Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia

Patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) are now routinely treated front-line with tyrosine kinase inhibitors (TKI), usually combined with chemotherapy, with unequivocal evidence of clinical benefit. The first-generation TKI imatinib induces hematologic remissions in nearly all patients, but these are rarely maintained unless patients undergo allologeneic stem cell transplantation (alloSCT), the current gold standard of curative therapy. The more potent second- and third-generation TKI display greater clinical efficacy based on molecular response data and clinical outcome parameters. It is still uncertain whether they may obviate the need for alloSCT in some adult patients who achieve a deep molecular response, whereas this appears to often be the case in pediatric patients. Which chemotherapy regimen is best suited in combination with the individual TKI in different subsets of patients is being explored in ongoing studies. Molecular analyses to measure MRD levels, detect BCR-ABL kinase domain mutations, or further subclassify patients according to additional genomic aberrations has become increasingly important in clinical patient management. A variety of novel targeted treatment approaches are in clinical development for patients with an unsatisfactory response to current therapy.

Learning goals
At the conclusion of this activity, participants should:
- know about the efficacy of first- and second-generation tyrosine kinase inhibitors (TKI) in terms of inducing hematologic and molecular responses;
- understand the role of chemotherapy intensity regarding efficacy and tolerability;
- be able to identify the current treatment paradigm as TKI combined with chemotherapy, followed by allologeneic stem cell transplantation (alloSCT);
- be able to identify BCR-ABL mutations as a principal cause of treatment failure;
- understand the role of minimal residual disease assessment prior to and after SCT and the therapeutic implications;
- have some knowledge of the therapeutic options in relapsed or refractory patients.

Introduction
The BCR-ABL translocation in Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) defines a subpopulation among adult ALL that encompasses approximately 25% of patients and is amenable to treatment with tyrosine kinase inhibitors (TKI) that target the oncogenic BCR-ABL protein. The availability of now three generations of ABL-directed TKI has fostered numerous clinical trials exploring different strategies of TKI-based therapy, and have unequivocally improved patient outcome. Moreover, the importance of molecular diagnostics not only for up-front identification of BCR-ABL positivity but for minimal residual disease (MRD)-guided treatment decisions during therapy and detection of mutations in case of resistance have become universally accepted. As a consequence, results of treatment for the very high-risk subset of Ph+ ALL have now surpassed those of BCR-ABL negative high-risk ALL in the German Multicenter Adult ALL (GMAIL) cooperative group trials. Despite these achievements, the precise impact of different TKI-based treatment regimens on long-term survival of patients with Ph+ ALL remains uncertain. This is due primarily to a paucity of large prospective phase III trials, with clinical research having focused on smaller phase II trials exploring specific treatment modalities within subgroups of Ph+ ALL patients. This article will review the current state of the art and the evolving concepts in therapy for Ph+ ALL, primarily of adult patients, will highlight unresolved clinical management issues, and will look towards future novel therapeutic approaches.

Role of tyrosine kinase inhibitors during induction therapy
Extensive data on first-line treatment for Ph+ ALL is available for the first-generation TKI imatinib, and experience with second-generation (dasatinib, nilotinib) and third-generation (ponatinib) TKI is growing rapidly. Current efforts to optimize utilization of these TKI have focused on rational therapeutic approaches.
tations of the different TKIs and the intensity and type of chemotherapy used during induction and consolidation cycles. It is widely accepted that TKI should be initiated as soon as the diagnosis of Ph+ ALL is established, i.e. typically after pre-phase therapy. Major conceptual differences regarding induction strategies concern the intensity of treatment, which may rely on TKI only in combination with corticosteroids, on their combination with reduced intensity chemotherapy, e.g. vincristine plus steroids, or combination with intensive multi-agent induction chemotherapy.

