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Invited review

Therapy of older persons with acute myeloid leukaemia

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ARTICLE INFO

Dedicated to Prof. Thomas Büchner who died whilst preparing this review and who focused his later career on exploring the mysterious *age-related factor* in AML.

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ABSTRACT

Most persons age ≥60 y with acute myeloid leukaemia (AML) die from their disease. When interpreting clinical trials data from these persons one must be aware of substantial selection biases. Randomized trials of post-remission treatments can be performed upfront or after achieving defined landmarks. Both strategies have important limitations. Selection of the appropriate treatment is critical. Age, performance score, co-morbidities and frailty provide useful data to treatment selection. If an intensive remission induction therapy is appropriate, therapy with cytarabine and an anthracycline is the most common regimen. Non-intensive therapies consist of the hypo-methylating drugs azacitidine and decitabine, low-dose cytarabine and supportive care. Feasibility of doing an allotransplant in older persons with AML is increasing. However, only very few qualify.

Results of cytogenetic testing are risk factor in young and old persons with AML. Adverse abnormalities are more frequent in older persons. Although data about the frequency of mutations in older persons with AML is increasing their prognostic impact is less clear than in younger subjects. Neither differences in the distribution of cytogenetic risk, mutations, nor differences in clinical risk factors between younger and older persons with AML completely explain the age-dependent outcome. Many drugs are in clinical development in older persons with AML. Their potential role in the treatment of older persons with AML remains to be defined.

1. Introduction—Utz Krug

Therapy of persons age ≥60 years with acute myeloid leukaemia (AML) is unsatisfactory with little progress in the last 40 years. Important problems and unsolved questions remain. The conduct of clinical trials and the interpretation of trial results in older persons with AML is hampered by selection biases and the issue of generalizability of study results to most older persons with AML. How can we effectively introduce new drugs into clinical trials? Is age *per se* an independent prognostic variable even after adjusting for age-related variables such as co-morbidities, performance score, cytogenetics, frailties and others? How do we gain more knowledge about the molecular bases of age as a risk-factor? Is there a scientific basis for selecting intensive *versus* non-intensive therapy for an older person with AML? Is there a *best* induction regimen and/or post-remission strategy? Should older persons with AML receive an allotransplant, who and when? Is there a role for autotransplants? What is the role and benefit of DNA-hypo-methylating drugs compared to other therapy options in different cytogenetic risk cohorts? Can we expect therapy advances in the near future? This review focuses on these questions, problems and challenges in treating

Abbreviations: ASXL1, additional sex combs like 1; BCOR, BCL6 corepressor; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CEBPA, *CCAAT*/enhancer binding protein alpha; DNMT3A, DNA methyltransferase 3A; FLT3, *fms*-like tyrosine kinase; IDH1/2, isocitrate dehydrogenase 1/2; ITD, internal tandem duplication; n.i., not included; KIT, mast/stem cell growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene homolog; MLL, mixed lineage leukemia; NPM1, nucleophosmin 1; n.s., no significant association with prognosis; NRAS, Neuroblastoma rat sarcoma viral oncogene homolog; PTD, partial tandem duplication; R140/R172, missense mutation in the codons encoding for the arginine residues on position 140/172 of the IDH2 gene; RAD21, RAD21 cohesin complex component; RUNX1, runt-related transcription factor 1; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and srginine rich splicing factor 2; STAG2, stromal antigen 2; TET2, Tet methylcytosine dioxygenase 2; TKD, tyrosine kinase domain mutation; TP53, tumor protein p53; U2AF1, U2 small nuclear RNA auxiliary factor 1; ZRSR2, zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2

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older subjects with AML.

2. Clinical trials strategies – statistical considerations—Robert Peter Gale

For subjects with AML at any age, but in particular for elderly subjects with poor prognosis with conventional therapy, there is considerable debate regarding the best randomization strategy in clinical trials to answer important therapy questions. In some regards the answer depends on the question(s) being addressed. Assume we want to compare efficacy of two interventions such as further chemotherapy *versus* an autotransplant in persons with AML in 1st complete remission after completing consolidation chemotherapy. In this setting the appropriate approach is an intent-to-treat analysis of subjects randomized to one or the other therapy. Although this seems simple and is the most commonly-used strategy there are important limitations. One is that the conclusion of an intent-to-treat analysis of randomized subjects applies solely to subjects meeting the entry-criteria for randomization.For example, subjects in our AMLCG99 study [1,2] had a median age of 61 years compared with a population-based median age of 67 years [3]. In a recent US-based study 60 percent of persons with AML ≥65 years received no therapy in the 3 months after diagnosis [4]. A second problem is that even for the *chosen people* receiving therapy not all randomized subjects receive their assigned therapy [5]. Other unavoidable problems are non-compliance, withdrawal of consent post-randomization and/or leukaemia relapse before the assigned therapy can be given. If the proportion of randomized subjects not receiving their assigned therapy is high the question arises whether we are really testing the question we want to answer. This is especially problematic if the proportion of these subjects is dissimilar in the randomization cohorts. However, there is a more important limitation to this randomization strategy, the inability to quantify the impact of these therapies on the universe of persons with AML. This universe can be defined in several ways such as all persons with AML regardless of whether they meet the study-entry criteria or even all persons meeting these criteria but who never get to the randomization point. For example, what if 90 percent of persons with AML either never achieve remission, achieve remission but relapse before they can receive consolidation chemotherapy, are unsuitable candidates for collecting haematopoietic cells for an autotransplant or in whom the collection is unsuccessful, have no appropriate donor for an allotransplant, develop one or more co-morbidities precluding the planned therapy, are not approved by their health care provider/insurer, withdraw consent or die from a (seemingly) unrelated event such as an automobile accident.

