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Novel Therapeutic Strategies in Adult Acute Lymphoblastic Leukemia – A Focus on Emerging Monoclonal Antibodies

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Abstract

The outcomes in adult B-cell acute lymphoblastic leukemia (ALL) remain inferior to those achieved in pediatric populations. Targeted therapy with monoclonal antibodies may improve outcomes in adult B-cell ALL without significant additive toxicity. Rituximab is the best known monoclonal antibody and is routinely used in combination chemoimmunotherapy for treatment of adult B-cell ALL and Burkitts leukemia. A number of other monoclonal antibodies are currently under investigation for treatment of adult B-cell ALL including unconjugated antibodies (eg., ofatumumab, alemtuzumab and epratuzumab), antibodies conjugated to cytotoxic agents (eg., inotuzumab ozogamycin and SAR3419), antibodies conjugated to toxins such *Pseudomonas* or *Diptheria* toxins (eg., BL22 and moxetumomab pasudotox), and T-cell engaging bi-specific antibodies that redirect cytotoxic T lymphocytes to lyse target ALL cells (eg., blinatumomab). In this article we review the therapeutic implications, current status and results of monoclonal antibody-based therapy in adult B-cell ALL.

Keywords

Monoclonal antibody; Acute lymphoblastic leukemia; Rituximab; Ofatumumab; Epratuzumab; Alemtuzumab; Blinatumomab; Moxetumomab; Inotuzumab

Introduction

The age adjusted incidence of acute lymphoblastic leukemia (ALL) in the United States is approximately 1.5 per 100,000 population with a peak incidence between the ages of two and five years and a second peak after the age of 50 years [1]. Approximately 4000 cases of ALL are diagnosed annually in the United States [2]. Childhood and adolescent ALL comprise two-thirds of this number and ALL remains the most common malignancy in the pediatric population. Risk stratified intensification of chemotherapy, improved supportive care, and optimization of chemotherapy combinations and dosage schedules have resulted in

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improved survival rates in pediatric ALL with current 5-year event free survival rates of approximately 85 % in children and adolescents receiving ALL therapy in developed countries [3–6]. Similar strategies and increased use of hematopoetic stem cell transplantation have improved cure rates in adult populations from 20 % to 40 % over the last five decades, but these outcomes remain inferior to those attained in children and adolescent populations [7–12].

The outcome of adult ALL has significantly improved over the last two decades. For example, a recent analysis documented an improvement in 5-year survival rates from 22 % to 33 % between 1980–1984 and 2000–2004 [13]. Not surprisingly, the improvements in survival were age-dependent with a 20 % improvement in 5-year relative survival rates for patients 15 to 19 years of age versus no significant improvement in 5-year relative survival rates for patients above the age of 60 years [13]. A number of factors contribute to the decline in overall survival with increasing age including increased frequency of adverse biological features such as Philadelphia-chromosome positive ALL, increased drug resistance, lower rates of participation in clinical trials and poor tolerance to certain chemotherapeutic agents resulting in suboptimal dose administration or delayed frequency of administration of chemotherapy [14, 15]. Clearly, further improvements in management of adult ALL are needed.

Monoclonal Antibody Therapy in Adult B-cell ALL

One approach to improving outcomes in adult ALL involves intensification of existing chemotherapy combinations or addition of chemotherapeutic agents such as asparaginase to ALL regimens in adult patients. Intensifying chemotherapy in adult patients may reduce the incidence of leukemia resistance, but this occurs at the cost of increased toxicities, myelosuppression-related complications, and deaths in complete remission [10, 16–20]. Thus, novel anti-leukemic agents are needed to improve outcomes in adult ALL patients. Targeted therapy has shown promise in treatment of adult ALL. A number of cell surface antigen specific monoclonal antibodies have demonstrated encouraging activity in frontline and relapsed ALL [21–23, 24••]. The maximum amount of experience is available for antibodies targeted to CD20 such as rituximab, which has been combined with chemotherapy to treat adult ALL and has improved outcomes [22, 24••, 25, 26, 27•, 28]. Rituximab in combination with chemotherapy is now considered standard of care in Burkitt or Burkitt-like leukemia/lymphoma and B-cell ALL.

