Real World Evidence in Acute Myeloid Leukaemia

Interviews with two key opinion leaders in acute myeloid leukaemia took place during September 2021

Interviewees: Jean-Baptiste Micol,[1] Thomas Cluzeau[2]

1. Gustave Roussy, Université Paris-Saclay, Villejuif, France
2. Côte d'Azur University, Centre Hospitalier Universitaire de Nice, France

Disclosure: Micol has received grants for research or honoraria from Novartis, Jazz Pharmaceuticals, AbbVie, Astellas, and Astra Zeneca. Cluzeau has received research or educational grants from Novartis, Alexion, Celgene/Bristol Myers Squibb (BMS), Amgen, Syros Pharmaceuticals, Kartos Therapeutics, AROG Pharmaceuticals, Takeda, Sanofi, and Astellas; travel or attendance fees for international congresses from Sanofi, Pfizer, Celgene/BMS, and Novartis; and has participated in advisory boards for Celgene, AbbVie, Jazz Pharmaceuticals, Roche, Novartis, and Agios Pharmaceuticals.

Acknowledgements: Medical writing assistance was provided by Nicola Humphry, Nottingham, UK.

Support: Jazz Pharmaceuticals has proposed the topic and funded the publication of this article. Jazz Pharmaceuticals has had no influence on the key opinion leaders interviewed but has completed a medical accuracy review on aspects of the text regarding CPX-351 only.

Disclaimer: The opinions expressed in this article belong solely to the named interviewees, and may not necessarily reflect the views of Jazz Pharmaceuticals.

Citation: EMJ Hematol. 2021;9[Suppl 5]:2-7.

Interview Summary

In recent years, there has been an increasing appreciation of the role that patient characteristics such as age, gender, lifestyle, and genomics play in the response to therapy. This has led clinicians to look beyond randomised controlled trial (RCT) data and also consider safety and effectiveness of drugs in heterogeneous patient populations in real-world clinical settings.[1]

Real-world evidence (RWE) of the benefits and risks associated with treatment is derived from analysis of real-world data (RWD) sources such as electronic health records, medical claims, product and disease registries, and patient-generated data.[2] One of the most obvious advantages of RWE is its size and scope. It provides opportunities for understanding diseases in a way that is not possible with smaller or more circumscribed data sets.[3] In order to achieve robust, statistically significant outcomes, RCTs often need to restrict their patient population.[4,5] RWE is useful in clinical decision-making because it better represents the diverse patient populations encountered by healthcare professionals, and it can help to identify rare outcomes associated with long-term therapy.[4,6] RWE is also considered useful in expanding clinical trials into rarer diseases and cancers, where RCTs are more difficult to conduct.[7] It should be noted, however, that RWD can be of variable quality[4] and can be affected by biases which RCTs avoid.[7]

Acute myeloid leukaemia (AML) is a highly heterogenous disease, and the efficacy and toxicity of pharmacological treatments varies between patients due to differences in cytogenetics, molecular aberrations, performance status, and comorbidities.[8]

In this interview, Jean-Baptiste Micol, a member of the Gustave Roussy Haematology Committee at the University of Paris-Saclay, France, and Thomas Cluzeau, University Hospital of Nice, France, share their views on RWE in AML. They describe the current limitations to treatment, and the differences they have observed between clinical trial results and the real-world population that they treat.

CURRENT TREATMENT FOR ACUTE MYELOID LEUKAEMIA (EXCLUDING ACUTE PROMYELOCYTIC LEUKAEMIA)

Both Micol and Cluzeau confirmed that the best first-line treatment for newly diagnosed, young patients with AML is an intensive treatment that includes a form of induction therapy such as cytarabine with an anthracycline (daunorubicin or idarubicin), either in a 3+7 regimen or as CPX-351 (a combined formulation of cytarabine and daunorubicin), followed by consolidation treatments +/- allogeneic stem cell transplant. Micol explained that there are still limited additional options for first-line therapy, other than enrolling patients in clinical trials of new drugs.

