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Novel Therapeutic Targets in ALL Therapy

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1. Introduction

ALL is a malignant disorder of the blood system characterized by uncontrolled proliferation of bone marrow-derived B- and T-lymphocyte progenitors that are arrested in an early stage of development (Pui et al, 2008). This arrest is caused by aberrant gene fusions or inappropriate expression of oncogenes. The lymphoblasts replace the normal marrow elements, resulting in a substantial decrease in the production of normal blood cells. Consequently, anemia, thrombocytopenia, and neutropenia occur to varying degrees. Moreover, the expanding lymphoblasts can escape the bone marrow niche, and manifest as heptospenomegaly, enlargement of lymph nodes, thymus, and gonads, and infiltration of the meninges (Pui et al, 2008).

ALL has a peak incidence between the ages of 2 to 5 years, representing 25% of the malignant disorders in childhood (Pui et al, 2006). Currently, ALL is treated by administration of cyclic induction chemotherapy, which is intended to kill the majority of leukemic cells, followed by a consolidation chemotherapy, which should destroy any remaining leukemic cells (Freycon et al, 2008; Pui et al, 2008). For high risk patients, myeloablative regimens followed by allogeneic hematopoietic stem-cell transplantation are indicated to achieve more extensive eradication of leukemia and to induce graft versus leukemia effects against the disease. The implementation of risk-adapted strategies, which tailor the intensity of therapy to the risk of relapse, has resulted in a cure rate of more than 80% in children being long-term survivors (Pui et al, 2006). In contrast to the successes obtained with paediatric patients, treatment outcomes for adult patients remain poor with less than 40% being long-term survivors (Vitale et al, 2006). Due to relative nonspecific action and narrow therapeutic indices of antileukemic medications, serious short and long-term complications arise as a result of the intensification of many current therapies (Barr et al, 2008).

The identification of genetic and epigenetic changes that are associated with leukemogenesis and altered drug response provides insights into the molecular basis of ALL. The translation to the clinic might serve as a model for optimizing the treatment and generate innovative therapeutic agents. Finally, these could be implemented in more effective, and potentially less toxic, individually tailored treatment protocols, based on the underlying molecular abnormalities of a patient's leukemia. This review will concentrate on novel agents that show promising anti-leukemic activity in pre-clinical studies or clinical trials.

2. CXCR4 inhibitors

Several studies have been reported on the involvement of chemokines and adhesion molecules in the process of mobilization of ALL cells. Among the most studied molecules are the chemokine receptor CXCR4 and the chemokine stromal cell-derived factor-1 (SDF-1, CXCL12); in particular CXCR4, was found to be highly expressed in bone-marrow derived ALL cells enabling these cells to migrate across a gradient of CXCL12 concentrations (Crazzolara et al, 2001). Elevated levels of CXCL12 are not only found in the bone marrow environment, but also at extramedullary sites associated with ALL induced organ infiltration (Muller et al, 2001). Subsequently CXCL12 can act as survival and proliferation factor for CXCR4 positive cells and protect them from spontaneous and chemotherapy-induced apoptosis (Burger et al, 2000). In several studies, CXCL12 is also reported in the process of homing of CXCR4 positive cells in NOD/SCID xenograft mouse models (Nagasawa et al, 1996). Of note is the direct correlation between high CXCR4 expression on lymphoblasts and the extent of extramedullary infiltration in patients with ALL (Crazzolara et al, 2001).

Direct evidence for the involvement of CXCR4 and CXCL12 in the release of ALL cells in the blood is demonstrated from the finding that treatment of mice with small compounds that target CXCR4 and its ligand can disrupt the interaction between ALL cells and the stromal microenvironment. The polyphemusin II-derived inhibitors T140, TC140012, T134, and the bicyclam AMD3100 effectively inhibit CXCR4, and CXCL12-driven migration into bone marrow layers *in vitro*, thus enhancing the cytotoxic and anti-proliferative effects of the currently used agents vincristine and dexamethasone (Juarez et al, 2003). Disruption of the interaction of CXCR4 and its ligand *in vivo* mobilizes leukemic cells into the peripheral blood, potentially rendering them more susceptible to cytotoxic effects (Juarez et al, 2006). The importance of CXCR4 in the context of therapy is further supported by the observation, that CXCR4 expression is dynamically up regulated by chemotherapy exposure in ALL cells. Up regulation of surface CXCR4 may therefore be considered as a mechanism of chemo resistance in acute leukaemias that is potentially reversible with CXCR4-targeted therapy.