**Imatinib**

The use of imatinib during induction has been most extensively studied over the past decade, and more than 90% of patients can expect to achieve complete remission, irrespective of whether imatinib is given alone or in combination with chemotherapy. Concurrent administration with cytotoxic drugs commonly used for induction (anthracyclines, cytarabine, cyclophosphamide, vincristine, 6-mercaptopurine) has proven to be feasible and reasonably well tolerated, but induction mortality may reach approximately 10% even in younger patients. Primary hematologic resistance is distinctly uncommon in previously untreated patients, in contrast to the relapse setting. One of the primary goals of combining imatinib only with steroids is the avoidance of induction mortality, and this has been evaluated in elderly as well as young patients. The rate of induction deaths is indeed exceedingly low using such an approach, with studies reporting no induction deaths with imatinib and steroids. The principal drawback of this approach appears to be an unsatisfactory depth of response by MRD analysis based on quantitative RT-PCR measurement of BCR-ABL transcripts. For example, only 4% molecular remissions after induction were reported for the GIMEMA LAL0201-B protocol. Concern that a poor molecular response is associated with early disease recurrence and a high relapse rate is borne out by clinical trials particularly, but not exclusively, in elderly Ph+ ALL patients who do not undergo allogeneic stem cell transplantation (alloSCT).

**Second-generation tyrosine kinase inhibitors**

The greater potency of second-generation TKI and their activity against a broader spectrum of BCR-ABL kinase domain mutations suggested superior efficacy compared with imatinib-based treatment. Dasatinib has been the more extensively studied second-generation TKI as frontline therapy for Ph+ ALL. Complete remission was achieved by 100% of patients receiving dasatinib and corticosteroids in a recently published GIMEMA study, with no induction deaths. Molecular responses were superior to imatinib monotherapy; the rates of BCR-ABL transcript levels below 0.01% after 43 and 85 days were 33% and 52%, respectively. As this study encompassed only the first three months of treatment and left subsequent management to the discretion of the investigator, the varying regimens used after the study confound the impact on long-term outcome. The lowest relapse rates were observed in patients who underwent alloSCT. Overall, the authors identified an MRD threshold of 0.001 as predictive of relapse-free survival irrespective of subsequent treatment, confirming the importance of achieving a deeper molecular response.

Several studies have investigated dasatinib in combination with either low-intensity or aggressive chemotherapy regimens. The European Working Group for Adult ALL (EWALL) conducted a prospective single-arm phase II trial in elderly Ph+ ALL patients in whom dasatinib was combined with mild induction chemotherapy (vincristine, dexamethasone and intrathecal prophylaxis), followed by more intensive consolidation cycles. Median age of patients was 69 years (58-83 years). Despite this low-intensity approach, the initial protocol was amended to further reduce toxicity in patients older than 75 years of age, by decreasing the dasatinib dose from 140 mg once daily (QD) to 100 mg QD, and the dexamethasone dose from 40 mg to 20 mg. Hospitalization rather than outpatient treatment was recommended for the early initial treatment phase to prevent or adequately treat tumor lysis and compromised renal function. In this multicenter trial, the complete remission (CR) rate was 94% and early mortality 5%. Major toxicities included sepsis, hemorrhage and renal function impairment. Molecular response rate after induction was approximately 25% and 50% based on 3 log and 4.5 log reduction of BCR-ABL transcripts, respectively.

Dasatinib in conjunction with intensive chemotherapy according to the hyper-CVAD regimen was similarly effective in terms of inducing remissions, with a CR rate of 94% and 6% induction mortality. Septicemia and hemorrhage were the major toxicities leading to death. SRC inhibition by dasatinib may have contributed to the higher rate of clinically significant hemorrhagic events due to its effect on platelet function. With short (14 months) median follow up, estimated 2-year survival was 64%. To date, the results of only 2 clinical trials examining nilotinib as first-line therapy for Ph+ ALL have been reported. This paucity of clinical trials is possibly related to the poor clinical activity against p-loop mutations that were observed in early phase I and II trials of nilotinib for relapsed or refractory Ph+ ALL, and the preponderance of these mutations in imatinib failure. As front-line treatment, nilotinib proved effective and tolerable in conjunction with chemotherapy: the CR rate was 90%, with median time to CR of 27 days. Already at the time of CR, 55% of patients had undetectable BCR-ABL transcripts, with further improvement over time, leading to a cumulative complete molecular response rate of 84%. Death in aplasia (in 8 of 91 patients) was the principal cause of treatment failure, and organ toxicity grade 3 or greater was primarily pancreatic and hepatic, ranging from 2% to 18%, respectively.