While younger patients (<60 years) with AML are likely to be treated with high-intensity therapy for curative treatment, Micol stressed that in older patients (>60 years), treatment decisions depend upon the expected tolerance to intensive therapy versus the chance of achieving a complete response (CR). As an example, he explained that the 2-year survival rate after intensive therapy is less than 10% in patients with a *TP53* mutation, so if there is a risk that the patient would not be able to tolerate this treatment, then it is better to enrol them in a clinical trial rather than using a standard 3+7 regimen. Conversely, if the patient has 30% chance of survival at 2 years and they are likely to tolerate intensive therapy, then this is the treatment approach Micol would take. He explained that the choice of intensive chemotherapy in patients aged 70–75 years is dependent not only on the molecular/cytogenetic characteristics of the disease, but also the patients' performance status and comorbidities, because some patients can be relatively healthy at this age. Micol usually offers less-intensive therapies to patients over 75 years old; however, these treatments are often palliative rather than potentially curative. Promisingly, a recent study has shown that combination therapy with new drugs may prolong survival in these patients.[9]

Micol also pointed out that, globally, patient preference is playing an increasing role in treatment decisions in AML. For example, patients might prefer to be treated at home rather than in the hospital, and with less intensive treatment. Micol does not feel that this is the case in France yet, but that with new drugs increasing the options for treatment, such as azacytidine as a lower-intensity therapy for older patients with AML,[10] patient preferences are likely to have an increasing impact.

TARGETED THERAPIES

Approximately 30% of patients with AML harbour mutations in the *FLT3* gene,[11] though Micol clarified that this mutation is slightly less common (25%) in his own cancer centre. He explained that a few years ago, the prognosis of patients with *FLT3* mutations was quite poor because these patients usually have higher white blood cell counts and are less likely to achieve a CR to therapy and are more likely to relapse compared to patients without an *FLT3* mutation, despite intensive treatment. However, although outcomes are still not favourable, Micol stressed that there are now better treatment options available, and Cluzeau noted that the development of haematological intensive care units has improved the early prognosis of these patients. Both Micol and Cluzeau regularly use a targeted therapy alongside 3+7 or CPX-351, such as an FMS-like tyrosine kinase 3 (FLT3) inhibitor or an isocitrate dehydrogenase (IDH) inhibitor (as part of a clinical trial) in patients with mutations in *FLT3* or *IDH*, respectively.

Micol indicated that in France, several clinical trials have been conducted with gemtuzumab ozogamicin, a CD33 antibody conjugated to a cytotoxin, and the patients with the best responses seem to be those with activating signalling mutations (including *FLT3* mutations).[12] *FLT3* inhibitors have also been shown to be effective in these patients such as midostaurin, crenolanib, and gilteritinib, and Micol emphasised that combining these targeted treatments with standard intensive chemotherapy improves outcomes.

For the last 20 years, advances in the management of treatment-related toxicity have been driving an increase in life expectancy for patients with AML. However, more recently, a lot of interesting new drugs have been developed and are being assessed in clinical trials, and Micol indicated that he tries to include his patients in these trials wherever possible to give them the best chance of survival. He emphasised that the initial design of clinical trials was very important, since drugs can only be developed and approved if they achieve the primary endpoint of a trial, even if they have been shown to have *in vitro* activity and potential clinical benefits.

DIFFERENCES BETWEEN CLINICAL TRIAL DESIGNS AND THE REAL-WORLD SETTING

One of the differences between clinical trials and the real world, in Micol's view, is the follow-up time. Due to the urgent need for new treatments in AML, clinical trial data is published as quickly as possible, often with a limited follow-up period.

CR is an important predictor of overall survival and is an established early surrogate of long-term survival in clinical trials.[13] The International Working Group (IWG) criteria defines CR in AML as <5% myeloblasts in bone marrow, the absence of circulating blasts, haematologic recovery, and the absence of extramedullary disease.[14] However, clinical trials designed with an end point of CR may have limited power to detect real change in overall survival,[5] and since relapse after achieving CR is increasingly common with age, it may not be adequate as the sole predictor of long-term survival in older age groups.[13]

Micol stressed that sometimes this can make it difficult to compare clinical trial results with real-world results.

