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Toward effective targeted therapy for the treatment of adult acute lymphoblastic leukemia

“Among new agents, monoclonal antibody therapy represents one of the most exciting novel therapeutic approaches for acute lymphoblastic leukemia.”

Xavier Thomas¹

Through the effectiveness of combination chemotherapy and allogeneic stem cell transplantation (ASCT), the cure of acute lymphoblastic leukemia (ALL) in children evolved from the 1970s from an anecdotal wonder to a quantifiable reality. Although giving less spectacular results than those seen in children, these therapeutic approaches have been applied to adults over the last two decades, leading to an improved response rate and survival [1].

Retrospective comparisons demonstrating that adolescents with ALL significantly benefit from pediatric rather than adult chemotherapy regimens yielded to the recent development of pediatric-inspired regimens for adult ALL involving greater dose densities of many chemotherapeutic agents, such as L-asparaginase, vincristine, corticosteroids and methotrexate [2]. However, additional gains are unlikely to be achieved by simply intensifying therapy further, due to the offset of unacceptable toxicities. Furthermore, new procedures for ASCT modestly improve the outcome of adult ALL, while introducing higher risks of acute and late complications. There was therefore a clear and compelling rationale for developing therapies that specifically

target the molecular abnormalities that cause leukemia. Encouraging signs have recently emerged with the development of novel therapeutic agents, opening a new era of treatment in adult ALL. Several points of intervention have been identified that may respond to targeted drugs. Concomitantly, the biology of leukemia stem cell (eradication of which is considered as the relevant goal of leukemia therapy) was better understood. Several primary studies with targeted agents have demonstrated impressive clinical activity, even in heavily pretreated patients. Others have demonstrated synergistic effects with chemotherapy and the feasibility of such combinations in clinical trials.

The era of targeted therapy for ALL started about 15 years ago with the development of the first inhibitor of tyrosine kinase (TKI), imatinib mesylate [3]. Imatinib mesylate and then the other inhibitors of the ABL tyrosine kinase activity of the fusion protein BCR-ABL have revolutionized the treatment of Philadelphia chromosome-positive (Ph⁺) ALL [4,5]. TKIs are now integral components of therapy for Ph⁺ ALL. The current consensus is that they improve patient

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outcomes compared with historical control patients treated with chemotherapy alone, and increase the number of patients able to receive SCT [6,7]. Several novel TKIs with significantly more potent antileukemic activity are currently being developed [8].

Among new agents, monoclonal antibody (MoAb) therapy represents one of the most exciting novel therapeutic approaches for ALL [9]. The incorporation of antibody therapies into standard chemotherapy backbones represents a promising strategy. Several MoAb-based reagents with different mechanisms of action were developed, including unconjugated MoAbs, MoAbs (or fragments) conjugated to cytotoxic agents or toxins, MoAbs conjugated to radioactive molecules and bi-specific MoAbs, which are directed to two target antigens or recruit immunologically active cells to preselected surface antigens on ALL cells. Because ALL cells express a variety of specific antigens, those ones can serve as targets for MoAbs. Following the demonstration of its contribution to change the history of lymphomas, rituximab (anti-CD20) has been the first MoAb to be used with success in adult patients with B-cell lineage ALL in combination with chemotherapy in active and minimal residual disease (MRD) states [10,11]. Recent emerging resistances to rituximab [12] have led to the current development of newer anti-CD20 MoAbs, such as ofatumumab, ocrelizumab and veltuzumab.

CD22 represents also an ideal target for the treatment of B-cell lineage ALL because of its expression profile and its intracellular trafficking. Recently, a new humanized anti-CD22 MoAb, inotuzumab ozogamicin, conjugated with calicheamicin, showed an overall response rate in 57% of cases [13]. Among the patients with chromosomal abnormalities at diagnosis who achieved response, 89% showed a cytogenetical response. Among those who achieved a hematological response, 63% obtained a molecular remission. The median survival of the cohort was 4.5 months. Of note, 22% of patients undergoing HSCT developed veno-occlusive disease. Inotuzumab ozogamicin was then tested in combination with chemotherapy in adult patients with ALL: 91% of patients achieved morphological remission and flow cytometric MRD-negative status. Six-month disease-free and overall survivals were both of 90%. The most common adverse events observed with inotuzumab ozogamicin were myelosuppression and reversible

liver function abnormalities [14]. Epratuzumab is another anti-CD22 that modulates B-cell activation and signaling through antibody-dependent cell-mediated cytotoxicity, CD22 phosphorylation and proliferation inhibition. In adults with relapsed/refractory ALL, epratuzumab combined with a clofarabine and cytarabine-based regimen showed a response rate of 52%, significantly higher than that observed in the previous trial with chemotherapy alone [15]. ^{90}Y -epratuzumab tetraxetan radioimmunotherapy is currently under investigation.