Concerns have been raised regarding potential side effects from CXCR4 inhibition, since CXCR4 knockout mice display severe defects in hematopoesis, vascular and cardiac development (Nagasawa et al, 1996). However, these defects are related to CXCR4 functions in early development, and short-term exposure to AMD3100 for stem cell mobilization does not result in any significant toxicity (Broxmeyer et al, 2005). Activity of different CXCR4 antagonists in animal models for solid tumors (Smith et al, 2004) generalizes the potential anti-neoplastic activity and suggests further clinical development of these agents in ALL. It is anticipated, that a phase I pediatric study has recently started to study the addition of the selective CXCR4 antagonist plerixafor to enhance the conditioning regimen cytotoxicity (NCT01068301, www.clinicaltrials.gov). Though the primary goal is to determine the maximum tolerated dose (MTD), additional trials are necessary to study the use of plerixafor as a complimentary agent with conditioning as well as other chemotherapeutic regimens for patients with relapsed or refractory hematologic malignancies.

3. CD22 immunoconjugates

The approval of antibody-targeted agents for cancer treatment has provoked increased interest in the development of new and improved antibody-mediated therapies. This emerging approach centers on targeting cell clusters of differentiation on ALL cells with a

monoclonal antibody (mAb), conjugated to a cytotoxic agent. After internalization of the antibody-drug complex, vital survival pathways for malignant cells can be blocked or dyregulated. Among these, CD22 antibody-targeted agents have more extensively been explored with significant preclinical success in models of acute leukemia (Dijoseph et al, 2004).

CMC-544 (inotuzumab ozogamicin) is a conjugate of a recombinant humanized antibody directed against the CD22 antigen and calicheamicin. After internalization into the target cell, calicheamicin binds to DNA in the minor groove in a sequence specific manner, causing double-strand DNA breaks followed by apoptotic death. *In vitro*, CMC-544 binds to CD22 with subnanomolar affinity and potently inhibits growth of ALL cell lines (Dijoseph et al, 2007). When administered to xenograft models, CMC-544 prevents engraftment, but also induces dose-dependent tumor regression in mice presenting with leukemia. Whereas the level of CD22 expression is significantly reduced after incubation with CMC-544, the CD20 level can be increased (Takeshita et al, 2009). Therefore, sequential administration of rituximab increases the cytotoxic effect and supports the rationale for a combination with other antibodies.

Currently, a phase I study is recruiting patients for the aminstration of CMC-544 with or without rituximab in relapsed or primary refractory ALL patients (NCT01134575, www.clinicaltrials.gov). Preliminary results indicate liver function abnormalities in 25% of patients, including periportal fibrosis and venoocclusive disease after allo SCT, among the most relevant side effects (Jabbour et al, 2011). Overall, complete response plus complete bone marrow response is achieved in more than 50% of the patients.

Additional phase I studies are soon expected to open, including a single use of CMC-544 in refractory ALL patients (NCT01363297, www.clinicaltrials.gov) and a 2 dose level study in combination with cyclophosphamide, vincristine, dexamethasone, methotrexate, cytarabine in elderly ALL patients (NCT01371630, www.clinicaltrials.gov).

4. BCL-2 Antisense therapy

In several clinical studies alterations in the apoptotic threshold were proven to be predictive of poor response to treatment and adverse clinical outcome in patients with a variety of hematologic malignancies, including acute leukemia. Specifically, the up regulation of the BCL-2 family of proteins has been demonstrated to suppress caspase- and non-caspase-mediated apoptosis mediated by several agents, including γ-irradiation and chemotherapy (Reed et al, 1995). As such, over expression of BCL-2 has been associated with an increased risk of relapse in childhood ALL (Hogarth et al, 1999), suggesting the use of factors that override the BCL-2 pathway might restore chemo sensitivity in chemo resistant leukemic cells.

Since the discovery of BCL-2, a single antisense oligodeoxynucleotide - Genasense (G3139, oblimersen; Genta Inc.) - has been explored. *In vitro* studies have shown that when administered alone or in combination with chemotherapy, G3139 inhibits BCL2 expression, resulting in increased tumor cell apoptosis (Webb et al, 1997). Subsequently, its ability to effectively reduce BCL-2 protein levels has clearly been demonstrated in a mouse model transplanted with leukemia. This effect is correlated with enhanced induction of apoptosis, when cells are cultured with the anti-leukemic agents imatinib, daunorubicin, cytarabine and etoposide. Mice treated with G3139 have prolonged survival with some showing complete tumor regression. Of particular interest is the efficacy of G3139 in STI571 resistant

BCR-ABL transformed cells, suggesting its use in clinically acquired STI571 resistance (Tauchi et al, 2003). The very low toxicity observed in a phase I study of relapsed acute leukemia, demonstrates that G3139 can safely be administered with fludarabine and cytarabine salvage chemotherapy (FLAG) without dose limiting toxicity. Common side effects of this combination include fever, nausea; emesis, electrolyte imbalance, and fluid retention that are not dose limiting. Pharmacokinetics indicates steady-state concentrations within 24 hours and is associated with significant down-regulation of BCL-2 mRNA levels in 75% of patients (Marcucci et al, 2003). Despite an encouraging result of 45% overall survival is achieved, the specific role of G3139 cannot be discriminated from the antileukemic activity of FLAG. Based upon the results obtained so far, validation of the G3139 efficacy, still needs to be completed with phase II/III trials.