Other than the length of follow-up, Micol explained that whether we see a big difference between real-world results compared with clinical trials depends on the individual patients. For patients with the same characteristics as those in a trial, Micol feels that real-world results are similar; however, he admitted that this may be because his patients are commonly participants in clinical trials. He also emphasised that differences may depend on how you define a real-world population; his own 'real-world' differs from that of a secondary or tertiary care hospital, for example, because he is working at a specialist cancer centre that can provide advanced methodologies such as allogeneic stem cell transplant and participation in Phase I studies. Micol explained that the real-world population, and, therefore, the treatment results observed in different settings, may vary because staffing levels and available facilities can differ. Similarly, Cluzeau pointed out that medical centres that participate in clinical trials use a particularly rigorous approach to management and follow-up compared with centres that do not participate, yet outcomes from both types of centres are considered to be RWD.

Other studies have highlighted similar issues with the translation of clinical trial results into everyday practice. For example, the ACO-016 and DACO-017 studies showed a median time from first dose of decitabine to achieving CR was 4.0–4.5 cycles of treatment, yet retrospective analysis of a Belgian AML registry showed that just 47% of patients actually receive this many cycles.[15] Likewise, a retrospective review of medical chart data across 10 countries found that >39% of patients with relapsed/refractory AML did not receive the treatment recommended by National Comprehensive Cancer Network (NCCN) guidelines, and substantial heterogeneity was observed in treatment patterns.[16] Some physicians have suggested that these differences may arise in part because trials evaluate outcomes that do not reflect real-world settings and concerns, and that they need to be developed with patients in mind.[17]

DIFFERENCES IN TREATMENT BETWEEN CLINICAL TRIALS AND THE REAL-WORLD SETTING

The restricted populations of clinical trials are rarely representative of the real world. For example, an Australian study compared the relevance of the trial population in the RATIFY study[18] with real-world practice among patients with *FLT3*-mutant AML between 2010 and 2015. Chua et al. noted that the upper age limit for recruitment to RATIFY was 59 years, yet almost 29% of patients were aged between 60 years and 65 years in the real-world cohort.[19] Similarly, a real-world study of the efficacy and toxicity of CPX-351 in patients with AML noted that patients in the real-world population had multiple comorbidities, including concomitant active neoplasms, which would likely have excluded them from Phase II–III trials.[8]

The importance of assessing the performance of new drugs in routine clinical practice, rather than relying solely on clinical trial data, can be demonstrated by findings from comparisons of RWD and clinical trial data. Many studies have been able to confirm that new drugs are efficacious in a broader real-world population, including two retrospective analyses of CPX-351 treatment in France and Italy, which confirmed the efficacy and safety of this drug in patients with therapy-related AML or AML with myelodysplasia-related changes (AML-MRC) in a real-world setting.[8,20] Similarly, RWD have confirmed the efficacy and acceptable safety profile of decitabine in elderly patients with AML, who are unsuitable for intensive chemotherapy,[21] and the efficacy and safety of decitabine has also been confirmed using RWD from the Belgian AML registry.[15] In addition, azacitidine has been shown to be just as effective as first-line therapy in patients with AML in Australian clinical practice as it is in the more stringent populations of clinical trials.[22] However, other studies have found that results from clinical trials are not reflected in real-world clinical practice. For example, although clinical trials have reported positive data for the 3+7 treatment regimen in patients aged ≥60 years, such as a 4-week mortality rate of 11–12%, a study based on RWD demonstrated a 4-week mortality rate of 27–50%.[23]

TREATMENT OF PATIENT SUBGROUPS COMMONLY EXCLUDED FROM CLINICAL TRIALS

Micol agreed that there are subsets of patients with AML who would generally not be included in clinical trials. For example, in his cancer centre, he sees a large proportion of patients with therapy-related AML, of whom approximately one-third have an active cancer and are, therefore, usually excluded from clinical trials. However, he explained that these patients might have prostate cancer or thyroid cancer but still have a good performance status and a long life-expectancy, and in this case, he would usually treat them with drugs shown to be effective for other patients in clinical trials. Micol emphasised that because these patients have a history of other treatments, and may be receiving current treatment, he would expect efficacy results to be slightly lower than observed in the trials. However, he feels that since these new treatments are still an improvement on those previously available, they still provide a therapeutic advantage to these patients.

