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Agents for refractory/relapsed acute lymphocytic leukemia in adults

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Abstract. – Although treatment results for adult acute lymphoblastic leukemia (ALL) have improved considerably in the past decades, treating adult patients with relapsed/refractory acute lymphocytic leukemia (ALL) is still difficult. Adults with refractory/relapsed acute lymphocytic leukemia (ALL) processed to death rapidly associated with chemotherapy resistance, high mortality by reinduction, etc. Only 20% to 30% of those patients acquired complete remission (CR). Those patients are always of short duration unless an allogeneic stem cell transplant is feasible. Median survival is only ranging from 2 to 12 months. Therapeutic strategy on relapsed/refractory acute lymphocytic leukemia (ALL) is always a major therapeutic challenge bothering hematological researchers. Novel agents and unique therapeutic strategies have been developed in recent years. This review focuses on major clinical advances in the agents for refractory/relapsed ALL.

Key Words:
Acute lymphocytic leukemia, Refractory, Relapsed, Treatment.

Introduction

As development of chemotherapy, complete remission (CR) can be achieved in 70%-90% of adult patients with newly diagnosed acute lymphoblastic leukemia[1,2]. Around 10-20% of patients die early during induction treatment, and a further 10% is truly refractory to remission-induction programs[3]. More than half of the patients who achieve a complete remission are expected to relapse. Chemotherapy regimens are unable to induce durable remissions in the majority of patients post-relapse, and consequently overall survival (OS) at 5 years after relapse remains low at 7% with currently available salvage strategies[4,5]. The cure rate of adult ALL is estimated to be somewhere between 20 and 40%[6-9]. The reasons patients have refractory or relapsed acute leukaemia is not well known, but likely relates to multiple factors, including patients' age, leukocyte counts, Immunophenotypes, genes, time form chemotherapy to CR, minimal residual disease (MRD), et al[8,10-22]. We will focus on salvage chemotherapy regimens and novel targeted monoclonal antibodies appear promising in the pursuit of achieving a cure rate for refractory/relapsed ALL in this review.

Chemotherapy

Fludarabine

Fludarabine is an effective agent without untoward toxicity in the treatment of different lymphoproliferative disorders as well as acute myeloid leukemia and myelodysplastic syndromes[23-25]. Addition of fludarabine to cytarabine (AraC) increases the rate of accumulation of AraC-5 - triphosphate (AraCTP) in leukemia blasts which decided the clinical efficacy of this approach[25,26]. In 1993, Suki et al[27] reported the antileukemic efficacy and toxicity profiles of the combination of fludarabine and intermediate-dose cytosine arabinoside (ara-C) in refractory or relapsed adult acute lymphocytic leukemia (ALL). In their study, nine (30%) patients achieved a complete remission (CR), 8 (27%) died during remission induction, and 13 (43%) had resistant disease. The median CR duration was 22 weeks, and the median survival was 12 weeks for all patients, and 34 weeks for those who had a response to treatment. Myelosuppression-associated febrile episodes were the most common side effects, occurring in 28 (93%) patients. In 1997, Montillo et al[28] reported the efficacy of the combination of fludarabine and cytarabine followed by the administration of G-CSF (FLAG-GCSF) with relapsed ALL. They treated

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12 patients in first relapse, overall 10 patients achieved a second CR, one patient showed resistant disease and one patient died during remission induction. The addition of G-CSF reduced the period of neutropenia obtaining a low incidence of myelosuppression-associated problems. Clavio et al[29] reported a pilot trial to evaluate the association of fludarabine, Ara-C, and daunorubicin (FLAD) as salvage therapy for ALL patients. Their study includes 17 consecutive adult ALL patients, 10 patients (59%) were refractory to induction chemotherapy and 7 (41%) had relapsed (one of them following BMT). Four patients had t(9;22), one had t(11;15), and the remaining 3 showed complex karyotypes. Ten out of 17 patients (59%) reached CR after the first course of FLAD. In 2005, a study evaluated the efficacy of the combination of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA)[30]. Five patients had primary refractory disease, and 18 were in first relapse. Nine (39.1%) patients achieved complete remission (CR) following salvage therapy, whereas 13 (56.5%) patients were refractory, and one patient died in aplasia due to infection. They observed a lower incidence of infections and a reduced severity of febrile episodes with a lower mortality compared to the study of Suki et al[25,26].