5. Proteasome inhibitors

Malignant cells can harbour altered expression of proteasome subunits and their distribution between nucleus and cytoplasm can differ from normal cells. Subsequently, the ubiquitin-proteasome pathway is involved in malignant cellular hemostasis since it regulates the degradation of damaged, oxidized, or misfolded proteins and regulatory proteins that govern cell cycle, transcription factor activation, apoptosis, and cell trafficking. Key proteins degraded by this pathway include cyclins A, B and E, p21, p27, p53, cJun, cFos, IkB, Bcl2, BclX, and MAPK (Laney et al, 1999; Maki et al, 1996). Targeting proteasome subunits by proteasome inhibitors offers the possibility to sensitize surviving tumor cells to the effect of chemotherapy and to induce apoptosis in tumor cells.

Bortezomib (Velcade, PS-341; Millenium Pharmaceuticals) is the first proteasome inhibitor to be tested in humans and is currently approved for the treatment of relapsed multiple myeloma and mantle cell lymphoma. It is a potent and selective, reversible inhibitor of the 26S proteosome, a key regulatory multi-subunit protease, that controls cell cycle and apoptosis (Adams et al, 1998). As in a broad range of tumor cells, bortezomib has demonstrated significant activity in ALL cells, inducing apoptosis *in vitro* and *in vivo*. Additional studies have indicated that it may also potentiate the cytotoxic effects of chemotherapy. In particular, it enhances the *in vitro* cytotoxicity of dexamethasone, vincristine, asparaginase, cytarabine, doxorubicin, phenyl butyrate, trichostatin and HA14.1 (Horton et al, 2006; Sutheesophon et al, 2006).

A recent phase I clinical study in adults with refractory or relapsed acute leukemias indicates the dose of 1.25 mg/m^2 to be safely administered on a twice weekly schedule for a 4 week period (Cortes et al, 2004). This is similar to the currently recommended dose of 1.3 mg/m^2, given in multiple myeloma. Dose limiting toxicity includes orthostatic hypotension, nausea, diarrhoea and fluid retention. Evidence of biological activity is demonstrated by significant proteasome inhibition. It is anticipated, that few patients have achieved transient reduction of bone marrow blasts, with eventual recurrence of the initial blasts, usually during the time off therapy.

Unfortunately, experience in childhood is limited to a phase I trial of bortezomib in pediatric patients with solid tumors, showing minimal toxicity. Since it has non-overlapping toxicities with myelosuppressive agents used to treat ALL and promising *in vitro* activity, further investigation of bortezomib in this setting is warranted, particularly in studies with multimodal chemotherapy.

6. Inhibitors of γ-secretase

The detection of NOTCH1 gain-of-function mutations in more than 50% of T-cell ALL patients has attracted much interest in the understanding of its role in the molecular pathogenesis of this leukemic subtype. Although expression of an activated NOTCH1 allele has been shown to cause T-cell leukemia in mice, the molecular mechanism for cellular transformation is largely unknown. However, the identification of c-myc as a direct and critical NOTCH1 target gene (Weng et al, 2004) has urged the screening and development of NOTCH1 pathway therapeutics.

The NOTCH1 inhibitor MK-0752 (Merck & Co.) has been developed for the treatment of Alzheimer's disease, since it cleaves amyloid precursor protein and prevents the formation of amyloid ß-peptides (Evin et al, 2006). Its activity in leukemia is demonstrated by the conservation of the NOTCH1 receptor within the transmembrane domain, preventing the release of the NOTCH intracellular domain, and thereby suppressing the transcription of target genes. This results in the arrest of cells in $G_{0/1}$, reduces viability, and increases apoptosis (DeAngelo et al, 2006). In a phase I trial of adult and pediatric patients with T-cell malignancies MK-0752 has been shown to be well-tolerated with diarrhoea being the dose-limiting toxicity. Measurements of γ-secretase inhibition have shown a 24-69% decrease in plasma $Abeta_{40}$ peptide levels compared to predose levels (DeAngelo et al, 2006). Only one patient with a NOTCH1 activating mutation has achieved a significant reduction of a mediastinal mass at the end of the treatment, but has subsequently progressed.

Currently, an additional phase I study is examining the safety of a newer NOTCH1 inhibitor with improved biological availability (PF-03084014, Pfizer; NCT01068301, www.clinicaltrials.gov) in adult patients with relapsed T-ALL.

7. Heat-shock-protein antagonists

Heat shock protein 90 (Hsp90) is currently receiving considerable attention as a potential anticancer drug target. It is a molecular chaperone that regulates structural folding and active configuration of a variety of signal transduction and cell cycle regulatory proteins, including tyrosine and serine kinases such as c-src and Akt (Isaacs et al, 2003; Hawkins et al, 2005). Inhibition of Hsp90 disrupts the folding of these proteins, thus increasing their susceptibility to ubiquitination and proteosomal degradation. Although the exact mechanism by which Hsp90 inhibitors kill tumor cells remain to be defined, the ability to abrogate the AKT and BCR-ABL pathways makes these compounds particularly attractive for ALL therapy.

