The Bottom Line

The Significance of BCR-ABL Transcripts after Allogeneic Stem Cell Transplantation for Chronic Myeloid Leukemia

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The discovery of the BCR-ABL fusion gene was a landmark in our understanding of the molecular basis of chronic myeloid leukemia (CML) [1]. This led rapidly to the demonstration that BCR-ABL transcripts could be identified using the PCR [2]. Next, it was shown that some patients in complete cytogenetic remission after an allogeneic transplantation had no detectable BCR-ABL transcripts in their blood or bone marrow [3]. A technically rather demanding technique for quantitating BCR-ABL transcripts was then developed [4], which showed that, at least for CML patients, blood and marrow gave comparable results. The advent of Taqman methodology greatly simplified measurement of BCR-ABL transcripts in the blood of transplant recipients and today results are routinely expressed as a ratio of BCR-ABL transcript numbers related to a control gene. This ratio is usually reported as a percentage on a log scale, where 100% reflects a hypothetical untreated patient with CML. A patient with a 3-log reduction (0.1%) in BCR-ABL transcript numbers is said to have achieved a major molecular response and a patient with no detectable transcripts is said to be in complete molecular response (CMR).

Another landmark was the report by Kolb and colleagues in 1990 that patients in relapse after an allotransplantation could be treated successfully by infusion of lymphocytes collected from the original donor together with interferon [5]. Later, it was shown that this effect resulted from the donor lymphocytes and not interferon [6]. The capacity for these donor lymphocyte infusions (DLI) to restore CMR is presumed to be due to a “graft-versus-leukemia” effect and this observation remains one of the most convincing examples of the potential beneficial effect of immune therapy in man.

Kaeda et al. reported in 2006 that patients in seeming complete remission posttransplantation sometimes had BCR-ABL transcripts detected at low levels, yet relapse was not inevitable and subsequent testing may show no evidence of transcripts without any further therapy [7]. Because of the potential to treat the patients in relapse with DLI, it became important to agree on a definition of relapse and it was proposed that a patient with a transcript level of >0.02% on 3 consecutive tests or >0.05% on 2 consecutive tests should be classified as having relapsed and would therefore be a candidate to receive DLI. This, of course, raised the question of whether these low spikes of BCR-ABL positivity that then disappeared might actually predict much later relapse.

In the accompanying paper, Arpinati and colleagues report the results of following a series of allotransplant recipients over a 24-year period in Bologna [8]. Eleven of the 63 evaluable patients never had BCR-ABL transcripts detected; none relapsed. Six of the 52 patients who had BCR-ABL transcripts detected at least once posttransplantation relapsed. Relapse was defined as achieving transcripts levels in excess of 0.1% confirmed by the finding of Ph-chromosome positive metaphases in the bone marrow. Though the definition of relapse employed by Kaeda et al. was stricter than that employed by Arpinati et al., the results of the 2 studies are consistent; both studies showed that patients with persistent absence of detectable transcripts never relapsed. Patients who intermittently had low levels of transcripts detected did not inevitably relapse. Some but not all of the patients with higher levels of BCR-ABL transcripts posttransplantation were at risk of relapse. The conclusion must be that intermittent low-level positivity should not be interpreted as presaging hematologic relapse.

Taken together, these 2 papers raise a series of challenging questions. First, from where do these BCR-ABL transcripts detected posttransplantation actually come? Do they originate from residual leukemia cells that are clinically undetectable, from leukemia stem cells that were not eradicated by the transplantation, or from both? Why then do leukemia cells or stem cells respond to DLI later, as most usually do? Even at this stage, do some leukemia stem cells escape eradication because they are transcriptionally silent and so produce no BCR-ABL protein?

Second, do leukemia stem cells survive in all patients after an allotransplant? Late relapse can occur. A recent study from the International Center for Blood and Marrow Transplant Research [9] reported relapses occurring up to 18 years posttransplantation. Where were the stem cells that generated relapse lodged for so long? Were they held in a quiescent state by cytokine influences in a stem cell niche? If so, why and how did they escape control? Could this re-emergence result from a weakened graft-versus-leukemia effect and if so, why? Is there an analogous situation with tyrosine kinase inhibitors (TKIs)? Most patients who achieve CMR with TKIs, relapse when the drug is stopped again, suggesting that TKIs are highly effective in controlling most leukemia cells but perhaps not in eradicating leukemia stem cells.

Finally, can we use modern technology to identify residual leukemia stem cells after an allotransplantation and should we be concerned by positive findings? Some recent data suggest a PCR based on genomic DNA rather than RNA expression may be a more sensitive technique to detect...
residual leukemia [10]. This makes sense if the BCR-ABL transcripts currently detected come only from proliferating leukemia cells and while leukemia stem cells may not transcribe the BCR-ABL gene. Will digital PCR increase the sensitivity of a RT-PCR? Should we be studying CML patients posttransplantation with techniques designed to mobilize leukemia stem cells from their niche?

Much has been achieved in the treatment of CML transplantsations and TKIs in recent years. Many fascinating questions remain to be addressed.

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REFERENCES

Melphalan Continues to Rock the Myeloma World

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Since the first reports of its efficacy for myeloma in the early 1960s [1-3], melphalan has remained a key component of the oncologist’s armamentarium. High-dose melphalan therapy was introduced in the early 1980s [4] and has since been employed with stem cell rescue for “younger” myeloma patients, with the age limit now pushing 75 years with advances in supportive care measures [5]. The era of novel drug development has reawakened the debate of whether or not to approach the disease with a curative intent [6]. Some investigators have gone as far as proposing a pre-emptive strike with novel agent combinations in smoldering myeloma [7], but a similar approach with thalidomide has not provided improvements in overall survival [8]. The Arkansas Myeloma investigators have been proponents of a curative approach long before the era of novel agents, proposing the Total Therapy (TT) program that applies all effective antimyeloma therapies up front to eradicate all disease subclones and reduce the chance for drug resistance [9]. Melphalan has been at the front and center of the TT program, employed in high doses twice with stem cell rescue. To this day, myeloma therapy for transplant-eligible patients follows the TT paradigm in many ways; the only major difference has been the replacement of cytotoxic drugs with novel agents as induction, consolidation, and maintenance. Regardless of the therapeutic approach, most myeloma patients today relapse sooner or later after having received first-line therapy. High-dose melphalan with stem cell rescue remains a viable option for salvage therapy, even with the growing number of novel drugs for relapsed and/or refractory myeloma.

In the current issue, Michaels et al. [10] report on the role of employing high-dose melphalan with stem cell rescue as salvage therapy for relapsed and/or refractory myeloma. Using the Center for International Blood and Marrow Transplantation database, a retrospective study was conducted on 187 patients between 1995 and 2008 who had previously received an autologous hematopoietic stem cell transplant (AHCT-1) as part of initial myeloma therapy and subsequently received a second AHCT (AHCT-2) at the time of disease relapse or progression. The nonrelapse mortality was reported at 2% at the 1-year mark and 4% at the 2-year and 3-year intervals, suggesting that AHCT-2 is a safe option. It is also clear that AHCT-2 is likely noncurative for the majority of patients in this analysis, as only 5% of patients enjoy long-term disease control with longer follow-ups (progression-free survival 47% at 1 year; 13% at 3 years; 5% at 5 years). The multivariate analyses reveal that patients who relapse after 36 months from AHCT-1 are those who benefit the most from AHCT-2. A further subgroup analysis by time stratification shows that patients receiving AHCT-2 after the year 2004 have superior outcome compared to...