CLINICAL INVESTIGATION

New considerations in the design of clinical trials for the treatment of acute leukemia

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There is great need for improved therapy for patients with acute leukemia. The current systems of clinical drug development and delivery of leukemia care are imperfectly adapted to the optimal identification and testing of future regimens. Novel clinical trial design with increased enrolment and appropriate end point selection would facilitate more efficient validation of candidate therapies. Clinical outcomes registries and biological sample storage would allow patient and leukemic factor substratification for the development of the next generation of targeted personalized therapy. We believe that the standard of care for patients in the USA diagnosed with acute leukemia, if treated with curative intent, is referral to a specialized center where an appropriate clinical trial can be offered.

Keywords: acute lymphoblastic leukemia • acute myeloid leukemia • ALL • AML • end point • leukemia • personalized therapy

In 1980 the 5-year average survival rate following a diagnosis of leukemia was 38.9%, by 1990 this had improved to 46.8%. Unfortunately 10 years later, in 2000, this rate was only marginally better at 50.3% [1]. This relative plateau in the period 1990–2000 masks, however, a large degree of heterogeneity in patient and leukemia disease subgroups. While improvements in overall survival (OS) in acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia and all patients over 65 years of age was at best minimal during this period, dramatic progress was observed in those diagnosed with chronic myeloid leukemia (CML) and acute promyelocytic leukemia (APL); analogous in scale to the remarkable advances seen with childhood ALL in the period 1960–1990 [2].

The outstanding increases in survival from childhood ALL (from a universally fatal disease in 1960 to the greater than 85% 5-year survival rates seen today) resulted from several factors; the adoption of combination rather than single-agent treatment chosen from the wealth of new cytotoxic drugs introduced in the 1960s (e.g., vincristine, asparaginase, cyclophosphamide, daunomycin and cytarabine) [2], feed-forward design of clinical trials such that results and observations from prior clinical trials informed the design of the subsequent trials, the initially preclinical discovery that the CNS could act as a leukemic reservoir [3], and the institutional and individual will to push the limits of what was considered the medical standard. While the disease and host biology of pediatric ALL is not directly analogous to the challenges in other acute leukemias, the generalized lessons learnt of rapidly sequential iterative trials, the importance of translational science to assess mechanisms of treatment failures as well as success, and the importance of having institutional support to build and maintain a center of excellence capable of aggressively developing and testing new therapies, are all transferable to other settings.

Focus in leukemia drug development has more recently shifted from dose-escalation of cytotoxic agents in combination treatment regimens of prolonged

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duration to an approach of targeted exploitation of individual identifying features of a specific leukemia subtype [4]. This has allowed the highly successful development of noncytotoxic differentiation therapy using all-trans-retinoic acid (ATRA) in APL [5] and the development of tyrosine kinase inhibitors such as imatinib (Gleevec®, STI571) for the treatment of CML based on the molecular understanding that it is a clonal hematopoietic stem cell disorder characterized by the (9:22) chromosomal translocation with resultant production of the constitutively activated BCR-ABL tyrosine kinase [6]. These examples of targeted treatment represent an attractive and effective paradigm, but one that has not yet been able to be reproduced in other leukemia subtypes where multiple, genetically complex, driving forces are present.

