improve the classification of the disease and will lead to therapeutic biomarkers. In fact, there is a clinical need to extend our current limited therapeutic portfolio by the detection of innovative therapeutic targets.[20] In the interest of our patients, we hope that these efforts will extend our therapeutic armamentarium in the near future and will offer truly personalized approaches.

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## Aging and malignant hemopathies


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Aging was the theme of the 19th EHA Congress and a new scientific working group (SWG) was launched. Its first session was devoted to the increased incidence of malignant hemopathies in older patients. Three questions were addressed, and these are summarized below.

### The role of immune senescence in the development of cancer

Aging is associated with the functional alteration of multiple organs, including our immune system, thus affecting immune surveillance, one of the major barriers that prevent the development of cancer. Throughout life, our body is exposed to numerous aggressions and challenges (e.g. infections, inflammation, free radicals, carcinogens, etc.), leading to a progressive waning in our immune defences.[1]

Immune cells involved in cancer protection work in close collaboration. The first line of defence involves the 'innate' immune system: dendritic cells, natural killer (NK) cells and macrophages. These cells can eliminate cancer cells by themselves, but with age, innate immunity is impaired by downregulation of macrophages, alteration in cytokine production, increased production of IL-10 by the increased number of myeloid-derived supressor cells (MDSC), and reduction of NK-cell cytotoxicity. Although the number of aging macrophages is usually normal, their functions [chemotaxis, phagocytosis, signal transduction, cytokine production, toll-like receptor (TLR) expression and function] are significantly reduced.[2] PGE 2 production by macrophages is increased[3] that may directly suppress T-cell functions. Phenotypic changes occur in NK cells leading to remodeling of NK-cell subsets: CD56 bright cells, a more

immature population, are dramatically decreased, with a subsequent increase in the CD56 dim, CD57+ NK cells, which produce more pro-inflammatory cytokines.

T cells belong to the adaptive immunity, the second line of immune defence against cancer development. It is agreed that some age-related changes occur in T-cell phenotypes, such as decreased naive CD4+CD45RA+ and CD28+ T cells, and increased memory CD45RO+, CD95+, CD152+ and PD1 T-cell subpopulation. This is partly due to thymic involution and chronic antigenic stimulation. Though not fully understood, chronic antigenic stress may be caused by persistent viruses [cytomegalovirus (CMV), Herpes simplex and Zoster, Epstein-Barr virus (EBV)]; CD4+/CD8+ T-cell ratio is inverted due to an increased CD8+ T-cell population, characterized by higher resistance to apoptosis. One hypothesis is that dysfunctional CMV-specific CD8+ T cells accumulate resulting in a T-cell repertoire restriction and an increased susceptibility to infection and cancer.[4] This "inflamm – aging" is further detailed by Tchkonia who identifies other inducers of senescence through various pathways.[5] In addition to T-cell subset modification, functional properties of T cells are also reported, such as alteration in the TCR/CD3 and CD28 signaling pathways.[6-9]

The CD4+ Treg cells involved in immune tolerance with immunosuppressive properties are, by contrast, increased, and a disruption in the balance between the T-cell subpopulations is deleterious in terms of cancer prevention, progression and elimination.

B-lymphocyte functions are also altered in the elderly with a reduced production of specific antibodies (lower response to external antigens), an increased production of low affinity antibodies [higher incidence of monoclonal gammopathy of undetermined significance (MGUS)], and auto-antibodies (higher frequency of autoimmune disorders).

This decrease in immune function associated with aging is called immunosenescence. Immunosenescence is thus a combination of age-related immunodeficiencies (shrinking of naïve T- and B-cell compartments, reduced T- and B-cell receptor diversity, decreased T-cell receptor sensitivity to stimuli) and age-related pro-inflammatory state (excess production of inflammatory cytokines such as IL-6 and TNF and production of auto-antibodies).[10] This leads to an increased sensitivity to infections, autoimmune disorders, chronic inflammatory diseases and cancer development.

On a molecular level, the mTOR pathway plays a major role in immunesenescence as well as cancer development. There is an acquired resistance to mTOR inhibitor (rapamycin) in older individuals that would shift cell proliferation towards autophagy. This leads to a differentiation of T cells towards the sustained memory phenotype, resulting in a poor recognition of foreign antigens.[11] In addition, aging affects other mechanisms of natural protection against cancer, resulting in poor DNA repair, telomere shortening, chromosomal instability, altered intercellular communication, senescent environment, and loss in apoptosis-regulating genes.