17-allylamino-17-demethoxygeldanamycin (17-AAG) is a toxic derivative of geldanamycin and is undergoing clinical examination as it has significant Hsp90-dependent antitumor activity and a favorable toxicity profile (Goetz et al, 2005). Following exposure to 17-AAG results in a rapid decrease of AKT phosphorylation and total AKT protein levels in pediatric ALL patients. This effect can be relevant when 17-AAG is combined with drugs that induce AKT activation, such as arsenic trioxide (Pelicano et al, 2006). Sequential administration causes rapid decline of phosphorylated AKT, increasing the number of cells accumulating in $G_{0/1}$ phase as well as the rate of cleaved caspase-3.

Beyond the effect of 17-AAG on AKT function, BCR-ABL has also been shown to be a client protein for Hsp90 (Gorre et al, 2002). Treatment with 17-AAG results in significant down-

regulation of intracellular levels of BCR-ABL, followed by a decrease in cell survival and the induction of apoptosis. Of interest is the effect on imatinib mesylate-resistant cells, in which sensitivity to imatinib can be restored.
Based on this selective toxicity, 17-AAG has been examined in phase I and II clinical trials in patients with acute myeloid and chronic lymphatic leukemia. These studies have shown that 17-AAG is reasonably well tolerated, with transient elevation of serum transaminases, nausea, vomiting, and diarrhoea being dose-limiting when this agent is administered as a 60-minute infusion on a weekly schedule. Further studies are required to determine tolerability and effectiveness in leukemic patients.

8. Resveratrol

Recently, several natural or dietary substances have been shown to have antineoplastic activity. Much attention has been paid to the polyphenolic phytoalexin resveratrol (3,5,4'-trihydroxy-trans-stilbene), since it inhibits events associated with tumor initiation, promotion and progress (Jang et al, 1997). Potentially, it inhibits free-radical formation and reduces oxidative and mutagenic stress (Aggarwal et al, 2004). Subsequently, resveratrol suppresses the growth of transformed cells and induces apoptosis through interaction with kinase pathways and activation of the caspase cascade (Bernhard et al, 2000).
In leukemic cells resveratrol arrests cells in the S-phase of the cell cycle. A mechanism, by which the replication machinery is arrested, is demonstrated by the inhibition of the ribonucleotide reductase in murine lymphoblastic leukemic cells. Additionally, both the NOTCH and the PI3K/AKT pathway are inhibited at higher concentrations of resveratrol. This is modulated by the activation of signalling systems, such as p53, p21waf-1 and Bax (Cecchinato et al, 2007). Also, resveratrol has been shown to induce mitochondrial depolarization and subsequent activation of downstream caspases associated with the intrinsic apoptotic pathway (Dorrie et al, 2001; Fontecave et al, 1998). Independence of Fas- and TNFα signalling in resveratrol-induced apoptosis might be a desirable property of a potential new therapeutic agent, since tumor cells develop strategies to escape Fas-mediated apoptosis (Bernhard et al, 2000).
Preliminary results of a phase II study of the synthetic resveratrol derivative SRT501 (GlaxoSmithKline) in multiple myeloma patients reveal, that administration of this formulation is limited by the development of the acute renal failure (NCT00920556, www.clinicaltrials.gov). Whereas this complication might be restricted to the underlying disease, tolerability and efficacy of resveratrol in leukemic patients still remain to be clarified in further clinical investigations.

9. Fms-like tyrosine kinase-3 inhibitors

The fms-like tyrosine kinase-3 (FLT3) is a member of the class III receptor tyrosine kinase family and is largely expressed along with CD34 and CD117 in immature hematopoetic progenitor cells. Knock-out mice are associated with deficiencies in B-cell lymphopoesis and reconstitution of both T cells and myeloid cells after BMT, indicating a crucial role of FLT3 in the development of multipotent hematopoetic and lymphoid cells.
Similarly, FLT3 has been implicated in the pathogenesis of leukemia (Carow et al, 1996). In addition to the near-universal FLT3 expression in adult precursor B-ALL, gene expression analysis have shown, that the highest levels of FLT3 expression occur in infant and

childhood ALL with rearrangement of the MLL gene and in ALL patients with hyperdiploidy (Armstrong et al, 2002, 2004); . *In vitro* studies have shown that coexpression of FLT3 ligand and activating mutations on the FLT3 gene can constitutively activate downstream targets. These include signal transducers and activators of transcription (STAT), MAPK, and AKT pathways that regulate proliferation, differentiation, and survival (Mizuki et al, 2000). Considering the worse prognosis of MLL patients and understanding the molecular mechanism of FLT3, has prompted the development of specific FLT3 inhibitors.

Small-molecular FLT3 inhibitors have initially been developed for AML, in which FLT3 mutations represent the most common somatic genetic alteration. FLT3 inhibitors induce significant cytotoxic responses, and several of these agents have been tested in adult trials of AML (Fiedler et al, 2005; Smith et al, 2004). FLT3 inhibitors are well tolerated; toxicities include mild nausea, emesis and generalized weakness with the highest doses administered.