In 2010, even with 'state of the art' treatment, clinical outcomes in myelodysplastic syndromes, ALL in adults and acute myeloid leukemia (AML) in both children and adults are poor. Given our current era of 'billion dollar drug' development we begin this review by reflecting on the way new therapeutics are currently evaluated and approved in the acute leukemias, using gemtuzumab ozogamicin as an example. What follows are our personal suggestions of three key areas important in the development of future therapeutic agents. First, the opportunity for the adult leukemia oncology community to emulate the practice of the pediatric oncologists of treating the vast majority of patients in specialized 'leukemia centers of excellence', a proposed definition of which we will offer later in this review, where appropriate clinical trials can be offered to all patients treated with curative intent. Second, the importance of selecting appropriate, clinically meaningful end points in trial design where many of the novel agents being tested will have mechanisms of action other than the historical direct cytotoxicity. Finally, the importance of careful patient substratification in the inclusion criteria for any new trial, both for discriminatory patient (age, performance status, enzymatic/metabolic polymorphisms), etiological (*de novo* leukemia vs treatment related and/or with antecedent hematological disorder), disease biology (cytogenetics, molecular markers, assays of cytotoxic resistance) and treatment (primary vs refractory vs relapsed) factors will not only allow the development of targeted personalized therapy but, with careful registry data and correlative studies, will also provide predictive, prognostic and candidate biomarker/aberrant pathway identification for future use. Our thoughts regarding drug development and clinical trial design for leukemias represent our personal opinion rather than evidence-based conclusions. The controversial nature of these ideas is intentional. We hope that these new considerations will stimulate interest, discussion and innovation in our development of new treatments for these diseases for which there are still substantial opportunities for improvement.

Lessons to be learned from Mylotarg®

Gemtuzumab ozogamicin (Mylotarg®, CMA-676) is a humanized monoclonal antibody to CD33 linked to the cytotoxic agent *N*-acetyl-γ calicheamicin 1,2-dimethyl hydrazine dichloride [7]. This drug was approved by the US FDA on 17 May 2000 under the accelerated approval program for the treatment of adults aged 60 years and older with recurrent AML who were not considered candidates for other chemotherapy [8]. This approval was based on surrogate end point of response rate in three Phase II clinical trials representing a total of 142 patients with relapsed AML and was made on the condition that both ongoing studies of gemtuzumab ozogamicin in relapsed AML were completed, and also that randomized clinical trials comparing the effects of gemtuzumab ozogamicin in combination with conventional induction chemotherapy to conventional chemotherapy alone on survival to confirm clinical benefit be initiated [8].

After 10 years of approved clinical use, gemtuzumab ozogamicin was withdrawn from the US market on 21 June 2010. This action was taken when a confirmatory, postapproval, Phase III clinical trial initiated in 2004 by the Southwest Oncology Group (NCT00085709, S0106 [9]) on the addition of gemtuzumab ozogamicin to '7+3' style induction chemotherapy (daunorubicin IV on days 1–3, cytarabine IV continuously on days 1–7) in patients aged 18–60 years with previously untreated *de novo* AML was stopped early following a planned interim analysis in August 2009. The observation was made that patients treated with gemtuzumab ozogamicin and chemotherapy had no improvement in clinical benefit, but did have increased toxicity and mortality during induction compared with the group treated with chemotherapy [9]. Unfortunately, the study design gave a lower dose of daunorubicin (45 mg/m^2 on days 1–3) to patients on the gemtuzumab ozogamicin arm than those on the control arm (60 mg/m^2 on days 1–3) making interpretation of efficacy challenging. Nevertheless, even prior to this analysis, post-marketing reports of fatal anaphylaxis, tumor lysis syndrome, adult respiratory distress syndrome and frequent severe hepatotoxicity, especially venoocclusive disease, had already required labeling revisions of gemtuzumab ozogamicin and the initiation of a registration surveillance program [101].

As Clarke and Marks of Yale University School of Medicine (New Haven, CT, USA) have recently highlighted, this Phase III clinical trial to determine clinical benefit studied both different patient (younger vs older) and disease (*de novo* vs recurrent) populations

than the original studies on which the initial decision for conditional FDA approval was based [10]. The design of this confirmatory trial unfortunately did not address whether gemtuzumab ozogamicin is a useful agent in specific subpopulations (e.g., adults >60 years old) and/or disease states (e.g., refractory disease, APL) or whether different doses or schedules might limit toxicity and mortality while preserving the effects seen in the older adult and in refractory disease in earlier Phase II studies.