On the other hand, cancer cells are characterized by sustained proliferative signaling, uncontrolled growth, resistance to apoptosis, and the ability to escape the immune surveillance. There is also a tumor-related microenvironment that further impairs the immune response that has already been altered with aging by favoring the development of immune suppressor cell phenotype development (e.g. M2 macrophages, N2 neutrophils).

In this setting of age-impaired immunity, cancer cells can easily replicate leading to the higher incidence of malignant hemopathies that is indeed observed in older patients.

### *Fitness scoring in chronic lymphocytic leukemia: where do we stand?*

Physicians managing chronic lymphocytic leukemia (CLL) use a very effective so-called standard treatment (R-FC; rituximab, fludarabine, cyclophosphamide) that leads to a benefit in survival.[12] However, such benefits from R-FC treatment were observed in younger 'fit' patients while the median age of individuals diagnosed with this disease is 72 years.

Tolerance to full-dose chemo-immunotherapy with R-FC decreases with age and with age-related decline in fitness. Therefore, efforts have been made to develop alternative regimens for older patients with CLL. Dose-reduced R-FC was explored in younger and older patients in good physical condition.[13] However, in unfit older patients, dose-reduced R-FC resulted in loss of disease control.[14] Bendamustine plus rituximab (BR) is effective in younger and fit patients with CLL although not without toxicity (25% grade 3-4 infections).[15] Two randomized studies investigating BR or bendamustine plus ofatumumab in elderly patients are still ongoing. Addition of ofatumomab to chlorambucil was recently reported to be beneficial in older unfit patients compared to chlorambucil alone with a progression-free survival (PFS) of 22 months (median age 69 years). Combination of another anti-CD20 antibody [obinutuzumab (GA101)] with chlorambucil also offered a better PFS (27 *vs.* 11 months) compared to chlorambucil alone in older unfit CLL patients (median age 73 years).[16] New drugs, such as ibrutinib and idelalisib, appear to be well tolerated in older patients and may further change the therapeutical approach of this population in the future.[17,18]

For now, it is critical to identify the population of older CLL patients who can complete and benefit from standard R-FC treatment.

In cancer patients in general, the comprehensive geriatric assessment (CGA) and other abbreviated fitness scales (e.g. VES-13 – G8 – GFI – aCGA) were shown to be correlated with treatment-related toxicity or poor tolerance resulting in early treatment discontinuation, but were always evaluated in heterogeneous populations. Therefore, these fitness assessments can not yet be applied well in an individual with a specific cancer disease (i.e. CLL) following a specific treatment (i.e. R-FC).

Comorbidity has been studied in a cohort of 500 CLL patients included in two successive German trials. Looking at the different items in terms of number and severity, it appeared that 5-year mortality was 40% for patients with more than 2 co-morbidities, compared to 25% for those with less than 2 co-morbidities.[19]

Among the various scales of the CGA, a co-morbidity index (CIRS) has been correlated with overall survival and is currently used as a decision tool for inclusion in German CLL trials. Data from the CLL8 trial (n=817), where patients were randomized between FCR and FC and where CIRS was mandatory (exclusion if CIRS >6), showed that a CIRS

score over 3 in this selected population was a prognostic factor correlated with OS independent of age, ECOG status and other CLL prognostic factors. The merit of the CIRS score to predict toxicity is unclear and, for example, is not confirmed in an Australian CLL trial.[13]

In the CLL 9 trial (97 patients), 50%-60% of the patients were evaluated with an attenuated CGA [CIRS + TUG + instrumental activities performances (IADL) + cognitive functions (DEMTECT)]. Preliminary unpublished data suggest that impaired cognition and reduced TUG have an impact on OS. This underestimated impact of impaired cognition is also observed in our series of hematologic patients.[20]

In conclusion, there are very limited CLL-specific data available for the prediction of therapy-related morbidity, treatment adherence, and disease- or non-treatment-related mortality. Although CGA is reported to predict relevant clinical end points in solid tumors and hematologic malignancies, there are still no biomarkers of frailty specifically in CLL. A CLL consensus initiative is now underway to provide guidance for CLL-specific fitness scoring and recommendations for future clinical trials.