Many of Micol's patients carry a *TP53* mutation, and he explained that their life expectancy is very poor. He feels that there is an urgent need for new drugs in this population; however, although potential treatments are currently being assessed, about half of his patients are excluded from the clinical trials.

Micol also emphasised that it can be very difficult to conduct Phase III trials with new drugs for rare diseases such as blastic plasmacytoid dendritic-cell neoplasms, an extremely rare disease with a dismal outcome. Therefore, he will sometimes treat such patients off-label with drugs that have shown promising results in preclinical trials.[24]

WHAT HAPPENS WHEN A CLINICAL TRIAL ENDS?

Both Micol and Cluzeau stressed that they would not modify a patient's therapy substantially when the clinical trial they have been participating in ends. Micol clarified that he would make the same decisions regarding treatment modification or discontinuation whether a patient is in a clinical trial or not. If an issue such as toxicity occurs

during a trial, which might make it difficult for the patient to continue with treatment, he explained that it is usually possible to request an in-trial modification.

Micol added that the way in which a patient is followed up might change after the trial ends; for example, clinical trials in AML sometimes include bone marrow evaluations, and the frequency of these might decrease. He also explained that one situation where he would consider a post-trial modification to a patient's treatment would be if new treatment recommendations are published either during or after the clinical trial.

Micol felt that patients with AML generally want to be treated, regardless of whether they are participating in a clinical trial. However, he admitted that, for outpatients, there is a risk that if a trial includes regular visits at hospital, and this is later reduced, then this might impact treatment adherence. Provided there is adequate interaction between healthcare professionals and patients, Micol believes that this should not be a problem.

WHAT ABOUT FUNDING FOR DRUGS IN CLINICAL TRIALS VERSUS THE REAL-WORLD?

Clinical trials are often funded commercially but, in the real world, a country's health service or a patient's insurance company needs to pay for the treatment. Although Cluzeau feels that this issue has no impact on his treatment choices, Micol explained that it could present a problem in certain cases. The French healthcare system is based on a social insurance model, so patients do not pay for the treatment themselves. However, Micol pointed out that this means that if a drug is associated with a high cost for the community, it might not be approved for reimbursement. He explained that the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) may have approved many new drugs for AML, but there are comparatively few approvals to reimburse them in France. This means that a patient might be able to receive a new drug through a clinical trial, but when the trial ends, the same drug might not be available in the 'real world'. Micol provided the example of CPX-351, which is approved for use in France, but not for reimbursement; if a clinician wants to prescribe it then the hospital needs to find a way to pay for it. Depending on the availability of funds, some hospitals may be able to afford it, and some may not.

CONCLUSION

What is evident from the insights of these two key opinion leaders is that new drugs and supporting clinical trial evidence are greatly welcomed in the field of AML to give patients the best chance of survival. With a strong need for more effective treatments, clinical trials in AML often focus on short-term follow-ups rather than long-term survival. This, in addition to the broader treatment population with more comorbidities, prior treatment, and lower performance status in the real world, contributes to the disconnect between clinical trial results and real-world evidence. In this setting, clinicians aim to enrol their patients in clinical trials wherever possible, and they may use drugs off-licence in patients that are excluded from trials.