A variety of monoclonal antibodies are currently being evaluated in the therapy of adult ALL and early reports are encouraging. These include unconjugated monoclonal antibodies (eg., ofatumumab, alemtuzumab and epratuzumab), monoclonal antibodies conjugated to cytotoxic agents (eg., inotuzumab ozogamycin and SAR3419), monoclonal antibodies conjugated to toxins such as *Pseudomonas* or *Diptheria* toxins (eg., BL22 and moxetumomab pasudotox), and the recently developed class of T-cell engaging bi-specific single-chain 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 (eg., blinatumomab) [29, 30]. In this article we will review the therapeutic potential and current status of monoclonal-antibody based therapies in adult ALL.

Unconjugated Monoclonal Antibodies

Rituximab (Unconjugated CD20 Monoclonal Antibody)

Rituximab is a chimeric monoclonal antibody that targets surface CD20. CD20 is a B-lineage antigen that is expressed on the surface of normal and malignant B-cells during nearly all stages of differentiation [31]. CD20 has heterogenous surface expression on B-cells ranging from 40 % to 50 % in precursor B-cell ALL to nearly 100 % in Burkitt or Burkitt-like leukemia/lymphoma [32–34]. CD20 functions as a calcium channel that influences cell cycle progression and differentiation via downstream signaling pathways resulting in under expression of proapoptotic proteins such as Bax/Bak and overexpression of anti-apoptotic proteins such as Bcl-2 [35]. CD20 expression in ALL is associated with a worse clinical outcome [36]. In adult patients with ALL receiving hyper-CVAD therapy, CD20 expression was associated with significantly higher relapse rates (61 % *v* 37 %; $P < 0.01$) and lower 3-year overall survival (OS) rates (27 % *v* 60 %, $P < 0.01$) [10, 36, 37]. Similarly, CD20 expression was associated with a higher incidence of relapse in the GRAALL 2003 trial which evaluated treatment outcomes with pediatric regimens in adult patients with Philadelphia chromosome (Ph) – negative ALL[38].

Rituximab is an unconjugated monoclonal antibody that binds to surface CD20 and directly induces cell death by activating apoptotic pathways and suppressing proliferative pathways [31]. Indirect cell death occurs via antibody-dependent cell-mediated cytotoxicity and complement-mediated cytolysis [31]. The addition of rituximab was first shown to increase the complete-response rate and prolong overall survival without significant additive toxicity in elderly patients with diffuse large-B-cell lymphoma (DLBCL) who received chemoimmunotherapy with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as compared to those who received CHOP chemotherapy alone [39]. Similarly, addition of rituximab to fludarabine-based therapies resulted in improved progression-free survival and overall survival in patients with chronic lymphocytic leukemia (CLL) with good tolerance [40, 41].

Thomas et al. [27•] compared chemoimmunotherapy with rituximab and hyper-CVAD in 173 patients (97 with $CD20^+$ ALL) to chemotherapy with hyper-CVAD alone in 109 patients (53 with $CD20^+$ ALL). The complete remission (CR) rate with rituximab and hyper-CVAD was 95 %; 3-year rates of CR duration and survival were 60 % and 50 %, respectively. Younger patients (age < 60 years) with $CD20^+$ ALL had significantly improved CR duration (70 % *v* 38 %; $P < 0.001$ %) and overall survival (75 % *v* 47 %; $P = 0.003$) with hyper-CVAD and rituximab regimens compared with hyper-CVAD alone. However, addition of rituximab did not improve survival in older patients (age > 60 years) with $CD20^+$ ALL, most likely due to increased infection-related mortality in remission in this subset of patients. Similar results were reported by the German study group in the German Multicenter Study Group for Adult ALL (GMALL) 2002 protocol [28]. A total of 180 CD20+ patients were identified, of whom 117 (63 %) received rituximab and were compared with 70 (37 %) who received the same chemotherapy regimen without rituximab. Patients were stratified by risk groups wherein high-risk patients received three treatments with standard dose rituximab combined with chemotherapy followed by allogeneic stem cell

transplantation; standard-risk patients received eight doses of rituximab combined with chemotherapy. In the standard-risk group, addition of rituximab improved 3-year remission duration (64 % *v* 48 %; $P < 0.009$) and overall survival rates (75 % *v* 54 %; *P* = not reported). Rituximab similarly improved 3-year overall survival rates in the high-risk group (75% *v* 40 %; *P* = not reported).

