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Editorial

Hypomethylating Agents, Another Band-Aid for the Older AML Patient?

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Currently two hypomethylating agents (HA), azacitidine and decitabine, are available to clinical practice. Initial trials that led to the approval of HA, enrolled MDS patients with up to 30% marrow blasts based on FAB classification. Later, following inclusion of > 20% blasts under AML by WHO classification, HA were claimed to be active in the treatment of oligoblastic AML with 20-30% marrow blasts [1].

In a prospective trial, an overall response rate of 50%, including complete and partial remissions as well as hematologic improvement was reported with azacitidine given to 20 previously untreated older AML patients unfit for chemotherapy [2]. A single institution phase II study of 5-day per cycle decitabine in patients >60 years with untreated AML, reported 24% complete remission and median overall survival (OS) of 7.7 months [3]. Another single institution study administered 10-day courses of decitabine to previously untreated >60 year patients, and reported safety with 47% complete response (CR) rate and 12.7 months of median OS [4].

Recently HA have gained popularity for the treatment of older patients with AML since they are thought to be less toxic than chemotherapy and also carry the convenience of outpatient administration. Eisai Co., Ltd, the producer of decitabine, supported an open-label multi-institutional randomized clinical trial for the treatment of adults age 65 and older with previously untreated AML [5]. The study randomized patients between decitabine and either best supportive care or low-dose cytarabine (TC arm). The CR rate was 17.8% with decitabine and 7.8% in the TC arm (P = .001). With a total of 485 enrolled patients, after 396 deaths, median OS of 7.7 and 5.0 months for decitabine and TC arm were reported, respectively. However, statistical analysis failed to demonstrate significant difference in OS between the two arms (P = 0.108). One year later, after 446 deaths (92.0% of patients) an ad hoc analysis of OS indicated same values. Owing to lack of OS benefit, the US FDA declined approval of decitabine for the proposed indication. Decitabine as well as azacitadine, however, continues to be utilized off-label by many practices for the treatment of older AML patients.

A CR, which is predictive of improved OS, is achieved by induction chemotherapy (IC) in only 50% of older AML patients. Treatment with IC typically requires 3-4 weeks of hospitalization, and embraces risk of serious side effects and complications including death. After all, a great majority of patients who attain a CR experience relapse usually within a year. Moreover, many older patients are considered "unfit" for IC and never receive such treatment. Given unsatisfactory outcome with intensive chemotherapy in this group of patients, modified or alternative therapies have been experimented; yet none has shown efficacy beyond a temporary Band-Aid remedy. In this context, HA offer some advantages over IC, in particular the outpatient administration flexibility and the presumed acceptable toxicity profile.

Non-randomized single-institution studies have reported up to 50% response rate with HA in frontline therapy of AML. However, the only randomized multi-institutional phase III, yet un-blinded, study with an HA in AML reported a CR rate of 17.8% [5]. Chance of achievement of a CR with HA, therefore, seems to be significantly inferior to IC. Since the state of CR has shown to confer a survival advantage, in case of IC achievement of a CR is considered the only meaningful goal of therapy. However, with the introduction of biologic agents including HA, other measures such as hematologic improvement and transfusion independency have been contemplated as other potential goals. These measures may indeed translate to improvement of quality of life, longer progression free survival, or even perhaps better OS.

A challenge for both patient and clinician is to decide between therapeutic options, particularly in borderline or less-fit patients who may or may not be able to tolerate IC. A common tendency is to direct such patients towards less-intensive therapies such as HA. It is, however, important to be noted that prospective clinical trials with HA have excluded this patient population, accepting only those with better performance status and adequate organ function. Indeed, it has been demonstrated that such older but fit individuals without significant co-morbidities have minimal risk of 30-day mortality with IC [6,7]. For example, some patients who failed treatment in a decitabine trial, underwent subsequent IC [3]. Moreover, majority of data on IC-related mortality are from studies conducted 1-2 decades ago when supportive care was less advanced than today. In addition, most complications following IC are due to disease- and/or therapy-related cytopenia, an adverse effect that is also unavoidable with the use of HA. Studies with decitabine have reported 24-68% febrile neutropenia and 47-59% serious adverse events, numbers that are comparable with IC [3-5]. A phase II study with decitabine in patients > 60 years reported 25% mortality at 3 months, which per the authors "is similar to that seen in patients older than 60 years of age after induction with conventional chemotherapy". Furthermore, the phase III study with decitabine, which included patients > 65 years, reported 32% 30-day mortality rate in the decitabine arm.

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AML demonstrates a low-proliferative behavior in a group of patients, manifesting as acceptable blood counts with infrequent or no transfusion need and better performance status, which usually portraits a more "fit" picture. It is difficult to determine the patient selection process involved, beyond the published eligibility criteria, in HA clinical trials; but the median baseline WBC of patients in these trials has generally been below 3,000/μL [3-5], suggesting a tendency to enroll more of such low-proliferative/stable patients. Thus, it seems that the real-life question of how will our typical sick and less-fit older patient do with HA, has remained to be answered convincingly.

There is an inclination to prefer HA over IC for patients with poor-risk cytogenetics, given discouraging CR rates, as low as 25-30%, with IC in these cases [8]. Nevertheless, we need to remember that prospective trials with HA have also indicated sub-optimal responses with no suggestion of promising activity in these patients [2,5].

A major disadvantage of IC is the typical long inpatient stay, while HA offer the convenience of outpatient treatment. This is an attractive feature to older AML patients particularly considering their likely limited survival outlook. It can indeed be a pivotal factor in decision making regarding treatment choices. In this context, it should also be discussed with the patient that achievement of a CR with IC, if occurs, will usually offer a subsequent period of reasonable quality of life, prior to relapse; without risk of infection or need for frequent treatments or transfusions. On the other hand, following achievement of a CR, the treatment with HA typically needs to be continued indefinitely until relapse or unacceptable toxicity. It will require the patient to present 5-7 days every month for treatment, and will harbor risk of myelosuppression-related complications with each cycle.

In conclusion, the treatment of AML in older, particularly unfit, patients remains a challenge. Unfortunately, despite substantial investigational efforts, no more effective frontline therapy than cytarabine/anthracycline induction has been introduced over past 40 years [9]. HA have recently offered an effective and less-intense option to older AML patients. An increasing number of clinicians prefer treatment with HA for these patients owing to concern of high toxicity and lack of satisfactory outcome with IC. Patients are also commonly attracted to an outpatient treatment with chance of efficacy and claimed less toxicity. Closer look into the data from clinical trials with HA, however, raises some questions. At the end, one may conclude that HA in fact represent just another Band-Aid, rather than a significant breakthrough, for the old wound of AML. Even-though treatment with HA can offer temporary satisfaction in some cases, a generalization cannot be confidently entertained.

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