effects of these ribosomal defects on the cellular translation profile in T-ALL has still not been made. Moreover, it remains to be established whether these defects are promoting leukemia by altering the translational profile of the ribosome (Figure 1) or by affecting translation-independent extra-ribosomal functions that have been assigned to these proteins.

Is the occurrence of defects in the ribosome and in the regulation of translation a specific characteristic of T-ALL? As far as we are aware, residue R98 in RPL10/uL16, a strong mutational hotspot in T-ALL, is not targeted by mutations in other cancer types, including other acute leukemias such as B-ALL or AML. At this point, we do not understand the reason for the unique occurrence of this mutation in T-ALL. In contrast, *RPL22/eL22* and *RPL5/uL18* were identified in the pan-cancer project as genes that are recurrently mutated in various cancer types. The dependence on cap-dependent translation is also not unique for T-ALL cells. Silvestrol and 4EGI-1 were shown to have therapeutic effects in xenograft models for various leukemias and solid tumors.[17-19] It still needs to be determined, however, if this addiction to cap-dependent translation drives cell type specific translation programs in different tumor types.

In conclusion, in addition to the extensive list of defective processes and molecular aberrations already known in T-ALL, a central role of defective translation machinery and regulation was recently revealed in this disease. These findings offer novel opportunities for T-ALL therapy. Current treatment regimens consist of intensive schemes of chemotherapy and are associated with a multitude of long-term side-effects, while failing to induce long-term remission in 25% of pediatric and 50% of adult patients. For patients with one or several lesions driving cap-dependent translation, such as *PTEN*, *NOTCH1* or *FBXW7* mutations, drugs like 4EGI-1 or silvestrol could be considered. In contrast to what one might expect, off-target toxicity of these compounds seems limited. 4EGI-1 shows no toxicity on human CD34$^+$ cells,[20] and numerous studies showing therapeutic effects of these drugs in *in vivo* application in mouse tumor xenografts support the concept that there is a therapeutic window for treatment in humans.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

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Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia

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Philadelphia chromosome (Ph)/BCR/ABL-positive acute lymphoblastic leukemia (ALL) is the most common genetic abnormality associated with adult ALL and has been shown to confer the worst prognosis to both children and adults.[1,2] Approximately 3%-5% children and 25%-40% adults with ALL have a malignant clone expressing the Ph chromosome. The presence of the Ph chromosome in adults increases with age.[1,2]

Ph-positive (Ph+) ALL patients often present with an aggressive leukemia that is resistant to standard therapies

resulting in high relapse rates. In the era of pre-tyrosine kinase inhibitors (TKIs), Ph+ ALL patients who were treated with conventional chemotherapy showed a long-term survival rate of only 10%.[3-6] Upon standard chemotherapy, disease-free survival (DFS) was found to be 25%-30% in children[7] and less than 20% in adults.[3-6]

Hematopoietic stem cell transplantation (SCT) has been the gold standard therapy for maintenance of complete remission (CR) in Ph+ ALL patients. Previous studies have shown that SCT from matched related donors significantly decreases the relapse rate leading to a DFS ranging from 40% to 60% in both children[8] and adults.[9-6] However, the persisting relapse rate and the non-relapse mortality (NRM) are still considered limiting factors for SCT. As a result, disease recurrence is one of the most frequent causes of treatment failure.[8-10]

The prognosis of Ph+ ALL patients has dramatically improved upon the approval of a 1st-generation BCR–ABL tyrosine kinase inhibitor (TKI), imatinib mesylate, as first-line treatment. Although TKI monotherapy may lead to CR rates of 90%-100% with a remarkable low toxicity profile even in older patients,[11-12] combining TKI treatment with standard chemotherapy has led to an overall higher long-term DFS in both adults[6,13-22] and children.[23,24] The use of TKIs as front-line therapy of Ph+ ALL has led to improved outcome not only because of a higher number of patients achieving CR, but also due to a lower early death rate and decreased disease recurrence. As a result, an increasingly higher number of Ph+ ALL patients are now becoming eligible for SCT. In this regard, imatinib-based induction and consolidation regimens followed by matched related or unrelated allogeneic SCT (allo-SCT) in CR1 (whenever possible according to patient age and drug intolerance) have been shown to be highly effective against Ph+ ALL.[25]

In the present issue of *Haematologica*, Brissot *et al.* describe the impact of TKI treatment on the outcome of *de novo* Ph+ ALL patients who underwent allo-SCT, while addressing controversial and still unanswered questions about the treatment of Ph+ ALL in the context of allo-SCT.

Brissot and co-workers report data from the International Bone Marrow Transplant Registry of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Despite being a retrospective analysis rather than a controlled trial, this study represents the largest analysis carried out on Ph+ ALL adult patients undergoing allo-SCT in CR1 with a 5-year follow up. The authors examined a total of 473 *de novo* Ph+ ALL patients from 77 participating centers undergoing first-line treatment followed by matched sibling or unrelated donor SCT in first CR. Most of these patients (82.5%) received conventional chemotherapy in combination with 1st- or 2nd-generation TKI (TKI before allo-SCT), with imatinib mesylate being the most frequently used TKI (89% of cases). Myeloablative conditioning (MAC) was the most commonly performed regimen (79.3%).