Future efforts at enhancing the efficacy of rituximab are underway. These include attempts to up-regulate surface expression of CD20 by means of a prophase with either corticosteroids or induction chemotherapy. Recent studies have shown up regulation of CD20 in children with B-cell ALL after exposure to corticosteroids [24••, 25, 42]. These data support the notion that changes in antigen expression on leukemic blast cells is likely to be a consequence of corticosteroid-induced modulation, and not merely an outcome of sub-clone selection [42]. Similarly, studies have reported increased frequency and expression of CD20 during and after induction therapy for B-cell ALL [43–45]. Dworzak et al., noted an increased frequency of CD20 expression on B-lymphoblasts of patients with ALL; from 45%in preinduction samples to 81 % at the end of induction therapy. They also noted increased intensity of expression with 52 % of leukemic cells having ≥ 90% CD20 expression at the end of induction therapy as opposed to only 5 % of leukemic cells having such intense expression at diagnosis [43]. The up-regulation of CD20 by either corticosteroids or induction chemotherapy might result in acquisition of increased sensitivity to rituximab and might improve response rates to rituximab in patients with low or absent CD20 expression at initial diagnosis. Another strategy to improve the efficacy of rituximab includes prolonged administration of rituximab beyond the initial eight doses. This could be achieved by administering rituximab during the maintenance phase of B-cell ALL in combination with methotrexate, mercaptopurine, vincristine and steroids. Similar strategies have safely been implemented in non-Hodgkin's lymphoma (NHL) wherein prolonged administration of maintenance rituximab resulted in improved event-free survival and progression-free survival in patients with newly diagnosed follicular lymphoma [46, 47]. A third potential strategy includes concomitant administration of novel molecularly targeted therapeutic agents such as anti-Bcl-2 agents or mTOR (mammalian target of rapamycin) inhibitors with rituximab [24••]. These novel agents may not only abrogate resistance to rituximab but could prove to be synergistic with rituximab.

Ofatumumab (Novel Unconjugated CD20 Monoclonal Antibody)

More potent CD20 antibodies such as ofatumumab are currently under investigation. These are intended to demonstrate improved efficacy as compared to rituximab or to demonstrate activity in patients who become resistant to rituximab. Ofatumumab (Arzerra; GlaxoSmithKline, Collegeville, PA and Genmab, Copenhagen, Denmark) is of special interest in this setting as it has already shown activity in patients with chronic lymphocytic leukemia who are refractory to rituximab [48, 49]. Ofatumumab is a second generation anti-CD20 type I human monoclonal antibody that binds to a small-loop epitope of CD20 that is different from the binding site of rituximab [50]. It binds with greater avidity than rituximab which may be responsible for the enhanced antibody-dependent cellular cytotoxicity effect seen with ofatumumab as compared to rituximab [51]. Ofatumumab also binds closer to the cell membrane than rituximab which results in higher complement-dependent cellular

cytotoxicity effect [50, 52]. Clinical trials combining chemotherapy with ofatumumab are currently underway.