In a second trial, nilotinib was alternated with imatinib using a 6-week rotation schedule during front-line treatment of 39 elderly Ph+ ALL patients over 60 years of age or unfit for intensive therapy. Disease-free survival was 51% at 12 months; overall survival (OS) was 64% at two years. Among 13 patients who relapsed, median time to relapse was 7.6 months. The T315I and p-loop mutations predominated, suggesting no benefit over imatinib or dasatinib alone.

**Third-generation tyrosine kinase inhibitors**

The potent activity of ponatinib against native BCR-ABL and essentially all clinically relevant TKD mutations, including the T315I mutation resistant to all other
clinically approved TKI makes this compound of particular interest for Ph⁺ ALL, which shows a high prevalence of this gatekeeper mutation at the time of clinical resistance to TKI. 23 Preliminary results of a phase II trial employing ponatinib in combination with the Hyper-CVAD regimen for treatment of newly diagnosed Ph⁺ ALL showed a 100% CR. 24 Seventy percent of patients achieved a complete molecular remission at a median of ten weeks from start of therapy. Major toxicities of grade 3 or more included elevated liver function tests, thrombotic events, myocardial infarction, and pancreatitis.

**Long-term results with TKI-based therapy**

**Imatinib**

Several studies, none of them randomized, have demonstrated improved outcome with the addition of imatinib to previous treatment regimens. Another common theme of most of these studies is the central role of alloSCT in facilitating long-term survival, 27,28,29,30 although smaller studies showed no benefit for alloSCT when imatinib was combined with intensive chemotherapy. 31,32

A recently published large, prospective phase III trial conducted by the MRC UKALLXII/ECOG2993 compared the outcome of adult patients who received imatinib in addition to induction and/or consolidation chemotherapy and those treated in the pre-imatinib era up to 2003. 33 The CR rate was significantly higher in the imatinib cohort than in the pre-imatinib cohort (92% vs. 82%) and OS at four years was significantly longer in the imatinib cohort, 38% vs. 22%, respectively. In the pre-imatinib cohort, 31% of those starting treatment achieved allogeneic hematopoietic stem cell transplant (alloHSCT) compared with 46% in the imatinib cohort. Overall, addition of imatinib to standard therapy improved CR rate and long-term OS for adults with ALL, with a proportion of the OS benefit derived from the fact that imatinib facilitated alloHSCT. An advantage of imatinib-based therapy over no TKI was likewise demonstrated by the North Italian Study Group (NILG), which evaluated short imatinib pulses given in addition to chemotherapy, comparing the results with those of a historic control group not receiving imatinib. 34 SCT rates were greater in the IM-positive group (alloSCT: 63% vs. 39%), and patients in the IM-group had significantly greater probabilities of OS (38% vs. 23%) and DFS (39% vs. 25%) and a lower incidence of relapse at a median observation time of five years. With SCT, post-transplantation mortality (28%) and relapse were the major obstacles to further therapeutic improvement. While it is commonly agreed that earlier initiation of imatinib therapy is superior to delayed onset imatinib, the role of chemotherapy intensity and possibly type of regimen remain an issue of ongoing investigation. Although imatinib combined with intensive chemotherapy has yielded encouraging results in the above as well as several smaller phase II trials, 35,36 recent evidence suggests that deescalating chemotherapy, in particular during induction, while maintaining a high imatinib dose may yield similar molecular responses and at least comparable survival. 6,27

**Second-generation tyrosine kinase inhibitors**

Results from what has so far been the largest study with the longest follow up examining the combination of dasatinib with age-adapted chemotherapy in elderly Ph⁺ ALL patients were reported by the European Working Group for Adult ALL (EWALL). 18 Median follow up was 3.3 years. Three-year survival was estimated as 44.7%, a result that is in the range of reported survival in younger adults. Relapses were associated with the T315I mutation in most cases and a T315I signal by highly sensitive allele-specific PCR predicted hematologic relapse, independently of MRD.

