. In this issue of *Haematologica*, another collaborative study of the role of imatinib in the therapy of Ph$^+$ ALL from the PETHMA and GETH groups is published.[1] This commentary gives a background to the current, standard management of Ph$^+$ ALL, to set the context for the new data from the CSTIBES02 study.

The role of allogeneic bone marrow transplantation

Ph$^+$ ALL responds to combination chemotherapy, although complete remission is significantly less likely after standard induction regimens than in Ph$^-$ ALL.[2] Combined with a short remission duration, there is a median event-free survival of 8 months; prognosis is poor. Five-year overall survival rates of between 10-20% are typical when treatment is chemotherapy alone.[3-8] For this reason, myeloablative allogeneic HSCT has been a promi-

nent focus in studies of Ph+ ALL. Many studies suffer from considerable selection bias, particularly when they only report results from patients who actually receive a transplant. For example, Laport *et al.*[9] reported a 10-year overall survival of 54% for patients with Ph+ ALL in first complete remission treated by sibling allogeneic HSCT. However the denominator from which this series of patients was selected for transplantation was unknown, so the relevance of this finding to a general population of patients presenting with *de novo* Ph+ ALL is not clear. The problem in generalizing the outcomes from transplant only studies is highlighted by the surprisingly low transplantation rate reported in the UKALL12/ECOG2993, the largest study of patients with Ph+ ALL.[10] In this study, all patients with Ph+ ALL were assigned to undergo allogeneic HSCT, using sibling or unrelated donors as a source of stem cells. However, only 28% of patients registered in the study actually received a transplant. Disease resistance or relapse prevented transplantation in many cases.

Limitations notwithstanding, the body of evidence has long been interpreted to indicate that, in appropriately selected individuals with Ph+ ALL, treatment with allogeneic HSCT results in an apparently better disease-free survival or overall survival than would be expected from treatment with chemotherapy alone. The strongest support for this conclusion comes from two studies. In the LALA94 study, Dombret *et al.*[8] demonstrated that, among patients eligible for HSCT, having an allogeneic donor was independently predictive of remission duration. In the UKALLXII/ECOG2993 study,[10] the overall outcomes for patients undergoing allogeneic HSCT (sibling donor, 44% overall survival at 5 years; unrelated donor, 36% overall survival at 5 years) were apparently considerably superior to those of patients receiving chemotherapy alone (19% overall survival at 5 years). A donor *versus* no donor analysis in this UK/US collaborative study was unable to reach the same conclusion as the French study, since many people in the no sibling donor arm underwent allogeneic HSCT using stem cells from an unrelated donor. Hence, the 5-year overall survival of patients with a sibling donor was non-significantly better (34%) than that of patients with no sibling donor (25%). It is important to keep in mind that, when adjustment was made for sex, age and presenting white cell count in patients participating in the UKALLXII/ECOG2993 study, as well removing from the analysis chemotherapy-treated patients who had relapsed or died before the median time to allogeneic HSCT, only relapse-free survival remained significantly superior in those undergoing receiving a transplant. This suggests that although the benefit of allogeneic HSCT in the population presenting with *de novo* Ph+ ALL, taken as a whole, is real, it is modest in magnitude.

In childhood ALL, t(9,22) is one of the few remaining indications for allogeneic HSCT. Studies have confirmed the apparent superiority of sibling allogeneic HSCT over chemotherapy alone.[11] Given the rarity of the disease in childhood, large international co-operations have been required for these studies and the evaluation of allogeneic HSCT has been by comparison of treatment received. Nonetheless, in the largest study in children to date, the magnitude of the difference between allogeneic HSCT (approximately three quarters of patients were long-term disease-free survivors) and chemotherapy alone (only one quarter of patients were disease-free survivors) was compelling.[12] As a result of high treatment-related mortality, there has been less evidence of the benefit of unrelated donor allogeneic HSCT for children and there is more caution about applying this therapy in such patients than in adult patients.[12]

Clearly, in view of the toxicity of myeloablative allogeneic HSCT, it is very reasonable to examine reduced-intensity conditioning transplantation as an alternative way to supply a graft-versus-leukemia reaction. Low levels of residual disease at the time of transplantation would likely be of greater importance in this setting and one can hypothesize that this is much more likely to be achieved with TKI, although this has not been formally studied. Reduced-intensity conditioned allogeneic HSCT has been described in several retrospective series, all of which included patients with both Ph+ and Ph- ALL.[13,14] Inevitably, since this is a relatively new approach to the treatment of ALL, series include patients beyond first complete remission. The largest series to date comprises 97 patients reported to the EMBT registry who received a mixture of conditioning regimens. Many received some form of T-cell depletion.[15] A 2-year overall survival of 52% for those transplanted in first complete remission was reported. This approach merits consideration, but careful prospective study is still required to define its role in Ph+ ALL.