In 2006, a phase II study by the Polish Adult Leukemia Group (PALG) was done to evaluate safety and efficacy of FLAM consisting of sequential fludarabine, cytarabine, and mitoxantrone[31]. 50 patients were included with primary (n=13) or secondary (n=5) refractoriness, early (< 12 months) first relapse (n=15), first relapse after hematopoietic cell transplantation (HCT) regardless CR duration (n=13), and second or subsequent relapse (n=4). CR rate equaled 50%. Eight (16%) patients died in aplasia and 17 (34%) patients experienced leukemia regrowth after initial cytoreduction.

In 2009, Basquiera et al[32] reported a study to evaluate the chemotherapy regimen fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) in patients with relapsed/refractory acute leukemia including acute myeloblastic leukemia (n=17, 52%), ALL (n=24, 42%),) and biphenotypic (n=2, 6%). Complete remission (CR) was achieved in 15 cases (45.5%) and seven patients dead resulting in a mortality of 21.1%.

In 2012, Mehrzad et al[33] reported a study evaluated the mortality and response rate after FLANG (combination of novantron, cytarabine, fludarabine, and granulocyte-colony stimulating factor) regimen in 25 patients with refractory/relapsed acute leukemia. Out of the 25 patients, 8 patients (32%) had acute lymphoblastic leukemia (5 refractory and 3 relapsed cases) and 17 patients had acute myeloid leukemia (7 refractory and 10 relapsed cases). One month after FLANG regimen, 10 patients (40%) had responded to treatment. On the other hand, 13 patients (52%), who had not entered the CR period, died during the follow-up. In their study, associations between disease type and responsiveness to treatment were not significant.

Augmented Hyper-CVAD

The hyper-CVAD (cyclophosphamide/vincristine/doxorubicin/ dexamethasone) program is a well-established regimen for the treatment of adult patients with ALL for many years[34,35].

In 1997, Koller et al[36] reported a study to evaluate the efficiency and toxicity of the hyper-CVAD regimen in relapsed acute lymphoblastic leukemia. Sixty-six adults with refractory acute lymphocytic leukemia received salvage therapy with the "hyper-CVAD" regimen and growth factor support comparing with 63 control patients treated with high-dose Ara-C plus mitoxantrone with or without GM-CSF. The CR rates were similar in the treatment and control groups (44% vs 38%). More patients in the treatment group were with primary resistant disease (15% vs 2%, p = 0.006). Recovery of granulocyte counts was significantly faster in the treatment group when compared to high-dose Ara-C-treated patients who were given GM-CSF (20 vs 25 days, p = 0.04). Survival was prolonged in the treatment group, with most of the benefit seen in first salvage patients (42 vs 20 weeks, p = 0.016). Difference in DFS (disease-free survival) in the two groups was significant (52 vs 20 weeks, p = 0.008).

In 2011, Faderl et al[37] designed an augmented hyper-CVAD with intensified doses of non-myelosuppressive components including vincristine, dexamethasone, and asparaginase (L-asparaginase and pegaspargase). 90 patients with a median age of 34 years (range, 14-70 years) have been enrolled. 70 patients (78%) had pre-B ALL and 68 patients were in first salvage (76%). 10 (11%) patients had primary refractory disease. Of 88 evaluable patients, 41 (47%) achieved complete remission (CR). 8 patients (9%) died within the first 30 days. Median CR duration, progression-free survival, and overall survival were 5,

6.2, and 6 months, respectively. Median overall survival of CR patients was 10.2 months (range, 1.4-69.5+ months). Twenty-eight patients (32%) proceeded to stem cell transplantation.

Alkylator

In 1993, Schiller et al[38] reported a phase II study of ifosfamide, etoposide, and mitoxantrone for the treatment of resistant adult acute lymphoblastic leukemia. 11 adult patients with relapsed or refractory ALL were enrolled. 8 of 11 (73%) achieved a complete remission, 2 patients failed to enter remission, and 1 patient died of multiorgan system failure shortly after receiving therapy. Median DFS is 96 days and median survival from remission is 234 days. Five patients who achieved CR subsequently relapsed with a median time to relapse of 80 days (50-151 days).

In 1999, Martino et al[39] evaluated the efficiency and safety of intensive salvage chemotherapy (cyclophosphamide, vindesine, mitoxantrone, intermediate-dose Ara-C, prednisolone and methotrexate) for forty-five patients with primary refractory (n=17) or first relapsed ALL (n=28). Twenty-eight patients received granulocyte colony-stimulating factor (G-CSF). Thirty-four patients (74%) achieved CR, 2 died in aplasia due to infection and nine were non-responders. Twenty-three of 34 patients (68%) reached the planned SCT (nine autologous and 14 allogeneic). The median overall survival was 5.7 months, and the median disease-free survival for those achieving CR was 4.6 months.