Dasatinib in combination with hyper-CVAD yielded an estimated 2-year survival of 64%, although median follow up was only 14 months. 19 No long-term outcome data for Ph⁺ ALL are available with bosutinib or nilotinib or ponatinib.

**Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia in children**

The BCR-ABL positive subtype of ALL is distinctly uncommon in children, occurring in less than 5% of pediatric ALL. 20 While it constitutes a high-risk feature in children as well, CR rates exceeded 80% and survival was in the range of 40-56% after 3-5 years in the pre-imatinib era, far superior to results in adults. 20,21 Addition of imatinib to intensive chemotherapy regimens significantly improved these results, particularly when imatinib was given from the start of treatment immediately after diagnosis. 22,23

In a prospective, randomized trial involving several national study groups, patients up to 18 years of age with the t(9;22)(q34;q11) and good risk as determined by their early treatment response were randomly assigned to receive post-induction imatinib with chemotherapy or chemotherapy while all poor-risk patients received post-induction imatinib with chemotherapy. The “as treated” analysis showed significantly superior 4-year disease-free survival for good-risk patients receiving imatinib compared to those who did not receive imatinib (75% vs. 56%; \( P=0.06 \)). Four-year event-free survival for poor-risk patients was 53.5% (40.4-65.0%). Tolerability was similar in both groups. 24

Taken together, available data strongly suggests a beneficial effect of adding imatinib to current chemotherapy regimens in pediatric patients. Outcome improved further in studies using dasatinib instead of imatinib, to an extent that SCT appears unnecessary in the majority of children. The biological and genetic basis for this superior responsiveness to TKI (plus chemotherapy) compared to adult patients remains to be established. 25

**Allogeneic stem cell transplantation**

Allogeneic SCT is the only treatment modality that has been shown to facilitate long-term disease-free survival in a substantial proportion of adult patients when used as definite post-remission therapy. Imatinib has had a tremendous impact on the frequency with which SCT can be realized by inducing remissions in a larger proportion of patients, and preventing relapse prior to the transplant procedure. 13 The increasing availability of matched unrelated and alternative donors has contributed to the higher transplant frequency, with SCT rates in first CR of 46% to 90% in newly diagnosed Ph⁺ ALL patients. 5,7,9,11,12,26,27,35,36
Moreover, responses are deeper than in the pre-imatinib era as determined by molecular MRD analysis. Only one retrospective analysis failed to observe a benefit of TKI use either prior to or after SCT.37 Overall, it is likely that second-generation TKI may further improve these results, but results of large-scale prospective clinical trials are not yet available.

In several prospective clinical trials using imatinib as front-line TKI, survival after SCT ranged from 50% to 66% at three years or more.7,9,11,25,36,38 When considering pre-transplant treatment regimens, type of donor and stem cell source, degree of matching, conditioning regimens, immunosuppressive strategy and post-transplant interventions, comparability of these trials is limited. Myeloablative conditioning regimens based on total body irradiation (TBI) are currently the most widely used and considered to be the gold standard. With these regimens, non-relapse mortality (NRM) after SCT is the principal cause of treatment failure and increases with age. In view of the higher median age of patients with Ph+ ALL, and its increasing frequency in older patients, reduced intensity conditioning regimens are used particularly in older patients to reduce NRM. In a retrospective EBMT analysis, RIC alloSCT from a human leukocyte antigen-identical donor was considered as a potential therapeutic option for ALL patients aged 45 years or over in complete remission and not eligible for MAC alloSCT.8,39,40 In another study evaluating the outcome of non-myeloablative conditioning (fludarabine and 2 Gray total body irradiation) and allogeneic transplantation in patients with high-risk ALL, patients with Ph+ ALL in first remission who also received post-grafting imatinib had 3-year overall survival rate of 62%. For the subgroup without evidence of MRD at transplantation, OS was 73%.41 While conclusive assessment of the efficacy of non-myeloablative SCT regimens is not yet possible, the latter data indicate that non-myeloablative conditioning and alloHSCT, with post-grafting imatinib for Ph+ disease, can result in favorable long-term survival.

