ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Can We Cure Ph+ ALL Without Chemotherapy or Transplant?

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H&O What is Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), and how is it typically managed?

RF Ph+ ALL is the most frequent genetic ALL subgroup in adults. It accounts for about 25% to 30% of all ALLs in adults overall and becomes progressively more frequent with age, being less common in young adults and accounting for approximately 50% of ALL in adults older than 50 years. Ph+ ALL is much rarer in children. In the past, before the advent of tyrosine kinase inhibitors (TKIs), the prognosis for patients with Ph+ ALL was dismal. It was, by far, the most lethal condition in hematology. The only chance for survival was allogeneic stem cell transplant (SCT), but this was difficult to do because patients responded poorly to chemotherapy and many patients were elderly. In those days, only about 10% to 15% of patients were long-term survivors, an extremely low figure. As a result, many older patients received only palliative treatment.

This scenario changed about 25 years ago, following the introduction of TKIs in the management of Ph+ ALL. TKIs had markedly improved outcomes for patients with chronic myeloid leukemia (CML), a condition that shares the same genetic abnormality. Following the results obtained in CML, it was obvious to consider integrating TKIs into the treatment of Ph+ ALL.

H&O Can you provide an overview of how TKIs were integrated into the management of adult Ph+ ALL?

RF The first TKI introduced was imatinib. Initially, the approach was straightforward: supplement the existing chemotherapy backbone regimens with imatinib. However, it soon became apparent that this approach had its drawbacks. The community realized that adding a TKI to standard intensive chemotherapy increased toxicity. To address this issue, 2 approaches emerged.

One was simply to reduce the intensity of the chemotherapy administered while at the same time giving a TKI, which proved successful. It was found that by giving less chemotherapy together with the TKI, toxicity decreased while response rates increased.

The second option was the one utilized by the GIMEMA multicenter study group in Italy. From the year 2000 up to today, we have in fact been treating adult Ph+ ALL patients with only a TKI plus corticosteroids during the induction phase, omitting systemic chemotherapy. The initial study focused on elderly (>60 years) Ph+ ALL patients, given their limited tolerance of chemotherapy. The decision to target this population represented a departure from the conventional approach of chemotherapy for the most severe form of leukemia. It was quite a paradigm shift not to use chemotherapy. We reasoned that because chemotherapy was not well tolerated by the elderly and a transplant was not feasible for most of them, it was worth exploring alternative treatments with the approval of the ethics committees. In this initial study, we administered imatinib along with corticosteroids as induction treatment, omitting systemic chemotherapy altogether. To our pleasant surprise, virtually all the elderly patients achieved a complete hematologic remission. Furthermore, the toxicity observed was minimal, resulting in no observed

deaths during the induction.

The key point of all this is a rapid diagnostic work-up. It is of paramount importance to determine quickly whether a patient harbors the BCR-ABL genetic abnormality. This should ideally occur within 1 week from diagnosis, during the so-called corticosteroid pre-phase. If present, the patient can proceed to receive TKI therapy. As mentioned, we have been using a TKI alone in induction plus corticosteroids. Initially, we used imatinib because it was the first available TKI. Given the results obtained, we then progressed to the second-generation TKI dasatinib (Sprycel, Bristol Myers Squibb) and then the third-generation TKI ponatinib (Iclusig, Ariad), always omitting systemic chemotherapy during the induction phase. Overall, this approach was matched with complete response rates between 94% and 100%, and virtually no deaths during induction for patients of all ages.

These results clearly determined a major change in our frontline strategy to treat all adult patients with Ph+ ALL.

> Chemotherapy-free regimens represent the most promising data ever reported in Ph+ ALL.

However, obtaining a complete hematologic response is not sufficient, and most patients remained positive for measurable residual disease (MRD). Consolidation with chemotherapy, followed when possible by allogeneic SCT, was therefore the standard post-induction treatment.

H&O How did the idea of a possible chemotherapy-free strategy for the treatment of Ph+ ALL come true, and what evidence supports the idea that chemotherapy-free regimens may eliminate the need for SCT in Ph+ ALL?

RF In our latest phase 2 study, which was published in the *New England Journal of Medicine* in October 2020, the induction with dasatinib and glucocorticoids was followed by consolidation without chemotherapy, but with the addition of immunotherapy. This targeted therapy involved utilizing a bispecific monoclonal antibody, blinatumomab (Blincyto, Amgen), which targets CD19 on the leukemic B cells and CD3 on T cells to activate the host immune system. Blinatumomab has demonstrated efficacy in relapsed ALL and MRD-positive cases. Preliminary results indicated very high rates of molecular MRD response and favorable progression-free survival (PFS) and overall survival (OS) rates at 18 months. The study also showed that this approach led to an in vivo modulation of the host immune system, according to a 2021 study by Puzzolo and colleagues published in *Blood*.