For example, a 2007 study by Taksin and colleagues [11] showed that fractionated doses (3 mg/m^2 on days 1, 4 and 7) of gemtuzumab ozogamicin could be used efficaciously (complete response [CR] + CR without platelet recovery [CRp]: 33%; median OS: 8.4 months) in relapsed or refractory AML without the severe hepatic toxicity seen elsewhere when this drug was administered at the FDA-approved dose of 9 mg/m^2 on days 1 and 8. In addition, a recent CALGB Phase I/II study for adults aged 52–69 years with relapsed or refractory AML demonstrated that HiDAC (cytarabine 3 g/m^2 over 3 h/day for 5 days) followed by a single dose of gemtuzumab ozogamicin at 9 mg/m^2 on day 7 resulted in 12 of 37 patients (32%) achieving complete remission, with a median OS of 8.9 months and no cases of grade 4 hepatic veno-occlusive disease observed [12].

In addition, gemtuzumab ozogamicin demonstrated utility in APL in combination with ATRA and arsenic trioxide in the initial induction of high-risk patients [13] and in the relapsed setting both in combination with ATRA and arsenic trioxide [14] but also as a single agent [15].

In leukemia refractory to, or quickly relapsed from, standard conventional induction chemotherapy, the risk to benefit ratio may tip in favor of considering an agent with toxicities that would be unacceptable in the initial induction setting; especially if that toxicity can be limited by modification of the dosing approach. Unfortunately, given the history of this agent, industry sponsorship may not be immediately forthcoming for additional large Phase III clinical trials under an investigational new drug paradigm to determine if gemtuzumab ozogamicin might have utility with minimal toxicity at different dosing and/or administration schedules in alternate leukemic disease states and patient subpopulations. For example, at the time of writing, Burnett and colleagues have reported from the results of AML15 that younger adults with favorable cytogenetic AML appear to have significant benefit from a single dose of gemtuzumab ozogamicin at 3 mg/m^2 given on day 1 of induction with minimal toxicity [16]. Thus, after clinical trials involving thousands of patients and hundreds of millions of dollars in costs, this drug with potential utility in some limited specific disease and patient populations, is unavailable for clinical use in the USA. From this example, it would appear that our current drug development, clinical trial and drug approval paradigm does not have the flexibility, responsiveness or capacity to encompass the subtlety necessary to develop truly targeted and personalized leukemia treatment approaches for selected populations.

Clinical trials in adults with acute leukemia

Acute leukemias in adults have no universally accepted standard of care and, with the exception of APL and arguably the core binding factor leukemias, all available regimens have unacceptably poor results. Clinical trials are therefore essential for the development of the next generations of drugs and drug combinations.

Clinical trial participation for adult cancer patients in the USA however is poor. The President's Cancer Panel 2004–2005 Annual Report: *Translating Research into Cancer Care: Delivering on the Promise* [102] referenced the testimony of Michaele Christian of the Cancer Therapy Evaluation Program (CTEP) of the NCI to the US House of Representatives on 13 May 2004 where she discussed the differences in adult and pediatric participation in cancer clinical trials. She noted that only 3% of newly diagnosed adult cancer patients are enrolled in clinical trials (compared with ~60% patients within the pediatric age range) and speculated that this is likely due to the fact that "most children with cancer are treated in tertiary care centers, the majority of which are associated with medical schools, whereas the vast majority of adult cancer patients are treated in community practice settings. The higher priority that academia places on research compared with the community setting facilitates the enrollment of children with cancer into clinical trials. Another important factor is the culture of the pediatric oncology discipline. This culture is driven by a history of progressive improvements in childhood cancer outcomes that has reinforced in these specialists the belief that the best way to identify more effective treatments is through well-designed clinical trials. A key characteristic of the pediatric oncology culture is the willingness of researchers to collaborate in conducting multi-institutional clinical trials, which are essential since few single institutions see sufficient children with cancer to conduct the clinical trials that are needed to reliably identify more effective therapies. The remarkable efficacy of many pediatric cancer treatments and the dramatic progress that has been achieved by application of the pediatric oncology paradigm has created incentives for childhood cancer researchers to maintain their high rates of participation in clinical trials in the hope of continuing progress into the future" [103].