The findings of Brissot *et al.* provide further evidence that pre-SCT TKI treatment dramatically improves the outcome of Ph+ ALL while reducing disease recurrence. In this regard, the 5-year overall survival (OS) in TKI-treated patients before allo-SCT was significantly higher compared with patients undergoing allo-SCT without TKI pre-treatment (47% *vs.* 38%, respectively; P=0.04). This improved outcome was mainly due to a reduction in disease recurrence as the use of TKIs before allo-SCT reduced the 5-year cumulative incidence of relapse (RI) (33% in patients receiving TKIs before SCT *vs.* 50% in those patients who did not). Overall, these results strongly agree with previous studies showing improved post-SCT outcome in patients treated with a TKI-based schedule followed, whenever available and feasible, by allo-SCT, when compared to historical control groups (no-TKI-based regimens). Indeed, in the TKI era, CR1 has been reached in more than 90% of patients while 3-5 year OS and DFS have been reported to be over 50%-60%;[6,13-22] a significant improvement with respect to the pre-TKI era.[3-10]

Despite these advances, the prognosis for Ph+ ALL patients has still remained very poor in both children and adults as relapse frequently occurs after allo-SCT. To date, the development of mechanism(s) of resistance to imatinib is considered one of the most common causes of disease recurrence. Second-generation TKIs (e.g. dasatinib, nilotinib, and bosutinib) have only partially overcome the resistance mechanism conferred by the T315I mutation.[26,27] In this regard, the development of 3rd-generation TKIs such as ponatinib might represent a major step in overcoming drug resistance in Ph+ ALL.[28]

Another controversial issue addressed by Brissot and co-workers in their study concerns the impact of minimal residual disease (MRD) pre- and post-SCT on Ph+ ALL outcome prediction.

Several data from various study groups have clearly demonstrated that MRD detection plays a crucial predictive role in Ph+ ALL. Lee *et al.* and Ottmann *et al.* have shown that high levels of BCR/ABL transcript monitored by real-time quantitative polymerase chain reaction (RTQ-PCR) at different early phases of treatment prior to allo-SCT are a good predictor of a poor prognosis and risk of disease recurrence.[29-31] However, when Brissot and co-workers analyzed BCR/ABL transcripts before SCT (median 16 days before SCT), they found that "high risk" (MRD >10-4) MRD patients presented a pattern of OS, LFS, RI and NRM that was not significantly different from that observed in "low risk" (MRD ≤10-4) MRD patients. These findings are similar to those reported by Pfeifer *et al.*, showing a lack of correlation between BCR/ABL transcripts at SCT, and the frequency and kinetics of MRD positivity after SCT.[32] This could be potentially explained by a more profound molecular response achieved in patients receiving TKI before SCT, which, in turn, determines the need of a lower MRD cutoff to obtain MRD values that are informative for prognosis. Interestingly, Brissot and co-workers could not find any correlation between TKI treatment before transplant and MRD level at transplant compared with the no-TKI pre-SCT patient group.

In contrast to MRD levels at SCT, several studies have shown that the presence of BCR-ABL transcripts, detected at initial engraftment and/or at different time points after allo-SCT, is associated with an increased risk of relapse.[33,34] Thus, MRD detection could provide the basic rationale for intervention with TKIs in the post-SCT scenario.

Although the beneficial role of TKIs during early phases or treatment appears to be well established, the efficacy of TKIs in the post-transplant period is still a subject of controversy. TKI administration subsequent to SCT might prevent

relapse, but it is unclear whether TKI therapy is feasible and tolerable after SCT, and how and when such treatment should be administered. To date, only a few single-institution studies addressing these open questions have been published. Carpenter *et al.* examined the efficacy of giving imatinib treatment after SCT in 15 Ph+ adult ALL and 7 chronic myeloid leukemia patients, who prospectively received imatinib from the day of engraftment until day 365 after SCT.[35] Imatinib treatment was well tolerated with grade 1-3 emesis and serum transaminase elevation being the main common toxicities. Seventeen Ph+ ALL patients were alive and only 2 of them relapsed during imatinib treatment. Anderlini *et al.* obtained similar results in 15 Ph+ ALL patients who received allo-SCT and developed grade 3-4 cytopenia.[36] Wassmann and co-workers assessed the therapeutic action of imatinib in the setting of MRD positivity with the aim of reducing the high relapse rate. In a prospective multicenter study, 27 Ph+ ALL patients received imatinib upon detection of MRD after SCT. BCR/ABL transcripts became undetectable in 52% patients after a median of 1.5 months. All patients who received an early molecular CR remained in remission for the duration of the treatment with only 3 patients relapsing after imatinib discontinuation. The failure of achieving early MRD negativity predicted relapse; in fact, all patients except one relapsed. One-year DFS rate in early molecular CR was 91% *versus* 8% in patients who had MRD (P<0.001).[37] Similarly, Burke *et al.* described a single-institution retrospective study of 32 Ph+ ALL: 15 patients were treated with imatinib either pre- or post-SCT, 11 patients did not receive TKI, and 6 patients received imatinib only after relapse. At two years, OS, RFS and relapse rate were 61%, 67% and 13% for the imatinib group compared to 41%, 35% and 35% for the no-imatinib group, respectively.[38]