Epratuzumab (Unconjugated CD22 Monoclonal Antibody)

Epratuzumab is an unconjugated humanized monoclonal antibody that binds to the third extracellular domain of CD22 with subsequent internalization of the receptor/ antigen complex [53]. Post internalization, epratuzumab exerts its action via antibody-dependent cellular cytotoxicity, CD22 phosphorylation, and inhibition of cellular proliferation [54]. Interest in this drug was heightened after studies documented an overall response rate of 43 % with single-agent epratuzumab in patients with recurrent follicular lymphoma [55]. Raetz et al., administered epratuzumab alone and epratuzumab in combination with re-induction chemotherapy to children with relapsed ALL whose blasts expressed CD22 (≥ 25 %) [56]. Therapy consisted of a single-agent phase wherein epratuzumab was administered twice weekly at a dose of 360 mg/m^2/dose for four consecutive doses, followed by four weekly doses of epratuzumab in combination with standard four-drug re-induction therapy. Therapy was well tolerated with dose-limiting toxicity including seizure in one patient and asymptomatic transaminitis in another patient. Of the 15 patients treated, nine patients achieved a complete remission with no detectable minimal residual disease (MRD) in seven of these patients. A recent follow-up of this study noted that although addition of epratuzumab to chemotherapy did not improve CR rates when compared to historical controls treated with chemotherapy alone, those treated with epratuzumab and chemotherapy were significantly more likely to become MRD negative [57].

Alemtuzumab (Unconjugated CD52 Monoclonal Antibody)

Alemtuzumab is an unconjugated CD52 humanized monoclonal antibody directed against CD52. CD52 is a surface antigen protein expressed at high density on most normal and malignant B and T lymphocytes but not on CD34 hematopoietic stem cells [58, 59]. Binding of alemtuzumab to CD52 results in target cell death via complement activation, antibody-dependent cellular cytotoxicity, and apoptosis [60–62]. Alemtuzumab induced significant responses with acceptable toxicity in CLL resulting in its approval by the US Food and Drug Administration for treatment of frontline or refractory CLL [63, 64]. Initial reports suggested that alemtuzumab had limited activity with increased toxicity in relapsed or refractory ALL. No responses were noted in six adult patients with ALL treated with alemtuzumab [65]. Similarly, single agent alemtuzumab produced poor results in a Children's Oncology Group (COG) pediatric ALL study. Only one (8 %) of the 13 patients enrolled in that trial achieved a CR with alemtuzumab and four (31%) had stable disease with dose limiting toxicity in two of nine evaluable patients [66]. Stock et al., evaluated the role of alemtuzumab for eradication of minimal residual disease (MRD) in newly diagnosed adult patients with ALL whose blasts expressed CD52 [67]. Twenty-four patients in CR following intensive chemotherapy received alemtuzumab at a target dose of 30 mg administered subcutaneously three times a week for 4 weeks (total of 12 doses) during post-remission therapy. Serial MRD using quantitative clone-specific PCR was performed in 11 of 24 cases and a median 1-log decrease in MRD was documented during alemtuzumab therapy. Alemtuzumab was well tolerated with grade 3/4 myelosuppression in four patients,

transient CMV viremia in two patients, and *Staphylococcus aureus* empyema in one patient. An encouraging disease-free survival of 53 months and median overall survival of 55 months were noted.

Interestingly, alemtuzumab may have enhanced potency in patients that develop resistance to rituximab. This may be secondary to down-regulation of CD20 and up-regulation of CD52 and complement inhibitory proteins CD55 and CD59 in patients that acquire resistance to rituximab [68]. Preclinical studies in NHL cell lines suggest that blocking CD52 with alemtuzumab may have the potential to reverse acquired resistance to rituximab [68]. Thus, combining rituximab and alemtuzumab may prove to be not only additive, but synergistic.

Conjugated Monoclonal Antibodies

Inotuzumab Ozogamicin (CD22 Monoclonal Antibody Conjugated to Calicheamcin)

Inotuzumab is an antibody drug conjugate that comprises a IgG4 antibody directed to CD22 linked to a derivative of calicheamicin [69]. Calicheamicin, which is isolated from the actinomycete *Micromonospora echinospora calichensis*, binds to the minor groove in DNA and induces double-strand DNA breaks ultimately resulting in cell death [69]. CD22 is expressed in 60–90 % of B-lymphocyte malignancies and is not expressed on hematopoetic stem cells; it is effectively internalized and is not shed into the extracellular environment. These characteristics make it an ideal target for antibody based therapy.