In MLL-rearranged ALL, treatment with the FLT3 inhibitor PKC-412 (Midostaurin, Novartis Pharmaceuticals) has proved to be cytotoxic to Ba/F3 cells dependent upon activating mutations of FLT3 (Armstrong et al, 2003). Similarly, ALL with high hyperdiploidy and t (4;11), has shown pronounced apoptotic responses to treatment with CEP-701 (Lesaurtinib, Cephalon) (Brown et al, 2005). Synergistic effects have not been noted, when FLT3 inhibitors are used simultaneously or immediately following exposure to cytarabine, daunorubicin, mitoxantrone or etoposide. These effects might be of interest, if used to overcome rapid development of resistance to FLT3 inhibitors (Levis et al, 2004). Of note, pretreatment with CEP-701 in combination with cytarabine may act antagonistically, due to its cell-cycle inhibitory effect in AML.

In MLL-rearranged ALL with wild type FLT3, FLT3 ligand induces quiescence and chemoresistance that can be overcome by FLT3 inhibition (Furuichi et al, 2007). It is possible that ligation of FLT3 in these ALL cases contributes to the poor response to chemotherapy by activating quiescence and self-renewal functions. It is therefore worth examining the ability of FLT3 inhibitors to reverse this response and increase chemosensitivity in this particularly difficult to treat group of patients. More specific FLT3 targeting has recently been developed by the application of anti-FLT3 antibodies (Piloto et al, 2006). IMC-NC7 consistently inhibits FLT3 phosphorylation, whereas IMC-EB10 stimulates its activation. Both treatments prolong survival and/or reduced engraftment of leukemic cells in a NOD/SCID mouse model, mainly through the recruitment of the host's immune system against targeted cells, independently of receptor activation.

A phase I/II clinical trial is currently recruiting patients that will evaluate the safety, tolerability, clinical response, pharmacokinetics and pharmacodynamics of PKC-412 in children who have relapsed or refractory acute leukemias, including MLL-rearranged ALL (NCT00866281, www.clinicaltrials.gov).

10. Farnesyl transferase inhibitors

Inhibitors of farnesyl transferase (FTI) have originally been developed to prevent attachment of intracellular Ras to the inner leaflet of the plasma membrane and, therefore, transduction of proliferative and survival signals (Gelb et al, 1997). Subsequent studies, however, have suggested that the cytotoxic actions of FTIs might also involve oncoproteins other than Ras, such as RhoB and members of phosphoinositide 3/OH kinase (PI3K)/AKT-2

pathway (Lebowitz et al, 1998), suggesting that the mechanism of action of FTIs is significantly more complex than initially presumed.
Results of *in vitro* exposure of several leukemic cells provide evidence for the efficacy of FTIs in suppressing tumor cell proliferation. Particularly, the nonpeptidomimetic enzyme-specific inhibitor R115777 (Tipifarnib, Johnson & Johnson) has been shown to decrease proliferation and sensitize apoptosis to chemotherapy-induced cell death. A phase I trial of R115777 in adults with poor-risk acute leukemia provides first evidence for *in vivo* efficacy. 29% of the 34 evaluable patients have shown a clinical response, including 2 patients with complete remission (Karp et al, 2001). Dose limiting toxicities on various schedules include central neurotoxicity and reversible nausea, renal insufficiency, polydipsia, paresthesia and myelosuppression.
Of note is the novel, orally active FTI SCH66336 (Lonafarnib, Schering-Plough), which competes with the enzyme for the CAAX portion of Ras and induces apoptosis in acute myeloid leukemia. It might be particularly attractive for a combination therapy with STI571, since it has been shown to inhibit the proliferation of STI571-resistant BCR-ABL-positive cell lines and synergize for the induction of apoptosis (Borthakur et al, 2006; Hoover et al, 2002).