Therapeutic implications of minimal residual disease analysis

Data from numerous studies and in various clinical settings, some pre-dating the TKI era, demonstrate that the presence of MRD is predictive of outcome in patients with Ph+ ALL.2,3,7,9,42-46 While this appears intuitively plausible, attention should be directed to the methodology employed for quantitation of MRD (e.g. flow cytometry vs. RT-PCR), the time points assessed, the treatment regimen and specific TKI used, the stage of leukemia (front-line vs. salvage), and utilization and type of SCT. It is noteworthy that no stringent criteria for MRD analysis and appropriate thresholds have yet been defined for Ph+ ALL. Thus, measurements of BCR-ABL transcripts and Ig rearrangement to assess MRD could conceivably yield different results due to differences in sensitivity of the methodology, lack of BCR-ABL transcription despite presence of the fusion gene at the genomic level, or clonal evolution during therapy resulting in loss of the original markers defined by Ig rearrangement.37,40 To date, no systematic comparison of these methods has yet been performed. Thus, in a study examining the prognostic relevance of MRD levels determined at an early treatment stage for outcome after SCT, a reduction in BCR-ABL transcript levels of at least 3 log after the first 4-week imatinib therapy was the most powerful predictor of lower relapse (12.1% vs. 45.1%) and better DFS (82.1% vs. 41.7%) rates after SCT.49 In contrast, Rousselet showed in a largely non-transplanted elderly population receiving dasatinib combined with chemotherapy, that the molecular response during consolidation, but not after induction, was predictive of better DFS and OS.18 MRD at the time of transplant was a negative predictor for relapse in a study by the JALSG.50 Taken together, these data nevertheless indicate that measurement of MRD in a quantitative manner may often be a valid surrogate marker for outcome, and that BCR-ABL1 transcript levels in particular are able to discriminate between subsets of Ph+ ALL patients with a different prognosis. Molecular relapse after alloSCT carries a high risk of relapse and should prompt intervention.51 In addition to classical approaches such as rapid tapering of immunosuppressive therapy and donor lymphocyte infusions (DLI), TKIs are an easy to use, reasonably safe and rapidly effective modality after SCT.3,37,41,52,53 As shown in a recently published randomized trial, prophylactic imatinib reduced the incidence of molecular relapse after SCT, and was as effective in preventing hematologic relapse as imatinib administration in response to detection of BCR-ABL transcripts.54 There was no significant difference in long-term outcome between the two treatment groups, with probability of remission after five years of 91.6% with prophylactic and 75.5% with MRD-triggered imatinib, and survival probability (5 years) of 80.1% and 74.5%, respectively. The optimal duration of TKI treatment after SCT remains to be resolved, particularly as tolerability issues led to premature discontinuation of imatinib in a significant number of patients. The role of other TKI in this setting have not been systematically explored, but efficacy of second- and third-generation TKI in Ph+ ALL relapsed after SCT suggest the potential for use in the pre-empptive or prophylactic setting. Patients not receiving prophylactic TKI after alloSCT should be closely monitored for evidence of molecular failure, which should then prompt initiation of TKI therapy.

**Autologous stem cell transplantation**

Autologous stem cell transplant (ASCT) was largely abandoned as a strategy for Ph+ ALL in the 1990s because of a lack of efficacy even when using autografts from MRD negative patients or after in vitro purging of leukemic cells.55-57 Interest in ASCT has been rekindled following anecdotal reports and experience from small series of patients consistently showing essentially absent transplant-associated mortality and remarkably good outcome in patients who received an ASCT after achieving a very good molecular response to TKI-based therapy, with additional post-transplant TKI maintenance.7,35,58 These studies reported 3- to 5-year DFS of 50-67%. In one series, 5-year DFS and OS was 47% and 51%, respectively, similar to alloSCT, although the number of patients was small.59 In the largest study reported to date, 176 patients treated with ASCT in CR1 were analyzed.60 The probability of OS at three years increased from 16% for transplants performed between 1996 and 2001 to 57% between 2007 and 2010. Relapse incidence decreased from 70% to 45%
(P=0.01), non-relapse mortality was 19% and 3% (P=0.08). In a subgroup of 22 patients actually treated with TKIs who were in complete molecular remission at the time of ASCT, the leukemia-free survival (LFS) rate at three years was 65%. This improvement is most likely attributable to the use of TKI both before and after ASCT, but data are limited, highlighting the need for prospective studies to verify the role of ASCT in this patient setting. With a greater proportion of patients achieving molecular negativity with second-generation TKI in front-line treatment regimens, ASCT may become a relevant option in a sizeable number of patients, with the greatest potential for improving therapy in elderly patients ineligible for alloSCT.