In 2007 and 2013, Xue et al[40] reported two retrospective studies to assess the efficacy of the CAG regimen (cytarabine, aclarubicin, concurrent granulocyte colony-stimulating factor). 25 patients with relapsed or refractory ALL were enrolled in their later study, including 11 T-ALL and 14 B-ALL patients (age range, 11-61 years; median age, 26 years). One course of the CAG regimen resulted in a CR rate of 56% and generally mild adverse effects. An overall response was observed in all 11 T-ALL patients (10 CR and 1 PR) and 35.7% of B-ALL patients (p = 0.0009).

Clofarabine

Clofarabine is resistant to deamination by adenosine deaminase and phosphorolytic cleavage by bacterial purine nucleoside phosphorylase as a novel deoxyadenosine analog. In 2003, Kantarjian et al[41] reported a phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. Responses were observed in in 2 (17%) of 12 with ALL. In 2005, Faderl et al[42] reported a phase 1-2 study to evaluate the efficacy of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias. But no responses occurred in 3 patients with ALL. In 2007, Karp et al[43] reported a phase 2 clinical and pharmacologic study of clofarabine in 18 patients with refractory or relapsed acute leukemia. Overall response rates were 50% and 30% at dose level 1 (20 mg/m^2 clofarabine+cyclophosphamide, 6 patients) and dose level 0 (10 mg/m^2 clofarabine + cyclophosphamide, 12 patients). Responses occurred in 4 (67%) of 6 patients with refractory acute lymphoblastic leukemia. In 2009, McGregor et al[44] reported three cases with relapsed acute lymphoblastic leukemia by higher dose clofarabine (52 mg/m^2). Two patients were able to proceed to allo-HSCT following higher dose clofarabine therapy. The third patient, although unable to proceed to transplant, also achieved a hematologic response. Also in 2009, Papayannidis et al[45] report a 23-years-old man with refractory B-acute lymphoblastic leukemia successful treated by combination of clofarabine, cytarabine, and gemtuzumab-ozogamicin. Vitale et al[46] reported 2 cases with relapsed acute lymphoblastic leukemia patients successful response to clofarabine and cyclophosphamide, even in the presence of adverse prognostic factors like the BCR-ABL rearrangement, relapse after TKI administration and presence of the T315I mutation in 2009. In 2012, Zeidan et al[47] reported a phase 1 dose-escalation trial of daily-infused clofarabine followed by escalating dose of fractionated cyclophosphamide for 4 consecutive days in adults with relapsed or refractory acute leukaemias. Forty patients with relapsed or refractory acute leukaemia were enrolled (28 AML, 12 ALL). The overall response rate (ORR) was 50% (6/12) for ALL. Also in 2012, Barba et al[48] reported a Spanish experience in 31 heavily pretreated relapsed/refractory ALL and lymphoma (LL) patients treated with clofarabine-based regimens including 26 ALL and 5 LL. CRs were observed in 8 patients with ALL (31%).

Nelarabine

Nelarabine is the 6-methoxy derivative of 9-beta-D-arabinosylguanine (araG), which can be rapidly deaminated by adenosine deaminase in vivo to araG. Nelarabine is 10-fold more soluble than araG[49]. In 2005, Kurtzberg et al[50] reported a phase I study of nelarabine in 93 children and

adults with refractory hematologic malignancies between April 1994 and April 1997. The overall response rate was 31%. 54% of patients with T-lineage ALL achieving a complete or partial response after one to two courses of drug. In 2007, DeAngelo et al[51] evaluated nelarabine in 26 patients with T-cell acute lymphoblastic leukemia (T-ALL) and 13 with T-cell lymphoblastic lymphoma (T-LBL). All patients were refractory to at least one multiagent regimen or had relapsed after achieving a complete remission. The rate of complete remission was 31% and the overall response rate was 41%. The median DFS was 20 weeks, and the median overall survival was 20 weeks. The 1-year overall survival was 28%. In 2011, a single-arm phase 2 study evaluated the efficiency of nelarabine in adults with relapsed/refractory T-ALL/LBL. 45 of 126 evaluable patients (36%) achieved CR, 12 PR(10%), and 66 (52%) were refractory. A total of 80% of the CR patients were transferred to SCT[52].