In summary, Ph+ ALL is one of the few diseases in which hematologists have reached almost unequivocal agreement that a myeloablative allogeneic HSCT in first complete remission is the most appropriate therapy for both children and adults who are sufficiently fit and have a well-matched donor. However at a conservative estimate, approximately half of all patients receiving standard induction therapy without a TKI will never undergo transplantation, even if a donor is available. Relapsed and resistant Ph+ ALL is the predominant event preventing transplantation. Furthermore, myeloablative allogeneic HSCT, while having a highly significant effect on relapse in ALL, remains a dangerous treatment and the high mortality rate is delicately balanced against the benefits of the graft-versus-leukemia effect.[16]

The role of tyrosine kinase inhibitors

In a setting of a deadly disease for which the best available therapy is only applicable to a fraction of patients and is itself potentially lethal, novel agents specifically targeted to the molecular lesion, which are easily administered and of limited toxicity are almost too good to be true. Not surprisingly, TKI have been quickly studied and readily adopted in Ph+ ALL. Several studies have now reported early results of the addition of imatinib to combination chemotherapy.[17-20] A consistent feature of all these studies is the increased complete remission rate. Where relevant to the study population, the higher complete remission rate typically translates into an increased allogeneic transplant rate. However, in many ways the most impressive studies of the potential benefits of imatinib are those in older individuals who are destined to have poor outcomes with combination chemotherapy and are not eligible for allogeneic transplantation. In a study reported by

GIMEMA,[21] a combination of imatinib and steroids resulted in all patients (median age, 69 years) achieving hematologic complete remission, with a median survival from diagnosis of 20 months. Most patients were treated on an out-patient basis.

Interestingly, although we are now clear that imatinib can be safely and effectively combined with other chemotherapeutic drugs, it is far from clear whether and how it should be combined with allogeneic HSCT. The current working assumption is that best outcomes in Ph$^+$ ALL are achieved when TKI are used as a "bridge to transplant". However a recent provocative study of imatinib in childhood ALL has challenged this assumption. Ph$^+$ ALL accounts for only a small proportion of childhood leukemias, but a COG study managed to enroll 93 'children' (upper age limit, 21 years) in a study of step-wise addition of imatinib to blocks of chemotherapy, until the final cohort received imatinib with all blocks. Comparison with historical controls from previous COG studies suggested an enormous survival advantage for the patients treated with imatinib, but it is noteworthy that the historical controls included children treated over a long period in the past. Furthermore, the comparative survival curves highlighted the very short follow-up for the study cohort. This is particularly relevant since earlier studies examining the outcome of Ph$^+$ ALL evidenced the occurrence of late relapses in children treated with chemotherapy alone, whereas relapses following allogeneic HSCT typically occurred early or not at all.[11] In fact, the conclusions regarding allogeneic HSCT are controversial and of particular interest. Allogeneic HSCT was only permitted on protocol when a sibling donor was identified, making it possible to compare – by treatment received – the outcome of a group of patients who received chemotherapy in combination with imatinib but who did not proceed to transplantation. The outcomes at 3 years were not significantly different for those treated with chemotherapy plus imatinib (N=25) compared to those treated with allogeneic HSCT (N=21). There was also a relatively high rate of off-protocol use of unrelated donor allogeneic HSCT. The authors used these data to argue that imatinib/chemotherapy can replace allogeneic HSCT for children with Ph$^+$ ALL. Follow-up remains short and the study was not designed or powered to answer this question but it is a provocative and interesting issue and one that deserves due consideration.