**Treatment of relapse**

Relapse remains the single greatest clinical challenge and has a dismal prognosis. As single agents in patients with Ph+ ALL with resistance or intolerance to prior TKI, dasatinib and nilotinib induced major hematologic response (MHR; CR and no evidence of leukemia) in 42% and 45%, respectively. With dasatinib, MHR were sustained for at least eight months in 67% of patients, median progression-free survival was 3.3 months. Responses were seen in patients with most TKD mutations at baseline, but not in those with a T315I mutation. Salvage therapy with nilotinib was associated with median overall survival of 5.2 months and probability of survival of 27% after one year. As leukemia recurrence occurs most commonly during TKI therapy, the vast majority of cases are associated with TKD mutations known to confer a high-level resistance to TKI. The frequency of individual mutations varies according to the specific TKI being used; for example, the vast majority of patients relapsing on dasatinib carry the T315I mutation, whereas p-loop mutations predominate with imatinib or nilotinib treatment. The third-generation TKI ponatinib potently inhibits virtually all clinically relevant TKD mutations and showed encouraging clinical activity in relapsed and refractory Ph+ ALL in early phase I and II studies. Ponatinib has the advantage of being the only approved TKI to inhibit the T315I gatekeeper mutation. In the initial phase I and subsequent phase II trials of ponatinib in heavily pre-treated Ph+ patients, most of whom had received at least two tyrosine kinase inhibitors, major hematologic responses among the patients with Ph+ ALL or advanced phase chronic myeloid leukemia (CML) were 36% and 41%, and major cytogenetic responses 32% and 47%, respectively. Responses were short-lived, however, confirming the notion that prevention rather than treatment of overt relapse is crucial to the successful treatment of ALL. Nevertheless, when clinical trials are not available, treatment of relapse still relies primarily on TKIs, which need to be selected based on the type of mutation present. Combination with at least low-dose chemotherapy, e.g., vincristine, and potent corticosteroids such as dexamethasone is commonly used, particularly while awaiting the results of mutation analysis and in anticipation of an additive effect. In case of leukemic involvement of the central nervous system (CNS) at relapse, dasatinib is the only TKI demonstrated to penetrate the blood-brain barrier and have clinical anti-leukemic efficacy in adult and pediatric patients, some of whom experienced prolonged responses.

Blinatumomab had profound clinical efficacy in non-comparative phase II trials, but is not yet approved and can be given only in the context of clinical trials. Responding patients should be referred for alloSCT if possible, with special consideration given to the short window of opportunity. In conclusion, there is a dire need for novel experimental compounds to be explored in clinical trials.