Because of the increasing pressure on regulatory agencies to replicate clinical trial results in clinical practice,[22] the EMA intends to expand the use of patient registries to support regulatory decision-making,[25] and the FDA has created a framework to evaluate RWE for the same purpose.[2] Some approaches to the inclusion of RWE in clinical evaluations include pragmatic trial designs, which have elements that resemble routine clinical practice or that compare treatments in a real-world setting, and hybrid designs, which have elements that collect and analyse RWD.[2,3,26] For example, the Austrian Azacitidine Registry established a platform to document the off-label use of azacytidine even before the AZA-AML-001 clinical trial was initiated, reflecting the lack of alternative treatments and the promising data in high-risk patient groups.[22]

References

1. Mackowiak JI et al. Randomized clinical trial or real-world evidence: how historical events, public demand, and the resulting laws and regulations shaped the body of medical evidence. J Orthop Trauma. 2021;35(Suppl 1):S17-21.
2. U.S. Food and Drug Administration (FDA). Framework for FDA's real-world evidence program. 2018. Available at: https://www.fda.gov/media/120060/download. Last accessed: 1 November 2021.
3. Zura R et al. Real-world evidence: a primer. J Orthop Trauma. 2021;35(Suppl 1):S1-5.
4. Villines TC et al. Awareness, knowledge, and utility of RCT data vs RWE: results from a survey of US cardiologists: real-world evidence in clinical decision making. Clin Med Insights Cardiol. 2020;14:1-7.
5. Medeiros BC. Interpretation of clinical endpoints in trials of acute myeloid leukemia. Leuk Res. 2018;68:32-9.
6. Curtis JR et al. Tools and methods for real-world evidence generation: pragmatic trials, electronic consent, and data linkages. Rheum Dis Clin North Am. 2019;45(2):275-89.
7. Greenbaum D. Making compassionate use more useful: using real-world data, real-world evidence and digital twins to supplement or supplant randomized controlled trials. Pac Symp Biocomput. 2021;26:38-49.
8. Guolo F et al. CPX-351 treatment in secondary acute myeloblastic leukemia is effective and improves the feasibility of allogeneic stem cell transplantation: results of the Italian compassionate use program. Blood Cancer J. 2020;10:96.
9. DiNardo CD et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-29.
10. Dombret H et al. International Phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015;126(3):291-9.
11. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood. 2002;100(5):1532-42.
12. Fournier E et al. Mutational profile and benefit of gemtuzumab ozogamicin in acute myeloid leukemia. Blood. 2020;135(8):542-6.
13. Bloomfield CD et al. Time to repeal and replace response criteria for acute myeloid leukemia? Blood Rev. 2018;32(5):416-25.
14. Cheson BD et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-9.
15. Meers S et al. Real-world data confirming the efficacy and safety of decitabine in acute myeloid leukaemia – results from a retrospective Belgian registry study. Acta Clin Belg. 2021;76(2):98-105.
16. Griffin JD et al. Treatment patterns and healthcare resource utilization in patients with FLT3-mutated and wild-type acute myeloid leukemia: a medical chart study. Eur J Haematol. 2019;102(4):341-50.
17. Heneghan C et al. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18:122.
18. Stone RM et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377:454-64.
19. Chua CC et al. Treatment practice and outcomes in *FLT3*-mutant acute myeloid leukemia in the pre-midostaurin era: a real-world experience from Australian tertiary hospitals. Leuk Lymphoma. 2020;61(4):848-54.
20. Chiche E et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: a multicentric French cohort. Blood Adv. 2020;5(1):176-84.
21. Fili C et al. Efficacy and toxicity of decitabine in patients with acute myeloid leukemia (AML): a multicenter real-world experience. Leuk Res. 2019;76:33-8.
22. Pleyer L et al. Azacitidine for front-line therapy of patients with AML: reproducible efficacy established by direct comparison of international Phase 3 trial data with registry data from the Austrian Azacitidine Registry of the AGMT Study Group. Int J Mol Sci. 2017;18(2):415.
23. Kantarjian H et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J. 2021;11(2):41.
24. Micol JB et al. More on blastic plasmacytoid dendritic-cell neoplasms. N Engl J Med. 2019;380(7):696.
25. European Medicines Agency (EMA). Patient registries. Available at: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries#draft-guideline-on-registry-based-studies:-public-consultation-section. Last accessed: 1 November 2021.
26. De S et al. Leveraging real-world evidence: a paradigm shift in regulation. J Orthop Trauma. 2021;35(Supp 1):S13-6.