Clearly, the absolute number of children with cancer, and acute leukemia, is significantly less than seen in

the adult population in the USA; nevertheless, the 2011 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines state adult "AML patients should preferably be managed at experienced leukemia centers where clinical trials may be more available" [104].

The UK guidelines on the management of AML in adults [17] is more explicit stating that patients "should be treated by a multidisciplinary team that is experienced in the management of acute myeloid leukaemia" (which they define in part as intensively treating five or more patients per annum) and that all eligible patients with *de novo* or secondary AML should be asked to participate in the appropriate current National Cancer Research Institute (NCRI) clinical trial.

In the absence of a defined standard of care for adult AML or adult ALL we believe the standard of care should ordinarily be the offer of enrolment on an appropriate therapeutic clinical trial. Such trials are not limited to those originating from academic medical centers and may be organized by cooperative oncology groups or industry, but should be performed in centers with demonstrated experience and expertise in treating acute leukemias. Toward this end, such a center should embrace both clinical care and clinical research. In this regard, we would propose that a 'leukemia center of excellence' (LCE) be able to offer an array of clinical trials for diverse stages of disease, have the infrastructure to conduct such trials, and treat at least one to two new cases of leukemia per month. Additionally, LCEs should have a close association with basic and translational science investigators, routinely procure critical samples for current and future laboratory investigations and biologic tissue banks, and enroll patients in outcomes registries. These LCEs do not have to be primary academic medical centers. Community centers with special interest in hematological malignancies are capable of providing excellent clinical care for the acute leukemias and, as the almost 30 year experience of the NCI Community Clinical Oncology Program (CCOP) program has shown, recruiting for and participating in clinical trials.

It is not clear however that the traditional sequential Phase I, II then III clinical trials approach used so successfully for small-molecule cytotoxics is optimal in an era where specific biochemical pathways may be targeted based on the molecular typing of a individual leukemia on presentation. Interestingly, of 68 new oncology drugs (excluding hormone therapy and supportive care) that the FDA approved from 1973 to 2006, 31 were approved without a randomized clinical trial. Long-term follow-up on these drugs has demonstrated no safety and efficacy concerns [18]. Walter and his colleagues have recently highlighted that much of the inefficiency of the traditional lengthy sequence of clinical trials can be attributed to high frequency of false-positive results obtained from the early publication of single-arm, single-center Phase II trials using surrogate end points without sufficient consideration of patient and disease heterogeneity [19].

Randomized Phase II trials offer an attractive model for the clinical investigation of new therapeutics in acute leukemia given the need to test combination therapy in a clinical situation where RECIST evaluation is impossible and alternate end points must be used [20]. While historical data of baseline toxicity and outcome are available [21], multicenter, two-armed, randomized studies offer the benefit of controlling for trial-specific effects making biomarker identification and validation possible. If performed in a blinded fashion they would also have the theoretical opportunity that highly significant results in careful targeted subpopulations could form the basis of an accelerated FDA approval.

In an era when many of the new targeted agents being tested may have maximal biological activity at doses that are not limited by toxicity, traditional rigid frequentist clinical trials may not represent the most appropriate design. Estey and Thall have suggested that a Bayesian approach could allow more efficient evaluation of multiple new agents, schedules or combinations within a single, multiarmed, randomized Phase II trial [22]. Similarly, adaptive design using the continual reassessment method during dose-finding Phase I trials allows more patients to be treated at near-optimal dose but requires complicated trial design and significant biostatistician support [23]. Ideally, combined Phase I/II trials would be designed so that patients would be randomized into one of multiple, efficient, single-arm, Phase I dose-finding trials that could be seamlessly continued as a multiarm, dose-optimized, randomized Phase II trial to determine investigational agent efficacy [24]. Result analysis and publication at a prespecified time point in this dose-optimized Phase II trial (e.g., 2 years after study accrual) could trigger, if positive, authorization of additional cohorts at other LCEs allowing a larger scale, multicenter, Phase III trial without the usual delays. Such an approach would limit bias from early publication, under-reporting of negative results and delays in Phase III initiation.