**Novel therapies**

A host of new and diverse agents have recently entered the pre-clinical or clinical drug development stage. These agents hold considerable promise for ALL in general and Ph+ ALL in particular. Numerous oncogenic pathways have been implicated in contributing to leukemogenesis or progression of Ph+ ALL, including the PI3-kinase, AKT, mTOR pathway, B-cell signaling (e.g. SYK and BTK), JAK/STAT pathway, Hedgehog and WNT signaling, Aurora kinases, apoptosis pathways (survivin, bcl-2) and others. The expectations raised by pre-clinical studies have translated into sign of clinical efficacy only in few cases, e.g. with the Aurora kinase inhibitor MK-0457, which induced a CR in one of 3 relapsed Ph+ ALL patients with a T315I mutation. Therapeutic approaches that are currently attracting the most attention are antigen-directed therapies, novel BCR-ABL inhibitors, inhibitors of pro-survival pathways, and inhibitors of self-renewal. Among the immunotherapeutic approaches, CD22 and even more so CD19 have emerged as the preferred targets due to their selectivity for the B-cell lineage and stable expression on the majority of cells throughout B-cell development and in B-cell malignancies. Inotuzumab ozogamicin, a CD22-directed monoclonal antibody linked to the cytotoxic calicheamycin, has significant anti-leukemic efficacy in patients with relapsed/refractory ALL including Ph+ ALL, 40% of whom achieved a CR, which was, however, lower than for Ph-negative cohorts. Median response duration and survival were short, but this treatment provided a bridge to transplant for some patients. Blinatumomab, a T cell engaging bispecific single-chain antibody (BiTE®) that engages T cells for redirected lysis of CD19 positive target cells, has likewise shown substantial clinical activity in R/R ALL including a few patients with Ph+ ALL. Long-term outcome is particularly favorable in patients already treated for MRD, rather than overt relapse. CD19 negative and extramedullary relapses were the principal causes of treatment failure. Autologous T cells expressing a CD19-specific chimeric antigen receptor (CD19-CAR) have shown intriguing activity against B-cell malignancies including B-cell precursor ALL, with different constructs having entered early clinical testing.

**Recurrent genomic aberrations in Philadelphia chromosome positive acute lymphoblastic leukemia**

Microarray-based genome-wide profiling studies conducted predominantly in pediatric ALL patients have revealed novel submicroscopic genetic lesions in patients with Ph+ ALL. Most of these recurring genomic abnormalities involve single genes which are implicated in B-cell...
differentiation, cell survival, or cell-cycle progression, such as CDKN2A/B, IKZF1, PAX5, ETV6, RB1, BTG1 and EBF1. Deletions of the CDKN2A/B tumor suppressor locus and of the IKAROS and PAX5 genes that promote B-lineage development have received particular attention due to their high frequency in BCR-ABL1-positive ALL. IKZF1 deletions were observed in more than 80% of pediatric BCR-ABL1 ALL cases, and 63% of adult patients with Ph+ ALL. IKZF1 deletions have been linked to an inferior outcome in most pediatric ALL studies, as well as in 2 studies involving adult and adolescent Ph negative BCP-ALL and adult Ph+ ALL, respectively. These findings suggest that genetic lesions resulting in the loss of Ikaros function are an important event, not only in the development of BCR-ABL1 ALL, but may facilitate further subclassification of the disease with refinement of prognostic algorithms, provide novel targets for MRD assessment as well as analysis of the clonal structure of the leukemia at diagnosis and relapse, and be useful for improving therapeutic strategies.

Conclusions and outlook

The advent of TKI that potently inhibit the BCR-ABL oncoprotein has dramatically altered the therapeutic landscape for Ph+ ALL and improved treatment results to an extent that Ph+ ALL is no longer the subtype of ALL with the worst prognosis. Current treatment concepts utilize TKI in combination with chemotherapy regimens that vary in intensity depending on patients’ characteristics and on the treatment phase (i.e. induction, consolidation and maintenance) and allo-SCT. Serial molecular analysis of MRD, and in case of resistance of BCR-ABL TKD mutations, provides information that is essential for the rational clinical management of this disease. Maximizing molecular response during early treatment phases while minimizing toxicity is designed to minimize the risk of relapse, an event that still carries a disastrous prognosis. A remarkably large number of novel agents, representing small molecules, antibodies and cellular therapeutics with completely different mechanisms of action have recently emerged and entered early stages of clinical testing. These agents have the potential to further dramatically improve treatment results, and may eventually obviate the need for allo-SCT as definite curative modality. In view of these evolving novel treatment concepts and the small number of patients with this disease, treatment outside of clinical trials should be discouraged. Modern molecular genetics methodologies already generate an abundance of data on genomic aberrations and the clonal architecture of Ph+ ALL that should prove invaluable for further subclassification of the disease, risk stratification, target identification and understanding of resistance mechanism. Ultimately, this information will translate into improved treatment results only with well-designed, preferably randomized, phase II trials conducted on an international level that will provide robust outcome data.

References

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