Blinatumomab (BiTE[®]) is a bispecific single-chain antibody construct specific for CD3 and CD19 [16]. It engages and redirects cytotoxic T cells with its anti-CD3 arm to ALL cells with its anti-CD19 arm. Blinatumomab-activated T cells proliferate and induce perforin-mediated death of the targeted ALL cells. Topp *et al.* in a Phase II trial of 189 patients have recently demonstrated impressive clinical activity of single-agent blinatumomab with high MRD response [17]. After two cycles, 43% of patients achieved complete response. The most important adverse events were reversible neurological toxicities and aplasia. SAR3419 is another anti-CD19 monoclonal antibody, conjugated to a highly potent tubulin inhibitor (the maytansinoid DM4) [18], currently investigated in a Phase II study in relapsed/refractory ALL patients.

CD52 is a cell surface glycoprotein found on most lymphoid cells of both T- and B-lineage. The administration of alemtuzumab (anti-CD52) with G-CSF to adults with relapsed or refractory ALL was shown to produce good response, but of short duration [19]. Combined with chemotherapy, alemtuzumab has yielded promising response and duration of response [20]. Patients who received prophylactic donor lymphocyte infusion after conditioning with alemtuzumab were at low risk for relapse, but associated with a relatively high incidence of severe graft-versus-host disease [21].

Among immunotherapy, T cells genetically modified to express chimeric antigen receptors (CARs), that recognize specific targets on leukemic cells, are expected to revolutionize our way to fight against leukemia, by redirecting the immune system in order to eliminate relapse issues. First clinical trials, especially with anti-CD19 CAR T cells, report promising results [22].

A variety of intracellular oncogenic pathways are potential targets for ALL therapy. Agents

that can inhibit specific signaling molecules include inhibitors of transcription and inhibitors of cell proliferation and apoptosis, including protein serine/threonine kinase inhibitors (such as aurora kinase inhibitors, mammalian target of rapamycin inhibitors and protein kinase B inhibitors), proteasome inhibitors and gamma secretase inhibitors. Gamma secretase inhibitors block proteolytic activation of NOTCH receptors and induces G1 cell cycle arrest. They may provide a targeted therapy for T-cell lineage ALL [23].

Despite promising initial results together with the large number of new agents currently investigated, significant challenges remain for novel drug development in ALL and the application of these novel agents shows some major limitations. A major clinical challenge remains the ability to target sanctuary sites such as the central nervous system and testicular leukemia. Most drugs, investigated as single agents, will likely offer better results in combination with conventional chemotherapy and with other targeted agents. A main issue remains to know how and when these novel agents should be administered. Should we use them as induction/consolidation therapy or as maintenance therapy? Should we use them sequentially or concurrently to other therapeutic agents? This question has been initially raised with the use of TKIs in Ph⁺ ALL [5–7], but appears also of importance for other agents, such as MoAbs. Inotuzumab ozogamicin and epratuzumab have been successfully combined with chemotherapy [14,15] and synergistic effects have been described with rituximab [24]. Furthermore, combinations of several agents might reduce the risk of resistant clonal outgrowth. Most of MoAbs displayed short time efficacy. MoAbs

might therefore be use in combinations in order to obtain deeper response and remissions longer enough to get enough time to organize SCT. In the other hand, the dependence of blinatumomab on circulating immune cells seems to limit the ability to combine directly blinatumomab with myelosuppressive therapies. However, the recent development of immunotherapy with MoAbs (such as blinatumomab) or CARs, generates a great excitement and further trials are eagerly awaited. But the optimal placement of immunotherapy and immune modulating approaches has yet to be determined. The fast, deep, but short response displayed by blinatumomab could limit its use to a prephase or an interphase treatment serving as bridge to SCT. Activation of T cells has also generated interest of blinatumomab for a potential role in the management of MRD-positive disease or in case of molecular relapse after ASCT in order to potentiate the effect of donor lymphocyte infusion [25].

Overall, we should take advantage of the tremendous step forward done, over the past decades, in the knowledge of leukemia biology and design therapeutic approaches involving a combination of agents, taking advantage of all available new agents and therapeutic strategies.

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References

- Gökbuğut N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. *Semin. Hematol.* 46, 64–75 (2009).
- Huguet F, Leguay T, Raffoux E *et al.* Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J. Clin. Oncol.* 27, 911–918 (2009).
- Ottmann OG, Druker BJ, Sawyers CL *et al.* A Phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 100, 1965–1971 (2002).
- Lilly MB, Ottmann OG, Shah NP *et al.* Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: results from a Phase 3 study. *Am. J. Hematol.* 85, 164–170 (2010).
- Ottmann OG, Larson RA, Kantarjian HM *et al.* Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia* 27, 1411–1413 (2013).
- Yanada M, Takeuchi J, Sugiura I *et al.* High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a Phase II study by the Japan Adult Leukemia Study Group. *J. Clin. Oncol.* 24, 460–466 (2006).
- Lee KH, Lee JH, Choi SJ *et al.* Clinical effect of imatinib added to intensive combination chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia* 19, 1509–1516 (2005).
- Cortes JE, Kim DW, Pinilla-Ibarz J *et al.* A Phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N. Engl. J. Med.* 369, 1783–1796 (2013).