Vincristine Sulfate Liposome

Vincristine sulfate (VCR) liposomes injection (VSLI) is a novel nanoparticle formulation of VCR encapsulated in the aqueous core of sphingomyelin and cholesterol liposomes. The encapsulation of VCR prolongs the circulation of active drug and targets drug to tissues with fenestrated vasculature (eg, bone marrow, lymph nodes, spleen, liver, and solid tumors), thereafter leading to first-order release kinetics with deposition of drug over several days[53-55]. In 2006, Thomas et al[56] evaluated the efficiency and safety of VSLI on sixteen heavily pretreated, refractory patients (including 50% with Philadelphia chromosome [Ph]-positive ALL in the preimatinib era).

The overall response rate in that group was 15% (1 CR, 1 PR), 4 patients had transient bone marrow cytoreduction. Neurotoxicity was minimal, but dosing was limited. To further optimize dose intensity and to discern the tolerance of multiple doses in the salvage setting, a multicenter phase 1 clinical trial of weekly dose-escalated VSLI was designed[57], in which patients received VSLI concurrently with pulse dexamethasone to facilitate multiple dosing. Thirty-six adults with relapsed/refractory ALL were enrolled in the study, all previously treated with conventional VCR, received at least 1 dose of VSLI. The MTD of VSLI was 2.25 mg/m^2. A CR was achieved in 7 of 36 patients (19%); the CR rate was 29% for the 14 patients who underwent therapy as their first salvage attempt. In 2012, O'Brien et al[58] evaluated high-dose VSLI (2.25 mg/m^2 without dose capping) for 65 advanced, relapsed, and refractory adult Philadelphia Chromosome-Negative ALL. The CR/CRi(CR with incomplete hematologic recovery) rate was 20% and overall response rate was 35%.

Cytarabine-Containing Regiments

Welborn et al[59] summarized the results of 44 such regimens in 1994 and concluded that the most encouraging remission rates were found when high-dose ara-C was in combination with mitoxantrone, amsacrine, or idarubicin. She observed that these responses seemed superior to high-dose Ara-C alone or with L-asparaginase. But the duration of second CR is short for all chemotherapeutic regimens. In 2004, Reman et al[60] reported a clinical phase II study evaluated the efficiency of the rescue therapy combining intermediate-dose cytarabine with amsacrine and etoposide in 40 adults with relapsed acute lymphoblastic leukemia. 16 patients (40%) achieved a second complete remission. The median overall survival was 5.4 months. The median DFS was 3.2 months with a 3-year DFS of 12%. In 2007, Tedeschi et al[61] evaluated efficiency and safety of high-dose idarubicin in combination with Ara-C in patients with relapsed or refractory acute lymphoblastic leukemia in a clinical study, in which 25 patients with refractory or relapsed acute lymphoblastic leukemia received Ara-C, idarubicin and subcutaneous G-CSF. Eleven patients (44%) achieved complete remission with median disease free survival for 6 months.

Topotecan

Topotecan is a semisynthetic water-soluble inhibitor of topoisomerase I, and acts in the S-phase of the cell cycle exerting its antitumor activity[62-66]. In 2008, Hiwarkar et al[67] evaluated the feasibility of topotecan, vinorelbine, thiotepa and gemcitabine (TVTG) in 11 adult patients with relapsed/refractory acute lymphoblastic leukaemia/lymphoma. Three patients (37%) achieved CR (two B-ALL and one T-ALL), whereas eight were refractory to TVTG. The median time from achieving a CR to transplant was 48 days (range 19-65 days). Two patients who achieved CR after TVTG, underwent allogenic stem cell transplant and were alive and free of disease after 24 and 26 months from the start of TVTG respectively. Another patient who achieved CR after TVTG, underwent allogenic stem cell transplant but subsequently died of disease relapse 13 months after treatment of TVTG.

Annamycin

Annamycin is an anthracycline antibiotic with high affinity for lipid membranes and significantly more activity than doxorubicin which has an increased affinity to liposomes to improve drug targeting to the leukemic blasts and to reduce cardiac toxicity[68,69]. In 2013, Wetzler et al[70] reported a phase I/II trial of nanomolecular liposomal annamycin in 31 adult patients with relapsed/refractory acute lymphoblastic leukemia. Eight of the patients completed 1 cycle of the 3 days of treatment at the maximally tolerated dose (MTD). Of these, 5 (62%) had an efficacy signal with complete clearing of circulating peripheral blasts. Three of these subjects also cleared bone marrow blasts with 1 subsequently proceeding onto successful stem cell transplantation. The other 2 developed tumor lysis syndrome and unfortunately died before response assessment.

