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Intensive induction in older patients with acute myeloid leukemia: an initial struggle with later rewards?

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Sustained remission is a realistic goal of therapy in older adults presenting with acute myeloid leukemia (AML). Despite the fact that no prospective comparison demonstrated its superiority, the use of azacitidine-venetoclax combination has become popular even among patients that previously were considered "fit" and would have been offered intensive chemotherapy^{1,2}. The high burden of potentially associated devastating adverse events, as well as the unpleasant side effects (e.g anorexia and alopecia) swayed people away from intensive chemotherapy, particularly considering existing alternatives. It seems that with non-intensive regimens, the risks of tumor lysis syndrome, acute kidney injury and severe infections are slightly lessened. However, many patients with AML are already neutropenic at diagnosis and at risk for infection or other complications due to the leukemia, regardless of therapy. One popular consideration supporting the azacitidine-venetoclax combination over intensive chemotherapy in patients with advanced age is the benefit of duration of remaining at home ("home stay") over the prolonged admission to hospital that is mandatory following intensive chemotherapy induction.

In this issue, Jensen and colleagues from the University of North Carolina, published a simple but provocative analysis questioning the common wisdom that azacitidine-venetoclax combination is associated with a longer home stay than intensive chemotherapy³. Apparently, calculating the burden of all hospital visits and stays for any leukemia associated reason, as well as the need for repeated subsequent cycles of azacitidine infusions, leads to a surprising insight. The actual numbers are not in favor what seems obvious when only the first month that follow the diagnosis is considered. Reviewing Jensen's data, it is important to segregate patients treated with palliative aims from those who were targeting remission. For the purpose of the current discussion, data regarding patients with AML who were offered azacitidine alone or supportive care will be excluded, on the assumption that palliation was the main goal of therapy in these cases. Assuming patients treated with intensive chemotherapy or azacitidine-venetoclax combination shared a desired goal of achieving sustained remission and a lasting period with good quality of life, prolonged home stay is desired for patients in both groups. Surprisingly, and counterintuitively, the data report an enormous difference in the length of home stay between the two groups. The mean home time of patients treated with intensive chemotherapy was 7.6 months longer (13.1m vs 5.5m) than those assigned to azacitidine-ventoclax. Similar results were reported even when an age-adjusted model was applied, a 2.4-fold difference in favor of intensive chemotherapy. Moreover, despite identical remission rate, survival with intensive chemotherapy was significantly longer with a median overall difference of more than a year (19.9 vs 7.7 months) compared to survival with azacitidine-venetoclax. In conclusion, in older adults with AML, accepting upfront some loss of time at home, right after diagnosis, should be carefully considered in many patients as a worthwhile ultimate investment that is a feature of intensive chemotherapy induction. This will often be rewarded when reaching a sustained remission with a prolonged home-time with lesser need for repeat hospital visits. Of note, the feasibility of long-term remission in older adults treated with intensive chemotherapy was demonstrated in a prospective ECOG-ARIN study, E2906. In this prospective trial alloSCT was utilized in only 26% of patients and the median disease-free survival of FLT3wt patients (in which rate of alloSCT was even lower) reached 24 months⁴.

This work is a call for physicians to re-evaluate the way they present treatment options to patients debating which route of induction to take (Fig1). A frequently heard arguments guiding treatment selection is to favor home stay over hospitalization. While this is definitely an important parameter essential for good quality of life, the whole anticipated life period should be globally considered, not only the first month of treatment. The burden of adverse events during remission, considering the required repeat cycles for azacitidine infusions and the often resulting cytopenia, must not be neglected.

Notably, former research⁵ by the same group, highlights how surprising and worthwhile is a discussion are their current findings. Moreover, how preliminary assumptions on anticipated outcome may lead to misjudgment and suboptimal clinical decisions. In their former research, the authors asked patients for their views regarding home stay and demonstrated that patients greatly appreciate the value of home stay. Patients even declared that they are “willing to accept some reduction in treatment efficacy in exchange for increased home time” but as physicians our duty is to provide our patients the whole landscape of short- and long-term data regarding home-time so they, and us, can make the best educated decision.

Intensive chemotherapy is not easy, particularly in older adults. Yet, the outcome with intensive chemotherapy has improved significantly over the years with a reduction of induction mortality and morbidity due to improvements in supportive care. The reported quality of life collected within the E2906, a recent large prospective study of intensive chemotherapy in patients 60 years and older, confirmed that they experienced significant improvement in quality of life after recovering from nadir⁶. The current important study by Jensen et al. emphasis the importance of systematically data collection even of what may apparently look obvious. With a wide perspective supported by comparative data, the jury are still out, not only concerning efficacy, but also regarding the burden of adverse influence on quality of life between intensive and non-intensive therapies for AML.

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Legend to figure:

Fitness for intensive chemotherapy in patients with comorbidities is multifactorial and remaining time at home may serve as one of the arguments. Contrary to the immediate period of induction, in the long run, intensive chemotherapy is associated with longer home stay than treatment with hypomethylation-venetoclax combination.