- 9 Le Jeune C, Thomas X. Antibody-based therapies in B-cell lineage acute lymphoblastic leukaemia. *Eur. J. Haematol.* doi:10.1111/ ejh.12408 (2014) (Epub ahead of print).
- 10 Thomas DA, O'Brien S, Faderl S *et al.* Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in *de novo* Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J. Clin. Oncol.* 28, 3880–3889 (2010).
- 11 Jandula BM, Nomdedeu J, Marin P, Vivancos P. Rituximab can be useful as treatment for minimal residual disease in bcr-abl-positive acute lymphoblastic leukemia. *Bone Marrow Transplant.* 27, 225–227 (2001).
- 12 Stolz C, Schuler M. Molecular mechanisms of resistance to rituximab and pharmacologic strategies for its circumvention. *Leuk. Lymphoma* 50, 873–885 (2009).
- 13 Thorson JS, Sievers EL, Ahlert J *et al.* Understanding and exploiting nature's chemical arsenal: the past, present and future of calicheamicin research. *Curr. Pharm. Des.* 6, 1841–1879 (2000).
- 14 Kantarjian H, Thomas D, Jorgensen J *et al.* Inotuzumab ozogamicin, an anti-CD22-calicheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a Phase 2 study. *Lancet. Oncol.* 13, 403–411 (2012).
- 15 Advani AS, McDonough S, Coutre S *et al.* SWOG S0910: a Phase 2 trial of clofarabine/ cytarabine/epratuzumab for relapsed/ refractory acute lymphocytic leukaemia. *Br. J. Haematol.* 165, 504–509 (2014).
- 16 Hoffman LM, Gore L. Blinatumomab, a bi-specific anti-CD19/CD3 BiTE® antibody for the treatment of acute lymphoblastic leukemia: perspectives and current pediatric applications. *Front. Oncol.* 4, 63 (2014).
- 17 Topp MS, Gökbuğut N, Stein AS *et al.* Immunotherapy with CD19-targeting bispecific T-cell engager blinatumomab in relapsed or refractory B-precursor acute lymphoblastic leukaemia: an international, multicentre, single-arm Phase 2 study. *Lancet. Oncol.* doi:10.1016/S1470-2045(14)71170-2 (2014) (Epub ahead of print).
- 18 Blanc V, Bousseau A, Caron A, Carrez C, Lutz RJ, Lambert JM. SAR3419: an anti-CD19-maytansinoid immunoconjugate for the treatment of B-cell malignancies. *Clin. Cancer Res.* 17, 6448–6458 (2011).
- 19 Gorin NC, Isnard F, Garderet L *et al.* Administration of alemtuzumab and G-CSF to adults with relapsed or refractory acute lymphoblastic leukemia: results of a Phase II study. *Eur. J. Haematol.* 91, 315–321 (2013).
- 20 Van Besien K, Stock W, Rich E *et al.* Phase I-II study of clofarabine-melphalan-alemtuzumab conditioning for allogeneic hematopoietic cell transplantation. *Biol. Blood Marrow Transplant.* 18, 913–921 (2012).
- 21 Liga M, Triantafyllou E, Tiniakou M *et al.* High alloreactivity of low-dose prophylactic donor lymphocyte infusion in patients with acute leukemia undergoing allogeneic hematopoietic cell transplantation with an alemtuzumab-containing conditioning regimen. *Biol. Blood Marrow Transplant.* 19, 75–81 (2013).
- 22 Grupp SA, Kalos M, Barrett D *et al.* Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N. Engl. J. Med.* 368, 1509–1518 (2013).
- 23 Real PJ, Tosello V, Palomero T *et al.* Inhibition of NOTCH1 signaling and glucocorticoid therapy in T-ALL. *Blood* 112(Suppl.1), 298 (2008).
- 24 DiJoseph JF, Dougher MM, Kalyandrug L, Damle NK. Anti-tumor activity of CMC-544 in combination with rituximab. *Proc. Am. Assoc. Cancer Res.* 46, Abstract 700 (2005).
- 25 Thomas X. Blinatumomab: a new era of treatment for adult acute lymphoblastic leukemia? *Lancet. Oncol.* doi:10.1016/S1470-2045(14)71183.0 (2014) (Epub ahead of print).