Monoclonal Antibodies

Specific monoclonal antibodies have been demonstrated encouraging activity in frontline and relapsed ALL including unconjugated monoclonal antibodies (e.g., ofatumumab, alemtuzumab and epratuzumab), monoclonal antibodies conjugated to cytotoxic agents (e.g., inotuzumab ozogamycin and SAR3419), monoclonal antibodies conjugated to toxins such as Pseudomonas or Diptheria toxins (e.g., BL22 and moxetumomab pasudotox), and the recently developed class of T-cell engaging bi-specific singlechain antibodies (BiTE® antibodies) that engage CD3 on the surface of cytotoxic T-cells and redirect cytotoxic T lymphocytes to lyse CD19 positive target ALL cells (e.g., blinatumomab)[71-74].

SAR3419

SAR3419 is an antibody-drug conjugate targeting CD19 which has been applied on Relapsed/Refractory B-cell lymphoma[75]. It has been successfully applied on leukemia in preclinical models of acute lymphoblastic leukemia[76]. A phase II study of SAR3419 administered at a dose of 55 to 70 mg/m^2 IV once per week for 4 weeks and then once every other week over a period of 8 weeks is ongoing in adults with refractory/relapsed ALL[73].

Unconjugated Monoclonal Antibodies

Rituximab

In 2012, Chevallier et al[77] reported a pilot study about Rituximab for the treatment of adult relapsed/refractory CD20 positive B-ALL patients. In their study, nine adult patients (6 males and 3 females) with a median age of 57 (range, 19-70) years were treated for relapsed (n = 6) or refractory (n = 3) B-ALL. Four patients achieved CR, four other patients achieved > 50% of blast clearance in bone marrow from the baseline but without full peripheral count recovery. One patient failed to respond.

Ofatumumab

Ofatumumab is a second generation anti-CD20 type I human monoclonal antibody that binds to a small-loop epitope of CD20 with greater avidity than rituximab[78], which may be responsible for its enhanced antibody dependent cellular cytotoxicity effect[79].

Ofatumumab also binds closer to the cell membrane than rituximab which results in higher complement-dependent cellular cytotoxicity effect[80]. Clinical trials combining chemotherapy with ofatumumab are currently underway.

Epratuzumab

Epratuzumab is a humanized monoclonal antibody against CD22. In 2012, the Southwest Oncology Group combined epratuzumab with clofarabine and cytarabine in a phase 2 trial for adults with refractory/relapsed ALL[81]. 8 patients (28%) had CR and 5 patients (17%) had CRi. The overall response rate was 45%.The null response rate in the protocol was 10%.

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is a monoclonal antibody against CD22 that is bound to calecheamicin, a toxic natural product of Micromonospora echinospora[82]. In 2012, Kantarjian et al[83] reported a phase 2 study on Inotuzumab ozogamicin for refractory and relapsed acute lymphocytic. 49 patients were enrolled and treated. Median age was 36 years (range 6-80). CD22 was expressed in more than 50% of blasts in all patients. Nine (18%) patients had CR, 19 (39%) had marrow CR, 19 (39%) had resistant disease, and two (4%) died within 4 weeks of starting treatment. The overall response rate was 57%.

Moxetumomab Pasudotox

Moxetumomab pasudotox (HA22 or CAT-8015) is a recombinant immunotoxin composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38-kDa fragment of *Pseudomonas* exotoxin A. Moxetumomab pasu-

dotox is an improved, more active form of a predecessor recombinant immunotoxin, BL22 (CAT-3888)[84]. A phase 1/2 study of Moxetumomab Pasudotox in adult patients with relapsed/Refractory ALL started from December 2013.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52. Initial reports suggested that alemtuzumab had limited activity in relapsed or refractory ALL[85,86]. But it was suggested incorporated into front-line therapy of adult ALL for eradication of MRD[87].

Conclusions

Although agents for refractory/relapsed ALL has been developed greatly recent years, but the prognosis of refractory/relapsed ALL is still poor. Unfortunately, even patients with refractory/relapsed ALL treated with salvage chemotherapy regimens achieved remissions, the duration of the remissions is always short even with consolidation with haematopoietic stem cell transplantation (HSCT). And complications such as graft-versus-host-disease (GVHD), hemorrhagic cystitis continue to be a major limitation to successful HSCT[88-91]. Treatment of refractory/relapsed ALL remains a great challenge and there is no standard therapy for refractory/relapsed ALL. The molecular mechanisms underlying the pathogenesis of refractory/relapsed acute leukemia need to be further investigated to develop new agents and new therapy strategy. Molecularly targeted therapies in combination with HSCT, chemotherapy, immunotherapy show great promises.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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