Subsequent follow-up data from the ALBA study, published in the *Journal of Clinical Oncology* in December 2023, showed that at a follow-up of over 4 years, the PFS, OS, and event-free survival rates were between 75% and 80%, which was extremely rewarding to see. This marks a significant milestone in our understanding and management of the disease.

H&O How have these chemotherapy-free regimens improved outcomes for Ph+ ALL compared with historical results?

RF These chemotherapy-free induction and consolidation regimens represent the most promising data ever reported in Ph+ ALL. A particularly noteworthy finding is that in our study, half of the patients have been managed only with a TKI and blinatumomab and have not received systemic chemotherapy and transplant. What we found was that most patients became MRD-negative. The primary endpoint was the rate of molecular responses after induction with TKI and consolidation with the antibody, which we successfully met. This serves as indirect confirmation that chemotherapy and transplant can be spared for many patients and underscores the importance of the MRD status in making treatment decisions.

We have yet to formally establish criteria for determining which patients can safely forgo chemotherapy and transplant. This will be figured out through an ongoing study in Italy, the first ever phase 3 randomized study comparing the third-generation TKI ponatinib plus blinatumomab vs imatinib and chemotherapy. This study of 236 patients aims to identify those with a very good molecular response and negative MRD status and who do not have unfavorable genetic profiles at diagnosis. Patients with sustained MRD negativity and without an unfavorable genetic profile will not receive chemotherapy or transplant, even if they are young and have a sibling donor, and will instead be closely monitored. Recruitment is ongoing and expected to conclude by the end of the year.

This represents a major revolution in the field as it suggests that many patients, including the elderly, can be effectively treated with targeted therapies and immunotherapy without the need for chemotherapy or transplant. The absence of an upper age limit highlights the potential for broad applicability across all age groups. Additionally, advancements in the administration of blinatumomab,

such as subcutaneous formulations, will further enhance its feasibility and accessibility.

H&O In your perspective, how effective are TKIs plus immunotherapy in achieving a potential cure for Ph+ ALL without resorting to chemotherapy/SCT?

RF Let me make it very clear: all patients with Ph+ ALL should have access to a TKI. The first problem lies in diagnosing them. In a review published in the *New England Journal of Medicine* in 2022 on Ph+ ALL, which I wrote with Dr Sabina Chiaretti, we emphasized the issue of global testing rates. Ironically, this could be a cost-saving approach, because testing patients—even if they are 80 or 90 years old—for Philadelphia positivity allows for TKI administration. This could potentially reduce hospitalizations, which is also cost-saving. Additionally, avoiding complications from chemotherapy, such as infections, reduces the overall cost of treating side effects.

It is paradoxical that by embracing targeted treatments, which require laboratory testing and disease monitoring, we can not only improve prognosis, but also save costs. TKIs are a must today in the management of Ph+ ALL patients of all ages, but they should be given upfront. In many parts of the world, even in wealthy regions, samples are sent away for diagnosis, resulting in delayed responses. This makes no sense. Testing should be done locally, allowing for timely results. This applies also to MRD monitoring. In Europe, for example, we aim to provide results within a week, even including weekends.

The problem arises with immunotherapy, which is not approved yet for patients who respond very well. How can we give blinatumomab, which is not approved, if a patient is in complete remission and MRD-negative? That is a problem. In some regions, it may be available for purchase, but that places a financial burden on patients. This highlights a deeply unequal access to treatment, where those who can afford it receive it, while others do not.

H&O What are the common side effects associated with chemotherapy-free regimens?

RF Chemotherapy-free regimens dramatically reduce side effects compared with intensive chemotherapy. Traditional chemotherapy often leads to conditions such as aplasia, infections, and bleeding, necessitating support through antifungals and antibiotics. This is much more cumbersome and expensive for patients. One advantage of TKIs is that we have access to multiple options, and there is flexibility to switch among them if necessary. TKIs also have different side effects than chemotherapy. Furthermore, the difference in managing a patient with a TKI compared with chemotherapy is like night and day—akin to staying at home vs being hospitalized. In this respect, it is worth recalling that the dasatinib-blinatumomab frontline protocol could continue without interruption even during the first lockdown because of the COVID-19 pandemic that occurred in Italy in March 2020. Nevertheless, it is essential to monitor all patients, even those on TKIs. Blinatumomab, although generally well-tolerated, also has some side effects, particularly at the neurologic level. These are less severe compared with the side effects of chemotherapy and transplant. Overall, by adopting chemotherapy-free regimens, we are significantly reducing the burden of side effects on patients. This is undeniably positive news and represents a major step forward in improving the treatment experience and outcomes for patients with Ph+ ALL.

Disclosures

In the last 2 years, Dr Foà has served on the speakers bureau for Amgen, Novartis, and MSD.

Suggested Readings

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