11. DNA methylase inhibitors

Aberrant DNA methylation of multiple promoter CpG islands is frequently observed in patients with ALL both at initial presentation and at the time of relapse. Indeed these methylation marks are stable in over 70% of patients with ALL at the time of relapse. Importantly, methylation of specific molecular pathways has been associated with an extremely poor prognosis in patients with ALL. This has been demonstrated in the aberrant methylation of the promotor region within tumor suppressor genes such as the fragile histidine triad (FHIT) of members of the cell cycle pathway such as p73, the cyclin dependent kinase inhibitors p57KIP2 and p15 (Bueso-Ramos et al, 2005). Pharmacologic modification of aberrant methylation can therefore be an attractive approach to regulate leukemic cell proliferation.
Recently, the pyrimidine nucleoside analog 5-Aza-2'-deoxycytidine (decitabine/Daco-gene, SuperGen) has received much interest as a strong hypomethylating agent with clinical activity in myelodysplastic syndrome, and acute and chronic myelogeous leukemia (Richel et al, 1991). *In vitro* exposure of decitabine results in hypomethylation and reactivation of putative tumor suppressor genes. As a result, low concentrations of decitabine stimulate cellular differentiation, whereas high concentrations directly interfere with DNA synthesis and mediate cytotoxicity in acute leukemias (Pinto et al, 1984). Combination therapy with cytarabine achieves complete remission in the majority of patients in a clinical trial of ALL (Richel et al, 1991). Analysis of cell membrane markers shows a loss of the early differentiation antigens CD34 and CD33 in leukemic bone marrow cells, which is suggestive of leukemic cell differentiation. Addition of HDACIs might synergize in controlling gene transcription as has successfully been shown in a clinical trial for t(8;14) AML (Klisovic et al, 2003).
Temozolomide (Temodal, Schering-Plough) is a second-generation oral alkylating agent with DNA methylating properties. Although the exact mechanism for methylation is not fully elucidated, it results in an active mismatch-repair pathway with consequent DNA strand breakage and apoptosis (D'Atri et al, 1998). Temozolomide is well tolerated when it is administered as a single agent (Seiter el al, 2002). Because of the chance to deplete O^6-

alkylguanine DNA alkyltransferase levels, a potential mechanism of drug resistance, temozolomide should be administered in an extended low-dose schedule, as has been suggested in a clinical trial of malignant gliomas (Khan et al, 2002).

12. Histone deacetylase inhibitors

Epigenetic changes to promoter regions have been identified in recent years as important factors in the pathogenesis of acute leukemia. They include DNA modifications that regulate chromatin structure and change gene expression without altering the nucleotide sequence. A promising new therapeutic strategy is aimed at removal of acetyl groups from histone proteins as well as other non-histone protein targets with histone deacetylation inhibitors (HDACIs), which results in chromatin remodeling that permits re-expression of silenced tumor suppressor genes in cancer cells (Brown et al, 2002). This in turn, can potentially result in cellular differentiation, inhibition of proliferation and/or apoptosis.

Several classes of HDACIs are currently under development for treatment of leukemia, including the short-chain fatty acids sodium phenylbutyrate and valproic acid, the hydroxamic acids suberoylanilide hydroxamic acid (SAHA, Vorinostat, Merck & Co.), FK-228 (Depsipeptide, Gloucester Pharmaceuticals) and LBH589 (Panobinostat, Novartis Pharmaceuticals), and the benzamides MS-275 and C1-994.

In vitro studies have demonstrated that HDACIs trigger maturation, when administered at low concentrations, whereas at higher concentrations, apoptosis is induced. The factors that determine whether HDACIs engage apoptosis versus differentiation remain the subject of investigation, but they may involve the induction of death receptors such as Fas- and tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) (Bernhard et al, 2001; Inoue et al, 2004), the production of reactive oxygen species, which leads to mitochondrial disruption (Bernhard et al, 2001), independently of activation of caspase-8 or -3, followed by internucleosomal DNA fragmentation. Specifically in Philadelphia chromosome-positive (Ph+) ALL, HDACIs reduce viability and increase expression of the apoptosis associated proteins FANCG, FOXO3A, GADD45A, GADD45B and GADD45G (Scuto et al, 2008). If HDACIs are used at lower concentrations, they induce either $G_{0/1}$ or G_2-M arrest. These events are accompanied by induction of p53 and $p21^{WAF1}$, and down-regulation of cell cycle-promoting proteins, including cyclin D1 and D2.

In vivo FK-228 effectively inhibits HDAC in patients with chronic lymphatic leukemia (CLL) and acute myeloid leukemia (AML) (Byrd et al, 2005), but its use in the current schedule of administration is limited by progressive constitutional symptoms. Dose-limiting toxicities include anorexia, dehydration, diarrhoea, and fatigue. Several patients have evidence of anti-tumor activity following treatment, but no partial or complete response is noted. Both, SAHA and LBH589, have been reported to be tolerable for short- and long-term application in phase I clinical trials of adult refractory hematological malignancies (Garcia-Manero et al, 2008). Based on the safety and efficacy demonstrated in phase I/II trials, a single HDACI compound, SAHA, has been approved for the treatment of cutaneous T-cell lymphoma, after demonstrating activity in heavily pre-treated patients.

Regarding childhood ALL data, a recent phase I study of vorinostat has just been published. Drug disposition and tolerance in children is similar to that observed in adult patients, whereas the maximum tolerated dose (MTD) seems to be lower due to liver dysfunction. Furthermore, a phase II study is reported as currently recruiting participants (NCT00882206, www.clinicaltrials.gov). Specifically, this trial is investigating the use of decitabine and

vorinostat together with combination chemotherapy in treating patients with relapsed/refractory ALL or lymphoblastic lymphoma.