Finally, much has been written on the role of the FDA, lack of federal support and the burdensome clinical trials regulatory environment in the slow pace of drug development [25–27]. There are promising signs, however, that federal support for translational research in drug development is now a priority with the creation of the National Center for Advancing Translational Sciences [28] and the FDA's increasing awareness of the need for transparency and nuance in its decision-making regarding new drugs [29].

Are new end points needed for new agents?

Effective clinical trial design requires the prespecification of primary end points. With the exception of OS, the end points typically used in trials such as CR (defined as normal bone marrow morphology with less than 5% blasts and recovery of peripheral blood counts specifically neutrophils, >1 × 10^9/l and platelet count >100 × 10^9/l), CRp (specifically platelets <100 × 10^9/l) and partial response (PR; bone marrow blasts decreased by at least 50%, or decreased to 5–25% with recovery of peripheral blood counts as above) [30] have only indirect relationships to the actual therapeutic goals we agree at the bedside with our patients specifically to attempt to maximize the quantity and quality of their remaining lives.

Historically, CR has been taken as an acceptable surrogate for clinical benefit in acute leukemia from the observation in multiple trials using cytotoxic chemotherapy that those who achieve a CR have improved survival and that survival is due to the time spent in CR [31,32]. This assumption is unfortunately no longer valid in an era of agents for acute leukemia that have mechanisms other than direct cytotoxicity. For example, a recently reported Phase III trial compared azacitidine (Vidaza®; Celgene Corporation, Summit, NJ, USA) with conventional care regimens (CCR) in elderly patients with low bone marrow blast count AML [33]. This trial clearly showed an significant median OS advantage for those receiving azacitidine compared with CCR (24.5 vs 16.0 months; p = 0.005) and a large difference in 2 year OS (50.2 vs 15.9%; p = 0.001). By contrast, the CR rate of 18% (10 out of 55 patients) in the azacitidine group was not significantly different from the 16% (nine out of 58 patients) in the CCR group (p = 0.80). Conversely, of the patients randomized to CCR who were considered fit enough for intensive chemotherapy, the observed CR rate was 55% (six out of 11 patients); however, there was no statistically significant difference between OS in this subgroup compared with those in the azacitidine treatment arm. This important observation that achievement of traditional morphological responses such as CR are not required for prolonged OS in patients with low blast count AML treated with azacitidine has recently been independently validated in an additional cohort [34].

The exploitation of the immune system as a therapeutic agent for cancer is the focus of a great deal of current investigation and interest [35–37], but has special applicability for the treatment of leukemia. In the setting of bone marrow transplantation it is not currently possible to separate the efficacious graft versus leukemia effect from the wider clinically harmful graft versus host responses. The concept of specific vaccination against leukemia relapse without the limitations and toxicities associated with bone marrow transplant is therefore particularly attractive, especially if the immune response could be targeted to antigens presented by long-lived, chemotherapy-resistant leukemia stem cells. Clearly, this represents an entirely new category of therapeutic approach and clinical trials of efficacy will have to be designed with careful selection of clinically relevant end points to accommodate for the different mechanisms of action while new surrogate markers are developed and validated.

Given the prolonged follow-up required for clinical trials with an OS end point and the potential for confounding by differences in the (non-investigational) post-relapse therapy administered, some investigators have advocated for the use of relapse-free survival/disease-free survival end points [19]. The utility of these end points in situations where therapy is modulatory (e.g., epigenetic or immunological) rather than directly cytotoxic remains to be established.