Initial trials with inotuzumab were conducted in patients with B-cell lymphomas, including follicular lymphoma and DLBCL. Inotuzumab monotherapy was investigated in patients with indolent B-cell NHL who had progressed after two or more systemic therapies and exhibited refractory disease to rituximab or rituximab-containing regimens [70]. Inotuzumab ozogamicin was administered at a dose of 1.8 mg/m^2 every 28 days for four to eight cycles. The objective response rate was 53 %. The most common treatment–related adverse events included myelosuppression, liver function abnormalities, fatigue and gastrointestinal toxicities including nausea and decreased appetite. Advani et al., noted a response rate of 39 % with single agent inotuzumab in 79 patients with relapsed/ refractory CD22$^+$ NHL [71]. Inotuzumab was further investigated in combination with rituximab for patients with relapsed/ refractory follicular lymphoma or DLBCL [72]. Patients received rituximab 375 mg/m^2 on day 1 of each 28-day cycle and inotuzumab on day 2 at doses of 0.8 mg/m^2, 1.3 mg/m^2, and 1.8 mg/m^2 for a maximum of eight cycles. The overall response rate was 83 % in follicular lymphoma and 67 % in DLBCL. The combination was well tolerated with a safety profile similar to inotuzumab monotherapy. The most frequent adverse event was reversible thrombocytopenia.

We performed a phase II study of inotuzumab monotherapy administered at a dose of 1.3 to 1.8 mg/m^2 every 3–4 weeks in patients with relapsed/ refractory B-cell ALL [73••]. A total of 49 patients were enrolled and all patients had CD22 expression on more than 50 % of B-lymphoblasts. Thirty-six (73 %) patients received inotuzumab ozogamicin in second salvage or beyond. Nine (18 %) patients had a complete response and 19 (39 %) had a marrow complete response for an overall response rate of 57 %. Multi-parameter flow cytometry for

MRD revealed that MRD-negative status was attained in 17 of 27 evaluable patients (63 %). Eighteen of the 28 responders had chromosomal abnormalities at initiation of therapy and 16 of these achieved complete cytogenetic remission (89 %). Median overall survival for all patients was 5.1 months. Twenty-two of the 49 patients underwent allogeneic stem cell transplant with a censored median overall survival of 5.2 months in transplanted patients. Median survival for the 28 responders was 7.9 months and the estimated 9-month survival for the nine patients that achieved complete response was 78 %. Inotuzumab monotherapy was well tolerated; and the most frequent adverse events were fever, hypotension and abnormalities in liver chemistries. Two patients died within 4 weeks of initiating therapy from non-drug related complications. Inotuzumab is a highly active single agent in the treatment of patients with relapsed/ refractory B-cell ALL. Unfortunately, responses were short-lived and little effect was seen on median survival, likely due to the heavily pretreated population receiving therapy. Further strategies are needed to improve the efficacy and impact of inotuzumab in patients with B-cell ALL including earlier implementation of single agent inotuzumab for relapsed/ refractory disease, combination of inotuzumab and chemotherapy in frontline and salvage therapy for ALL, and combined monoclonal antibody therapy with rituximab and inotuzumab for treatment of MRD positive or relapsed B-cell ALL.

SAR3419 (CD19 Monoclonal Antibody Conjugated to Maytansin)

SAR3419 is a novel humanized IgG1 CD19 monoclonal antibody conjugated to a maytansin derivate through a cleavable linker [74]. Maytansin is a high-potency tubulin inhibitor and CD19 is almost exclusively B-cell specific making SAR3419 a potent and selective agent for B-cell malignancies. Internalization of the antibody-antigen conjugate precipitates release of active metabolites that result in apoptosis. Mouse xenografts of NHL that were relatively resistant to rituximab or cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) responded to SAR3419 at doses of 15 mg/kg or 30 mg/kg with significant improvement in survival [75]. Recently, phase I studies in patients with relapsed/ refractory NHL reported tumor reduction with SAR3419 in 17 of 27 patients (63 %) at a maximum tolerated dose of 160 mg/m^2. Dose limiting toxicity was ocular toxicity including blurry vision and vision impairment which were reversible in all patients on cessation of the drug [76, 77]. A phase II study of SAR3419 in adults with relapsed/ refractory B-ALL is currently accruing.