13. Mammalian target of rapamycin inhibitors

The mammalian target of rapamycin (mTOR) is a critical effector in cell-signalling pathways, such as the PI3K/AKT transduction pathway, that are up regulated in malignant transformed cells (Dann et al, 2006). After activation of G-protein coupled receptors by various growth factors, mTOR mediates the phosphorylation of the 70 kDa S6 ribosomal protein kinase and the initiation factor 4E-binding protein 1 (Vignot et al, 2005). Subsequently, activated cyclin D1, CDK4, and Rb initiate the $G_{0/1}$ to S phase progression. Accordingly, targeting the mTOR signalling pathway has extensively been analyzed for suppression of leukemic cell proliferation.

Inhibitors of mTOR include rapamycin (Sirolimus, Wyeth Pharmaceuticals) and the second generation analogs RAD001 (Everolimus, Novartis Pharmaceuticals), and CCI-779 (Temsirolimus, Wyeth Pharmaceuticals). Rapamycin was initially developed as immunosuppressive agent and was the first inhibitor to be used in a clinical setting for leukemic therapy. Rapamycin induces apoptosis in precursor B ALL lines *in vitro* and has *in vivo* activity in transgenic mice with pre-B leukemia/lymphoma (Brown et al, 2003). CCI-779 inhibits the growth of adult human ALL on bone marrow layers and reduces the number of blasts in the peripheral-blood and the degree of organ infiltration in human ALL engrafted NOD/SCID mice (Teachey et al, 2006). RAD001 reduces tumor mass *in vivo*, conferring prolonged survival of NOD/SCID mice engrafted with childhood ALL (Crazzolara et al, 2009). Mechanistic insight demonstrates the induction of autophagy in the absence of apoptosis, which is particular interesting in ALL, since resistance to current chemotherapies, such as dexamethasone, has been linked to certain defects in the apoptotic machinery.

Phase I trials in patients with various cancers show that mTOR inhibitors when used as monotherapy are well tolerated in humans, with little nephrotoxicity and neurotoxicity (Calne et al, 1989). They may further cause hyperlipidemia, mild myelosuppression, hypertension, skin rashes and mucositis. However, the toxicities of combining mTOR inhibitors with conventional cytotoxic agents have not been fully explored in both preclinical and clinical studies. Based on the preclinical work, a number of clinical trials evaluating the efficacy of mTOR inhibitors in ALL as single agents and in combination with other agents have been performed are still on-going (NCT01162551, www.clinicaltrials.gov). Two phase I/II trials of MTIs in patients with relapsed or refractory malignances, including one patient each with ALL, have shown that both patients have tolerated therapy, but neither have had an objective response. A recent interim result of an on-going phase 1 trial of sirolimus in children reveals that 3 of 7 patients relapsed/refractory ALL have stable disease.

14. Cyclin dependent kinase inhibitors

Loss of p16 (INK4A) in hematopoietic stem cells is associated with enhanced self-renewal capacity and might facilitate progression of damaged stem cells into pre-cancerous cells that give rise to leukemia (Bhojwani et al, 2006). Based on higher frequency of p16 (INK4A) deletions in relapsed ALL, inhibitors of cyclin dependent kinases (CDKs) have been

Substance	Synonym	Target	Clinical Trial	Identifier	Study Start	Study end	Condition	Age Eligibility	Combination
AMD3100	plerixafor	CXCR4	I	NCT01319864	03/2011	07/2014	R	3-29 y	eto, ara-c
CMC-544	inotuzumab ozogamicin	CD22	I	NCT01134575	06/2010	06/2013	R	>16 y	rit
			I	NCT01363297	07/2011	01/2015	R	>18 y	-
			I	NCT01371630	11/2011	09/2015	untreated	>60 y	cpm, vin, dex, mtx, ara-c
G3139	oblimersen	BCL-2	I	NCT00004862	completed		R	>16 y	flu, ara-c
PS 341	bortezomib	proteasome	I	NCT01075425	05/2010	02/2012	R	>18 y	berlinostat
			I/II	NCT00410423	01/2006	01/2013	R	>18 y	mit, eto, ara-c
			I	NCT00383474	completed		R	>18 y	tipifarnib
			I/II	NCT00440726	06/2006	02/2011	R	>18 y	asp, dox, vin, dex, mtx, ara-c
			II	NCT01312818	06/2011	06/2012	R	2-30 y	vor, dex, mtx, ima
			I	NCT00077467	01/2004	03/2006	R	1-21 y	-
MK-0752		γ-secretase	I	NCT00100152	07/2005	10/2006	R	>1 y	-
PF-03084014			I	NCT00878189	06/2009	01/2014	R	>16 y	-
STA-9090		Hsp90	I/II	NCT00964873	ongoing		untreated	>18 y	-
PKC412	midostaurin	FLT3	I/II	NCT00866281	09/2009	06/2012	R	3 mo – 18 y	-
CEP-701	lestaurtinib		III	NCT00557193	01/2008	06/2012	untreated	<1 y	asp, dau, vin, dex, mtx, ara-c, eto, mer, cpm, pre
R115777	tipifarnib	FTIs	I	NCT00022451	completed		R	<21 y	-
5-Aza-2'-deoxycytidine	decitabine	DNA	I	NCT00042796	completed		R	<21 y	-
			I	NCT00349596	07/2006	07/2012	R	any age	-
			II	NCT00882206	04/2009	11/2011	R	2-60 y	ara-c, dox, mtx, asp, pre, vin, vor, ima
LBH589	panobinostat	HDAC	I	NCT01321346	03/2011	03/2014	R	8-21 y	ara-c
SAHA	vorinostat		I	NCT00278330	completed		R	>18 y	alvocidib
AY 22989	sirolimus	mTOR	I	NCT01184885	07/2010	01/2013	R	>18 y	cpm, vin, dox, dex
			I/II	NCT00968253	08/2009	03/2011	R	>10 y	cpm, vin, dox, dex, mtx, ara-c
RAD001	everolimus		I	NCT00874562	07/2007	07/2010	R	>1 y	pre
			I	NCT00957320	06/2009	06/2017	R	>21 y	asp
HMR 1274	flavopiridol	p16 (INK4A)	II	NCT00016016	completed		R	>18 y	ara-c, mit