In patients who have undergone allogeneic HSCT, it remains unclear whether imatinib should be given after the transplant and, if so, for how long. A German study in which all patients who became BCR-ABL-positive after HSCT were given imatinib suggested a benefit – there were some long-term responses in patients responding to imatinib in this setting.[22] Burke *et al.*[23] reported the outcomes of a small, retrospective, transplant-only series of adults, with some patients beyond first complete remission, who had received a variety of conditioning regimens and stem cells from various different sources. Those who received imatinib prior to bone marrow transplantation had apparently better overall, event-free and relapse-free survivals than those who did not. However a notable difference between the imatinib and non-imatinib groups was the significantly greater number of umbilical cord blood transplants in the imatinib group and the younger median age of the imatinib-treated group. Post-transplant imatinib was only given in two cases so its role was not assessable.

Despite these very encouraging reports on the short-term benefit resulting from the use of imatinib in Ph$^+$ ALL, emanating from many major national and co-operative groups, there is still little or no evidence of a long-term survival advantage from using imatinib. Indeed, there are some important limitations to the activity of the drug, which suggest that the benefits might be limited. Although BCR-ABL is necessary and sufficient for the development of chronic myeloid leukemia, this is not the case for ALL, since other kinases are involved in the development of Ph$^+$ ALL, particularly SRC kinases[24] which are not blocked by imatinib. In addition, there is increasing evidence of imatinib-resistant mutations in Ph$^+$ ALL, even at diagnosis.[25] It is also possible that patients who harbor imatinib-resistant clones are more likely to develop further mutations when second line TKI are used, although the data suggesting this were generated in a population of patients in whom the majority of patients had chronic myeloid leukemia and only a minority had Ph$^+$ ALL.[26]

Unlike in chronic myeloid leukemia, it is still not clear how best to evaluate response to imatinib in Ph$^+$ ALL. Studies in Ph$^+$ ALL in which BCR-ABL transcript levels were monitored and correlated with response and long-term outcome are not as straightforward to interpret as studies in chronic myeloid leukemia and no clear definition of an appropriate response has emerged. Furthermore, even in landmark studies in which imatinib and consolidation/maintenance chemotherapy was compared to imatinib and allogeneic HSCT, the investigators monitored residual disease by flow cytometry, rather than by BCR-ABL status, missing the opportunity to determine the role of BCR-ABL monitoring in the determination of outcome.[27] Among the cases in which BCR-ABL was monitored, Lee *et al.* showed that a 3-log reduction in transcript levels after the first month of imatinib therapy was a powerful predictor of a reduced risk of relapse.[28] In contrast, Yanada *et al.*, for the Japanese Adult Leukemia Study Group, who studied transcript number, rather than predefining a cut-off for response, reported no association between BCR-ABL negativity and long-term outcome.[29] The presence of imatinib-resistant mutations and their development during therapy may explain why initial molecular response might not be predictive of overall outcome. Pfeifer *et al.*[25] reported the presence at diagnosis of small Ph$^+$ clones with kinase domain mutations which were below the level of detection by direct cDNA sequencing. While initial response rates did not differ between individuals with and without these clones, relapse was considerably more frequent among patients presenting with the mutations.

Dasatinib is a more attractive candidate than imatinib for the therapy of Ph$^+$ ALL because of its broader spectrum of action, but it is more toxic. There is good evidence of activity in relapsed or resistant Ph$^+$ ALL.[30] Tolerability in the context of combination chemotherapy is less clear. Data indicating benefits in the therapy of *de novo* ALL are presently only available in abstract form. Impressively, all patients treated with dasatinib and steroids in an Italian

study achieved complete remission within 1 month of therapy. Dasatinib is currently being evaluated in combination with the hyperCVAD regimen. It appears tolerable; complete remission rates are approximately 90% and molecular responses have been observed. However, the significance of any given molecular response to dasatinib in terms of long–term outcome is, as yet, unclear.

In summary, cumulative evidence indicates that imatinib is a very valuable addition to induction therapy for Ph+ ALL. Imatinib certainly increases the ability of therapy to generate complete remissions and highly likely allows more patients to undergo allogeneic HSCT. However, it appears unlikely to represent a long-term curative option for patients with Ph+ ALL. Standard practice remains that imatinib be used from diagnosis, in combination with chemotherapy, in order to achieve a rapid response to facilitate early allogeneic HSCT which is presently considered to offer the best anti-leukemic activity .