Moxetumomab Pasudotox and BL22 (CD22 Antibodies Conjugated to *Pseudomonas* Exotoxin)

Recombinant immunotoxins consist of a variable fragment (Fv) of an antibody fused to the cytotoxic portion of a protein toxin. The Fv fragment binds to the target antigen on the cell surface resulting in internalization of the antigen-antibody complex and release of the toxin with subsequent apoptosis [78]. Moxetumomab pasudotox, previously called HA22 or CAT-8015, is a recombinant immunotoxin composed of a variable fragment of an anti-CD22 monoclonal antibody fused to a 38-kDa fragment of *Pseudomonas areuginosa* exotoxin A, called PE38 [78]. Moxetumomab is a more active form of its predecessor BL22 (CAT-3888), which had significant activity in hairy cell leukemia (HCL). In an initial phase

I trial, 31 patients with relapsed/ refractory HCL were treated with BL22; the overall response rate was 80 %, including a CR rate of 61 % and a PR rate of 19 % [79, 80]. The most common toxicities included hypoalbuminemia, transaminase elevation, fatigue, and edema. In the phase II portion of this study 36 patients with relapsed/ refractory HCL were treated with an overall response rate of 72 %, including a 47 % CR rate [81]. In a phase I study of BL22 in $CD22^+$ pediatric ALL, a total of 23 children received BL22 at escalating doses from 10 to 40 μg/kg every other day for three or six doses every 21 or 28 days. Although 70 % of treated patients showed reduction of leukemic blasts, no objective CRs or PRs were documented [82]. Similarly, BL22 produced disappointing results in patients with NHL and CLL [81, 82]. The inferior activity of BL22 in ALL and CLL may be due to the lower density of CD22 expression in CLL (1,200 sites/cell) and ALL (4,500 sites/cell) as compared to HCL (40,000 sites/cell).

To improve the efficacy of BL22 in non-HCL tumors, further mutagenesis analysis was performed and resulted in the selection of an Fv with a higher binding affinity to surface CD22 by virtue of a slower off-rate [83]. This new compound was initially named high-affinity BL22 (HA22) and was later renamed moxetumomab pasudodotox. The higher-affinity moxetumomab demonstrated enhanced cytotoxicity and antitumor activity towards HCL and CLL cells by up to 50-fold. Phase I studies with moxetumomab in patients with refractory HCL demonstrated a CR rate of 31 % at all dose levels with no dose-limiting toxicity [84]. Median time to CR was 2.8 months and the majority of CRs were durable with only one of the 14 patients who achieved CR relapsing in less than 1 year. In a phase I study by Wayne et al., 21 children and young adolescents with relapsed/refractory ALL received moxetumomab pasudotox every other day for six doses [85•]. Cycles were repeated every 3 weeks. Grade 3/4 capillary leak syndrome was observed in two of the initial seven patients but was not seen after initiation of a dexamethasone pre-phase in the subsequent 14 patients. Of 17 evaluable patients, 24 % achieved CR, 6 % had PR and 47 % had hematological improvement for an overall clinical activity rate of 70 %. Further clinical trials with moxetumomab administered at higher doses or increased frequency in pediatric and adult ALL are currently underway.

Novel strategies are currently being implemented to enhance the potency and tolerability of immunotoxins. One such strategy includes the development of a lysosomal protease-resistant variant of moxetumomab pasudotox obtained by removal of the major protease binding sites in domain II of moxetumomab [86]. This lysosomal protease resistant variant is called LR-HA22 and has demonstrated up to 16-fold enhanced cytotoxicity as compared to HA-22 in CLL cell lines [86]. Another approach focuses on reducing the immunogenicity of moxetumomab pasudotox by identification and removal of immunogenic B-cell and T-cell epitopes. Preliminary efforts in this direction have been successful. Deletion of seven major immunogenic epitopes in domains II and III of HA-22 resulted in dampened response to antisera in patients who were previously immunized to HA-22. The immune epitope bereft variant has been named HA22-LR-8M and is currently under investigation [87].

