Elderly acute myeloid leukemia: patients are not all the same

In the present issue of Haematologica Pulsoni *et al.*[1] report a very large retrospective survival analysis of elderly patients with acute myeloid leukemia (AML). More than a thousand patients older than 60 years registered in the database of the GIMEMA co-operative study group were analyzed. Around two thirds of patients received remission-induction therapy, called aggressive treatment, and one third of patients were referred to palliative treatment strategies, called non-aggressive treatment. Not surprisingly, patients within the group treated *non-aggressively* had a worse performance status, more comorbidity and a higher incidence of previous myelodysplastic syndrome. This led to aggressively treated patients having a survival advantage of non-aggressively treated patients in the log rank test. In the multivariate analysis, however, survival was not influenced by the treatment strategy. Remarkably, even for patients with the best prognostic factor combination, median survival did not differ according to whether *aggressive* or *non-aggressive* treatment had been used. Patients with a higher white cell count, however, did better with remission-induction therapy. This seems to be in accordance with a study by Baudard *et al.*[2] who reported longest survival times in the palliative care group for patients with a low white cell countat diagnosis.

The here presented analysis of primary data has the important advantage of giving a good approximation to the realistic picture of AML in the elderly. Most other published treatment studies in the field have the obvious selection bias that patients have to fulfill certain admission criteria or were not even considered for a certain study due to poor clinical condition. This was also true for the often cited EORTC study, which provided the rationale that led to remission-induction therapy becoming standard therapy in elderly AML.[3]

However, the group of patients who are never referred to a hematology center is not represented in any study. Although we must, therefore, keep in mind that a true picture of elderly AML does not exist, the study by Pulsoni *et al.* points in one direction: elderly AML patients are not all the same. While most younger AML patients are already treated according to risk-adapted protocols, these are still withheld from elderly patients. As depicted by Pulsoni *et al.*, white cell count at diagnosis may be a risk factor for elderly patients, having implications for differential treatment strategies, as does age itself, performance status or co-morbidity. However, no data are reported about two other known major risk factors in the elderly AML, namely cytogenetics and MDR1 expression. Elderly patients with –5, -7 or complex cytogenetic aberrations do worse than patients with a normal karyotype or, although very rare, patients with balanced translocations, such as t(8;21) or inv(16).[4] Furthermore complete remission rates after standard induction therapy are higher in MDR1-negative patients than in their MDR1-positive counterparts.[5]

These data point to the need for differential treatment strategies for elderly patients with AML. Integrating the data provided by Pulsoni *et al.* into the treatment approach suggested by Estey,[6] a reasonable strategy could be the following: patients under 70 years old, with no significant co-morbidity, no high-risk karyotype or MDR1 expression and a high white cell count at diagnosis may profit from standard induction therapy, i.e. Ara-C plus daunorubicin. Another group of patients over 70 years old with a bad performance status may be best off with palliative care, especially if considering the aspect of quality of life. For the remaining relatively large group of patients with one or more high risk factors, such as complex karyotype, MDR1 expression or secondary disease, and a relatively good performance status, in whom standard induction therapy often fails, other treatment strategies are needed.

Replacing daunoubicin by idarubicin or mitoxantrone within the standard induction therapy or priming with granulocyte-macrophage colony-stimulating factor (GM-CSF) does not improve outcome.[7] Furthermore, intensification of double induction therapy using high dose Ara-C in combination with mitoxantrone, VP-16 and amsacrine[8] or daunorubicin[9] increased treatment related toxicity and mortality.

Therefore, alternative treatment protocols with less toxicity and other or more selective anti-leukemic mechanisms than conventional cytotoxic therapy may be the hope for many elderly AML patients. Some new investigational treatment strategies are evolving. Some examples are anti-CD33 monoclonal antibody conjugated to calicheamycin[10] or even allogeneic stem cell transplantation after dose-reduced conditioning for remission induction.[11] Moreover, targeted therapies are being focused as treatment options for elderly AML patients. Some promising new drugs in this context are anti-angiogenesis agents,[12] farnesyl transferase inhibitors[13] or FLT3 tyrosine kinase inhibitors.[14] Although the role of these agents in the treatment of elderly AML is far from being clear, they do offer the possibility to create new therapeutic concepts.

The study by Pulsoni *et al.* teaches us that for many

elderly patients with AML *less is more*. Many patients, surprisingly including the group with the most favorable prognosis, did not profit from standard induction therapy and had a comparable outcome with palliative therapy. However, in some patients, such as those with a high white cell count, standard induction therapy may be superior to palliative therapy. Clearly, further studies to evaluate risk factors, molecular biology and detailed quality of life aspects of the elderly patients with AML are needed. If we learn more about the diversity of AML in the elderly, we will be able to create differential treatment strategies with better risk-benefit ratios for the individual patient and responsible use of existing resources. This could result in a general improvement of the unfavorable outcome of elderly AML patients, which has remained almost unchanged sinche the 1980s.

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Familial lymphoid neoplasms in patients with mantle cell lymphoma

The concise, well-written paper by Tort *et al.*[1] is essentially an extended case report of three kindred with familial lymphoproliferative disease (LPD) presenting with mantle cell lymphoma (MCL). The authors are correct that this is the first report of familial MCL. The caveat that CLL and MCL may have been missed in earlier studies is undoubtedly also true. Since the earliest reports from Ardashnikov in 1937[2] and Videbaek in 1947,[3] various studies[5-8] have made it become more widely appreciated that of all of the leukemias, chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) shows the highest incidence of familial clustering.[9-12] This has led to the appreciation of familial LPD. In fact it is not uncommon to see three different LPD in the same family, i.e., CLL/SLL, Waldenströms macroglobulinemia and hairy cell leukemia, and in familial CLL one sometimes encounters non-lymphoid, hematologic malignancy in first degree relatives. The pattern can be sibling-sibling, parent offspring or a combination of both types.

This study shows that MCL can also be part of the familial LPD syndrome. The appearance of acute lymphoblastic leukemia (ALL), CLL and a lymphoplasmacytic lymphoma in these MCL kindreds and the observation of anticipation are not unexpected findings.[13,14] Both have been described in familial CLL. The probands in families 1 and 2 had unmutated germline Ig genes and no ATM mutations were found in the patients tested. This information is useful as it permits comparison with other familial LPD, i.e., no pattern of Ig gene or ATM mutations has been seen in CLL.[15,16] Other pathways must be sought for the molecular mechanisms of familial LPD. These findings are of clinical relevance. Early presentation of LPD in a 40-year old should raise the question of a familial disposition in either one of the parents or other siblings. Inquiring about a positive