(R= relapse, eto= etoposide, ara-c= cytarabine, rit= rituximab, cpm= cyclophosphamide, vin= vincristine, dex= dexamethasone, flu= fludarabine, mit= mitoxantrone, asp= asparaginase, dau= daunorubicine, dox= doxorubicine, mer= mercaptopurine, vor= vorinostat, pre= predinison, mtx= methotrexate, ima= imatinib)

Table 1. Active and completed clinical trials with novel therapeutic targets for ALL.

investigated for their antileukemic potential. Among them, the synthetic flavone derivative flavopiridol (Alvocidib, L86-8275; Behringwerke) is the first to undergo human trials.

Flavopiridol binds to the adenosine triphosphate (ATP) site of CDK, thereby reducing the activity of CDK1, CDK2, CDK4, CDK6, and CDK7, leading to cell cycle arrest in $G_{0/1}$ and G_2 (Sedlacek et al, 2001). In addition, flavopiridol disrupts the CDK9/cyclin T complex resulting in reduced phosphorylation of the carboxyl-terminal domain of RNA Pol-II and subsequent inhibition of mRNA synthesis (Chao et al, 2000). Consequently, short lived anti-

apoptotic proteins such as MCL-1 and BCL-2 and those that are cell cycle dependent such as cyclin D1 are depleted. This could provide an explanation for increased apoptosis observed following exposure to flavopiridol.

Pre-clinical studies have demonstrated the efficacy of flavopiridol in primary ALL samples. A phase I clinical trial of flavopiridol followed by cytarabine and mitoxantrone in patients with relapsed or refractory adult ALL has shown moderate biological and clinical benefits (Karp et al, 2005). Dose-limiting toxicities include sustained neutropenia, diarrhoea and mucositis. As suggested by a CLL clinical trial, a more sustained schedule of flavopiridol might be needed to improve the clinical response rate, without increasing neutropenia as the dose-limiting toxicity.

15. Conclusion

The future of treatment optimization resides in exploring the molecular pathways involved in the pathogenesis of leukemia and in understanding the pharmacogenomic factors of the host. If successful, new protein products can be generated that are administered as targeted therapy with a narrow therapeutic window. A primary example of such therapy is given by the inhibitor of tyrosine kinase imatinib, which is the first anti-cancer agent that specifically targets the genetic defect underlying Philadelphia positive ALL. Although imatinib is currently implemented in the treatment of BCR/ABL positive ALL and has improved overall survival, its use as single agent should not be overestimated. In fact, imatinib is targeting a specific molecular pathway that regulates gene transcription, cell proliferation or survival, but not the principal genetic lesion. Accordingly, imatinib produces relatively short-lived remission in Ph+ ALL as single agent, but has the potential to improve survival, when combined with current chemotherapy. Similarly, it is likely that the key to the successful use of other molecular targeted therapies will be in the careful combination of novel agents with traditional chemotherapeutic regimes and/or with other molecularly targeted agents. Indeed many agents, including imatinib, flavopiridol and oblimersen are being tested in combination with standard chemotherapy, while imatinib is also being combined with inhibitors of farnesyl transferase, HDAC, cyclin dependent kinases, HSP90 and BCL-2. Ultimately, these combinations need to be based on a thorough understanding of the molecular pathways driving disease in each patient. Additionally, pharmacogenomic information will be essential for the development of optimal effective treatment regimes with minimal side effects.

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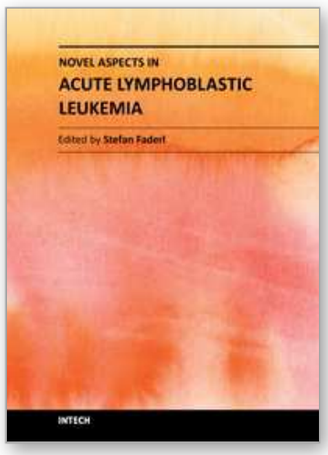

Novel Aspects in Acute Lymphoblastic Leukemia
Edited by Dr. Stefan Faderl

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Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

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