Bispecific Monoclonal Antibodies

Blinatumomab ($CD3^+CD19^+$ Bi-specific T-cell Engaging Monoclonal Antibody)

T-cell engaging bispecific antibodies are a novel class of therapeutic agents for treatment of NHL and adult ALL. Blinatumomab is a bi-specific antibody that transiently engages surface CD3 on cytotoxic T-lymphocytes and redirects them to lyse CD19 expressing B-lymphoblasts. Initial reports documented partial and complete tumor regressions with low doses of blinatumomab in patients with relapsed B-cell NHL. All seven patients treated at a dose level of 0.06 milligrams experienced tumor regression and clearance of tumor cells from bone marrow and liver [88]. Presence of MRD after induction chemotherapy is an adverse prognostic factor in adult ALL and is associated with a higher incidence of relapse. Preliminary results in B-ALL from Topp et al., suggested that blinatumomab was effective in eradicating ALL in adult patients with MRD-positivity post-induction chemotherapy [89]. Twenty-one adult patients in first CR with persistent or relapsed MRD received blinatumomab therapy at a dose of 15 $\mu g/m^2$ by continuous infusion over 24-hours daily for 4 weeks. Of the 21 patients treated, one was not evaluable due to early termination of therapy. Sixteen (80 %) of the remaining 20 patients became MRD-negative, including 12 patients who had been molecularly refractory to prior chemotherapy. Responses were durable with an overall probability of relapse-free survival of 78% at 15 months. For patients that did not proceed to allogeneic stem cell transplant the probability of relapse-free survival at 15 months was 60 %. Transient grade 3/4 lymphopenia was the most frequently noted adverse effect. Final analysis on this patient population has recently been published; with a median follow up of 33 months, the hematological relapse free survival for all 20 patients is 61 % [90]. The nine patients who proceeded to allogeneic stem cell transplantation (HSCT) after blinatumomab treatment had a hematological relapse free survival of 65 %. This proves that blinatumomab can induce long–lasting remissions in patients with B-cell ALL who have MRD induction therapy and may potentially result in European Medical Agency (EMEA) approval of blinatumomab for MRD-positive B-cell ALL. Similarly, blinatumomab was well tolerated and rapidly induced CR in three children with relapsed ALL post allogeneic stem cell transplant [91]. Interim analysis of an ongoing trial in adults with relapsed/ refractory pre-B ALL patients identified 12 (67 %) CRs among the 18 patients that have been enrolled thus far [92]. Median time to CR was two cycles and all 12 responders reached MRD-negativity at the end of two cycles. Blinatumomab was well tolerated. Pyrexia and chills were the most common adverse events and four patients had fully reversible neurological serious adverse events. No blinatumomab related deaths were identified. Single-agent blinatumomab is currently under investigation for patients with relapsed/refractory ALL.

Conclusion

A number of prospective trials are currently evaluating monoclonal antibodies either as monotherapy, in combination with cytotoxic chemotherapy, or in combination with other monoclonal antibodies in frontline and salvage therapy for pediatric and adult B-cell ALL. Strategies to improve the efficacy of monoclonal antibodies include prolonged administration, up regulation of target surface antigens with a pre-phase of chemotherapy or

corticosteroid therapy, overcoming resistance pathways by combining monoclonal antibodies with novel molecular therapeutic agents, developing novel bi-specific and T-cell engaging antibodies and reducing immunogenicity of existing monoclonal antibodies by selective deletion of immunogenic epitopes. It is hoped that such measures will enhance the efficacy and tolerability of monoclonal antibodies resulting in improved cure rates with abrogated toxicities in patients with ALL.

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