The concept of minimal residual disease (MRD) has been found to be an important end point in trials of ALL [38], CML [39], APL [40] and bone marrow transplantation [41]. In CML, response to treatment is stratified using the criteria of how sensitive an assay must be used to find MRD; this ranges from hematological (i.e., numerical abnormality in peripheral blood counts), to cytogenetic assessment, to molecular (i.e., quantitive PCR) detection methods. It has been shown that patients with at least a complete cytogenetic response or in whom the level of BCR-ABL transcript falls by at least 3 log have a significantly lower level of disease progression than do patients without a complete cytogenetic response (p < 0.001) [42]. Such an assessment is likely to be more challenging in acute leukemia subtypes where there is no universal molecular signature analogous to BCR-ABL; this is unlikely to be a lasting technical barrier however, especially as the majority of those adults presenting with AML have abnormal cytogenetics [43]. Highly sensitive MRD assays may represent a hard biological end point with true long-term clinical significance, especially if the degree of persistence of a leukemia stem cell population could be quantified. There is promise for the development of sensitive PCR-based techniques for MRD in AML [44], with multiparameter flow cytometry already available in some centers for this indication [45].

Finally, there is a pressing need for the development of reliable indices of quality of life, especially for use in clinical trials of palliative and supportive therapy. Clinical and response end points are of secondary import in this scenario and accurate, reproducible measures of patient quality of life will allow evidence-based improvements in this important component of leukemia care [46].

Targeting patient & disease heterogeneity

Ultimately, the clinical heterogeneity associated with acute leukemia means that one drug may not be equally useful in all situations and the concept of limited specific approval for a defined circumstance may make clinical, if not economic, sense. Unfortunately, this subtlety of indication is lost in the context of our current regulatory approval process that often requires evidence of effect from large numbers of patients enrolled on conventional Phase III clinical trials. It has been well documented that our current clinical trial process is wastefully inefficient; only 5% of new anticancer agents entering clinical development progress to FDA marketing approval [47]. The paradigm of needing to demonstrate that small treatment effects are statistically significant by confirmatory testing in large populations in Phase III trials is suboptimal as the focus moves toward developing personalized therapies for leukemia. The examples of molecular targeting in both CML and APL are instructive, but may unfortunately be unique in their broad impact.

It is likely that future progress in leukemia therapy will come from the development of agents specific not only for molecular targets but also for distinct clinical situations (as in the case of gemtuzumab ozogamicin). The challenge will be to integrate the relevant clinical patient information (e.g., age, performance status, past medical history, prior chemotherapy treatment and enzymatic/metabolic polymorphisms) with disease specific information (e.g., etiology, molecular markers, aberrant pathway analysis and prior treatment response) into an individual homogenous subcategory that can both be enrolled in clinical trials of sufficient size to observe a treatment effect and is large enough to provide sufficient economic incentive for clinical development. As the number of unique parameters under consideration increases, however, the size of each substratified patient group consequently becomes smaller. In an era where increasing attention is placed on controlling healthcare costs, the resulting constraints on drug pricing will require increased efficiency in the process of selecting and developing new agents and/or increased efficiency in the effect of the agents developed (such that smaller randomized trials are sufficient to demonstrate effect sufficient for regulatory agency approval).

As better molecularly targeted drugs become available, it is not clear that large Phase III clinical trials will continue to be necessary. Again, the example of imatinib is informative here. It was approved by the FDA after less than 3 months review based only on data from three Phase II open-label, single-arm studies [6]. While the success in development of imatinib is a prototype that is unlikely to be reproduced routinely it is instructive to appreciate that as more clearly defined pathway targets become available and more efficacious agents specific for them are developed, the scale of trial needed to demonstrate a positive effect decreases.

One approach to improve the efficiency of the process of selecting and developing new drugs is the concept of Phase 0 clinical trials as a bridge across the, often substantial, gap between preclinical development and first-in-human Phase I trials [48]. Essentially, these trials can allow validation of a molecular mechanism, target, biomarker or pathway seen in preclinical models and/or collect pharmacodynamic and pharmacokinetic data in humans to help choose the most promising of several drug candidates to proceed to Phase I safety testing [44,45].