An alternative approach to randomizing subjects at the time they are eligible for the therapy-intervention being studied is to randomize subjects to all future therapies at study-entry such as different induction chemotherapies, numbers of courses or cycles, different consolidation therapies and to maintenance chemotherapy or an auto- or allotransplant. Again the analysis needs to be by *intent-to-treat*. The obvious advantage of this strategy is we keep track of all subjects and determine what proportions reach each pre-specified landmark. By examining the final outcomes of all study subjects we can determine the impact to these therapies on the universe of persons with AML meeting the study-entry criteria. However, there are obvious disadvantages to this strategy. For example, it is almost certain many subject will never receive their assigned therapy, especially at late landmarks such as chemotherapy *versus* a transplant for persons in remission. Also, it is impossible to know at study-entry which subjects will be able to have haematopoietic cells successfully collected for an autotransplant or have an appropriate donor for an allotransplant. In our AMLCG99 study only 15 percent of subjects randomized at study-entry to an autotransplant received one and only 4 percent of subjects randomized or assigned to receive maintenance therapy for 3 years after CR completed the prescribed intervention [2]. The bottom line is the proportion of subjects not receiving therapy–assignments using the strategy of therapy-assignments at study-entry is obviously substantially greater than when randomization is done when/if the subject becomes eligible for the therapies being tested. However, is it really important to know if a therapy-strategy works if it applies to < 15 percent of people on a clinical trials and by extrapolation < 5–10 percent of the universe of people with the relevant diagnosis? An example of this strategy comes from MRC AML12 trial [6]. Of 1881 subjects eligible for randomsiation to 4 *versus* 5 cycles of consolidation therapy 865 subjects (46%) did not participate.

Thus, the randomization strategy one chooses, at study-entry or at a landmark, will depend on the question(s) the study is designed to answer and the relevance of the answer (assuming there is one) to the universe of persons with the relevant diagnosis. Sometimes questions answered by studies with different randomization strategies were not envisioned when the study was planned and/or effected. Both approaches are useful as we consider how to *best* treat AML and are complementary. Moreover, it is unsurprising studies using different randomization strategies reach different conclusions. Thoughtful people will consider the universe of evidence from randomized trials and other data such as results of meta-analyses and biological plausibility, conclusions from observational databases including left-truncation and matched-pair, instrumental variable and propensity score analyses to reach a conclusion. We favour a weight-of-evidence approach by which we mean considering all available data which are determining which point-of-view is best supported. And it is always important to consider biological plausibility in reaching a conclusion regarding the best therapy strategy for someone with AML. Elsewhere we discuss our lack of accuracy in predicting the outcome of someone with AML [7]. Conclusions derived from randomized trials with precisely-defined study-entry criteria often do not apply to many persons with the disease being studied. Most estimates suggest only 10–20 percent of people with a relevant diagnosis meet study-entry criteria of clinical trials. And this conclusion is not unique to studies in AML. Large studies from the US Veterans Administration in men with prostate cancer indicate conclusions apply to a minority of men with this condition [8]. The bottom line is, regardless of which randomization strategy one chooses the study is unlikely to result in a conclusion applicable to most older persons with AML. This is a problem we can improve on but are unlikely to ever solve.

Increasing knowledge of the molecular heterogeneity of AML has resulted in a drive to what is termed precision therapy where different targeted drugs are proposed to be used in persons with different mutations. Although this approach is intellectually attractive there are important limitations to applying this approach to AML which we discuss elsewhere [9]. Such a therapy-strategy will require new clinical trials designs and new bases for regulatory approval [7]. Time will tell whether this approach will work but a recent example is approval of midostarurin in persons with AML with a FLT3 mutation [10].

3. Selecting therapy strategies—Utz Krug

Potential therapy strategies in older persons with AML include intensive chemotherapy, less intensive therapy and supportive care only. Although intensive therapy including an induction regimen offers the potential for cure, only about 50 percent of older persons, defined as an age of ≥60 years at diagnosis, achieve a complete remission and only about 50 percent of these are in remission at two years [11,12]. Important prognostic factors in the elderly are general condition, typically quantified by the Eastern Cooperative Oncology Group (ECOG) performance score, and co-morbidities. Persons > 75 years with an ECOG performance score ≥3 receiving intensive chemotherapy have a 30-day mortality > 50 percent [13]. The haematopoietic cell transplant co-morbidity index (HCT-CI, [14] quantifies co-morbidities and is also correlated with survival after intensive induction chemotherapy [15]. These variables have been incorporated in various prognostic scores for older persons with AML receiving intensive therapy [16–18] which can