Another interesting study has recently been published by Pfeifer *et al.* which compared tolerability and efficacy of prophylactic (n=26) *versus* MRD-triggered (n=29) imatinib treatment after SCT in Ph+ ALL in a prospective randomized multicenter trial. Prophylactic imatinib significantly reduced the incidence of molecular recurrence compared with MRD-triggered imatinib (40% *vs*. 69%; P=0.046) and was associated with a longer duration of molecular negativity [median duration of molecular negativity 26.5 and 6.8 months, respectively (P=0.065)]. Nevertheless, there was no statistical difference in RFS and OS between the two treatment arms and relapse probability was consistently higher in patients who became MRD positive (P=0.017).[32] The authors concluded that early post-transplant imatinib can effectively prevent molecular occurrence and, as a consequence, subsequent hematologic relapse, resulting in excellent remission duration (83% at 5 years) and survival (77% at 5 years). The superiority of post-transplant TKIs has also been supported by historical comparison with studies that did not use TKIs after SCT.[8-10]

In Brissot's study, 157 patients received TKIs after SCT (124 imatinib, 27 2nd-generation TKI, 6 missing patients) at a median of 83 days post SCT, 60 of whom for prophylaxis of relapse. TKI post SCT was found to be the main favorable predictive factor for OS, compared to the no-treatment arm of the study. Furthermore, receiving TKIs post SCT was found to be associated with lower RI and a higher percentage of LFS.

Taken all together, the data in the literature and the findings by Brissot and colleagues strongly suggest that monitoring MRD early after SCT, as well as prophylaxis or prompt intervention with a TKI after-SCT, may prevent disease recurrence. Furthermore, these findings indicate that TKI treatment can adequately control MRD through an immunological response and delay leukemia re-growth at a time when the graft-*versus*-leukemia (GvL) response has not yet occurred. However, while it seems obvious that a post-transplant treatment with TKIs may further decrease the relapse rate, it still remains to be determined which TKI should be used. In this regard, the persistence or the re-appearance of an MRD-positive signal strongly indicates the presence of an intrinsic resistance to the TKI used before SCT (e.g. imatinib or dasatinib). Therefore, the use of a different TKI would seem to be the most appropriate choice. In this case, however, the expected toxicities in the specific post-transplant setting of new TKIs should be also taken into account. For example, the use of ponatinib after SCT should be clearly weighed up due to its skin toxicity, which may mimic the appearance of a graft-*versus*-host disease (GvHD), and vascular toxicity, which may worsen the endothelial toxicity promoted by calcineurin inhibitors. Further studies will be needed to clarify these important issues.

Lastly, Brissot and co-workers take a closer look at the role of GvHD in preventing relapse and how TKIs can influence the occurrence of acute and chronic GvHD. For this purpose, they analyzed 473 patients conditioned with MAC or reduced intensity (RIC) regimen, followed by sibling or unrelated matched SCT with bone marrow stem cells or peripheral blood stem cells as transplant sources. While some historical data indicated an inferior outcome using RIC, no statistically significant differences are reported in this study in terms of OS and DFS between MAC and RIC conditioning. Nonetheless, the findings of Brissot *et al.*, in strong agreement with results recently published by Bachanova *et al.*,[39] confirm the efficacy of RIC as an alternative option for patients ineligible for MAC.

Furthermore, Brissot *et al.* go on to show that NRM is caused by acute and chronic GvHD together with infections and veno-occlusive disease. According to their data, acute GvHD (grade ≥II) negatively influenced OS while it was associated with lower RI, in strong agreement with historical data. Similarly, chronic GvHD played a role in preventing disease recurrence due to its proven immunological effect in controling molecular disease.[32-34] The authors also confirm the unfavorable prognostic impact on OS and LFS of higher white blood cells count at initial diagnosis as well as timing from diagnosis to SCT.

Moreover, Brissot *et al.* show that while TKI pre-SCT treatment did not influence NRM, it was correlated with increased occurrence of acute (grade ≥ II) GvHD. Intriguingly, the use of TKI post transplant was associated with a lower incidence of GvHD. This observation supports previous findings on the efficacy of imatinib in the treatment of chronic GvHD, particularly when sclerotic/fibrotic clinical features are present.[40]

In conclusion, the use of TKIs has significantly improved the outcome of Ph+ ALL undergoing SCT. Thus, it is likely that this scenario will be further improved by the use of other innovative biological drugs such as the T-cell engaging

bispecific antibody blinatumomab. This molecule has been shown to be highly effective in inducing durable remission in refractory/resistant Ph+ ALL in both adults[41] and children.[42] Further studies will be needed to determine whether the combination of TKIs and blinatumomab can lead to deep molecular remission despite reduction, or even lack, of concomitant chemotherapy. These studies could then call into question the role of SCT in Ph+ ALL.

Funding: AB is supported by AIRC 9962 (5x1000) and IG 15992 grants.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

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