Analogous to the clinical development of cytotoxic chemotherapy treatments of childhood ALL from the 1960s it is possible that molecular targeted agents will also have to be tested as combination therapies [49]. According to the 2-hit model of leukemogenesis proposed by Gilliland and Griffin [50], the use of molecularly targeted agents to the activating type I mutations (e.g., FLT3 or RAS) that confer increased proliferation and survival capability to the leukemic clone may be insufficient, however, without also simultaneously targeting the type II abnormalities (such as *CEBPA* mutations or 8,21 translocations) that cause differentiation arrest and increase in self-renewal properties. Identifying the type I and II mutations present at diagnosis and again at relapse when they may be different [51], will become an increasingly important feature of initial diagnosis and treatment selection.

Whole genome sequencing is currently available for less than US$10,000 and within 10 years it is conceivable that the cost will be less than one tenth of that. This would offer the opportunity to fully sequence a leukemia at presentation and, based on the genetic signature, not only select appropriate targeted therapy but also more accurately predict risk and timing of relapse to inform a plan for the frequency of surveillance follow-up and, together with information on MRD, to risk stratify to determine the need for further consolidative therapy (e.g., bone marrow transplantation). Immune therapy vaccination strategies for relapse prevention personalized on the basis of sequenced leukemia-specific mutations would also be feasible. Finally, such information would speed the development of drug-effect predictive biomarkers that are essential if cost-effective use of multiple expensive recombinant agents is to be integrated into our standard of care for the acute leukemias.

Future perspective

In summary, we believe that acute leukemia care in adults will become increasingly consolidated in regional (both academic and non-academically affiliated) centers

of excellence, in analogy to the model that has worked so well in pediatric leukemia care. Professional organizations (e.g., ASCO, AACR, ASH, NCCN) will define care in a specialized leukemia center and documentation of discussion of an appropriate clinical trial in adult patients presenting with acute leukemia as reportable quality measures.

Increasing use of the FDA accelerated approval program will allow a transition from a paradigm where a drug is universally approved for all indications to a model where a combination of drugs can be tested in coordinated sequential iterative clinical trials for specific disease states in specific patients. This personalization will require the development of predictive biomarkers. Extensive molecular and genetic phenotypic analysis of newly diagnosed and relapsed leukemia should become standard allowing individualized, targeted, risk-adapted, therapeutic treatment plans to be designed. Routine whole-genome sequencing of leukemia should be investigated as it becomes more economically and clinically available.

Finally, the linking of institutional, regional, national and international databases of leukemia epidemiology, etiology, genetics, molecular phenotypes and clinical outcomes will allow efficient data-mining and hypothesis generation for the next generation of biomarkers and therapeutics.

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Executive summary

- Given the overall stagnant clinical outcomes in adult acute leukemias, the standard of care for treatment of most acute leukemia, outside of the palliative setting, should be to offer a clinical trial in the first instance. This includes adults with compromised host biology as well as poor-risk disease features. Only patients who consider and refuse this option should be treated with traditional cytarabine- and anthracycline-based cytotoxic induction chemotherapy regimens. However, exceptions to this general principle may reasonably be made in cases of acute promyelocytic leukemia where reasonable survival rates can be expected with standard therapy.
- All patients with a new diagnosis of leukemia should be referred to a specialist leukemia center; defined arbitrarily as a facility treating on clinical trials at least 12 new cases of acute leukemia a year, with the ability to offer clinical trials specific for age of that patient (i.e., children, adults aged <60 or adults aged >60 years), with active offering of enrolment for all patients, and the ability to offer or refer for bone marrow transplantation if indicated.
- Extensive phenotyping of patient and leukemia heterogeneity should be performed at diagnosis. This information, accompanied by biological samples for correlative studies, including biomarker discovery and hypothesis-generating retrospective laboratory translational studies, should be recorded in a clinical outcomes database linked with a biological sample library. Leukemia, bone marrow and peripheral blood cell banks should be established for this purpose either with leukemia centers themselves or centrally, under the control of the clinical trial co-operative group directing the trial.
- Where possible, clinical trials of novel agents targeting a specific biochemical pathway or molecular phenotype should be designed on a randomized Phase II basis and include the identification and/or validation of predictive and prognostic biomarkers. Moreover, integrated adaptive trial design should be used to maximize the efficiency of these dose-finding and efficacy studies.

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