This issue of Haematologica contains the report of a PETHEMA and GETH study on the role of imatinib in Ph+ ALL.[1] This small study aimed - in essence - to 'find out what happened' when adult patients with Ph+ ALL were given imatinib associated with chemotherapy during induction. Allogeneic HSCT was recommended for all patients and any number of donor sources was permitted. According to the protocol, imatinib was scheduled to be resumed after the transplant. The study showed a higher complete remission rate with the combination of chemotherapy and imatinib than in historical controls receiving chemotherapy alone. It also showed that a greater number of patients were able to undergo HSCT in first complete remission, again in comparison to the number of historical controls.

Although the study protocol called for imatinib to be administered continually for 1 year after the transplant, this was not often possible. The inclusion of an open spectrum of possible sources of stem cells /types of transplant (e.g. umbilical cord blood, reduced intensity conditioning) with different potentials for post-transplant complications makes interpretation of this situation problematic, due to the small numbers of patients studied. The value of imatinib post-transplant remains undetermined. However, it is telling for routine clinical practice that even in a small study, it was not pragmatically possible to administer imatinib post-transplant in many cases. Regarding overall outcome, the disease-free and overall survival rates at 4 years were both 30%, which is a rather disappointing outcome in the 'imatinib-era', Surprisingly, it compares unfavorably with the results of UKALL12/ECOG2993 in which overall survival rates for patients undergoing allogeneic HSCT in the 'pre-imatinib era' were 44% (sibling donor) and 36% (unrelated donor).

The data presented support the current approaches to the therapy of Ph+ ALL with imatinib and allogeneic HSCT. Although with longer follow-up than initial studies, the overall outcome of patients given combined treatment with imatinib and chemotherapy followed by allogeneic HSCT/imatinib treatment does not appear to differ substantially from what might be expected in the pre-imatinib era. These data are welcome and informative, but do not present any challenges to current practice. One can still conclude from this study that the overall value of imatinib in the long-term outcome of Ph+ ALL remains uncertain.

Residual issues in the therapy of Philadelphia chromosome-positive acute lymphoblastic leukemia

A number of very important questions remain about the role of our present therapies, standard combination chemotherapy, imatinib (or other TKI) and allogeneic HSCT, in the treatment of Ph+ ALL. It is clear that higher complete remission rates can be achieved by combining TKI with chemotherapy. Interestingly, some of the most impressive complete remission rates have occurred – with minimal toxicity – in cases in which a TKI was combined with a steroid alone. Is it possible that, if complete remission can be achieved more quickly and with less toxicity, allogeneic HSCT could be undertaken in a healthier patient with uncompromised organ function and a better performance status? If so, then perhaps the treatment-related mortality of what is undoubtedly the most potent anti-ALL therapy available could be reduced? By contrast, it is equally reasonable to suggest that because the risk-benefit balance of myeloablative allogeneic HSCT is so delicate, small improvements in outcomes in relation to imatinib or another TKI component of therapy may render allogeneic HSCT dispensable in the future. Since the predictive value of BCR-ABL status on outcome either pre- or post-transplantation remains unclear, there are still no clearly viable surrogate end-points for overall survival. Hence it will take a long time to answer these important questions in Ph+ ALL, particularly if small, descriptive phase 2 studies or modest trials focusing on a particular component of therapy remain the norm. We need to use the data we already have to plan bold but carefully designed phase 3 randomized controlled trials asking specific questions in respect of a sweeping approach to therapy and conduct a uniform set of molecular investigations in all study participants. This approach is vitally needed in Ph+ ALL. Due to the relative rarity of the disease, international collaboration is the only way to achieve this.

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Genetic lesions in chronic lymphocytic leukemia: what's ready for prime time use?

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Chronic lymphocytic leukemia (CLL) is a frequent CD5$^+$ B-cell neoplasia that involves peripheral blood, bone marrow, lymph nodes and other lymphoid tissues. The median age of patients at diagnosis of CLL is around 70 years old and the prognosis is extremely variable. In spite of some advances in its therapy, CLL continues to be incurable. Due to this fact, and to the prognostic heterogeneity of the disease, individual, risk-adapted therapies are needed.

A number of clinical parameters identified in the 1980s and 1990s, particularly clinical stages, enable a prediction of the clinical outcome of patients with CLL. These parameters do not, however, indicate which patients will have rapidly evolving disease and which will have stable