## When to say "No" in myelodysplastic syndromes/acute myeloid leukemia patients?

"Frail" patients are usually not included in clinical trials, and this is the main reason why there are no guidelines or recommendations on whether to treat and how to treat. What factors influence OS in acute myeloid leukemia?

### Age

Age is significantly associated with poor survival but "older age is not a reason to withhold a treatment". Indeed, older patients with good prognostic AMLs [i.e. acute promyelocytic leukemia (APL), core binding factor (CBF) leukemia and NPM1 mutated AML] can be cured with intensive chemotherapy (ICT).[21,22] Thus the issue is how to identify the elderly AML patients who could benefit from ICT.[23] Even though a retrospective study[21] reported similar OS with supportive best supportive care (BSC) compared to ICT in patients over 80 years of age,[24] some studies suggest that elderly patients could benefit from ICT. Another study of older MDS patients (median age: 83 years) showed a similar OS with azacytidine (AZA) for patients under and over 80 years of age. This is one of the rare studies evaluating hypomethylating agents in very old patients, but it did not consider fitness scoring and selection bias cannot be excluded, suggesting that age is not the main limiting factor for the treatment of elderly AML or MDS.[25]

### General condition of the patient

The general condition of the patient [evaluated by Performance Status (PS), activity of daily living (ADL), instrumental activities of daily living (IADL), 'timed up and go' (TUG), mini mental state examination (MMSE), co-morbidities] decreases with age and impacts on OS.[23-26] However, for an individual patient, we do not know and poor performance status can be related to the disease itself[20] and should not be considered as a limiting factor for active treatment as long as it is related to the malignancy and not to other medical conditions.

In a recent observational study (BSC *vs.* AZA *vs*. ICT) in older (60+) patients, a better OS was observed in the AZA arm for patients with normal ADL, but normal ADL score also impacted the best supportive care arm. In addition, when ICT was given, fatigue and impaired ADL did not correlate with OS, suggesting that the treatment was initiated on the basis of the clinical impression that the patient could tolerate the treatment.[27]

The role of co-morbidities in the causes of death is cancer-type dependant. It is significantly lower in breast or kidney cancers compared to AML, where the disease can kill the patient if left untreated.[28]

### Townsend Index

The Townsend Index measures material deprivation based on unemployment, car ownership, home ownership and overcrowding. The Index was analyzed by an English group and was found to be significantly increased in older patients and was correlated with survival. Socio-economical issues played a definite role in the outcome of older patients.[29]

### Acute myeloid leukemia/myelodysplastic syndrome disease characteristics

Acute myeloid leukemia/MDS disease characteristics also have to be taken into account. Most older patients have unfavorable cytogenetic profiles, especially in AML arising from MDS, but in a multivariate analysis, poor outcome or early death were significantly correlated with poor cytogenetic profiles and not with age or co-morbidities.[30] It should be noted that delaying treatment until the cytogenetic status is known does not modify OS in older leukemic patients,[31] suggesting that we could wait for the results of cytogenetic tests before making a treatment decision.

In older patient populations with good cytogenetic profiles, a poor general condition could be due to the disease, and should not be considered in isolation to decide whether to treat or not, as long as it does not preclude ICT.

One prospective randomized study presented during the 19th EHA Congress concluded that azacytidine could provide longer survival in older patients.[32] To answer the question concerning the best treatment in the UK registry, there was no difference in early death rate and this was even lower in elderly AML patients treated with ICT.[21]

## Conclusions

In AML/MDS, cytogenetic evaluation is a critical part of the decision process for the best therapeutic approach. Geriatric assessment should be performed to better evaluate the needs of older patients, but its use to select fragile patients and to adapt the therapeutic approach remains unknown. Other concerns such as loss of quality of life and loss of autonomy require further evaluation. Thus, the message is that we have to identify the older patients likely to benefit from ICT and discuss the final therapy decision with them. To achieve these objectives, we need to: a) define the best geriatric instruments to measure the functional reserves of the elderly; b) include more elderly subjects in randomized controlled trials; c) establish a better collaboration between hemato-oncologist and geriatricians; and finally, d) move oncology on from chronological aging to biological aging in accordance with the desire of the patient.

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