

started an initiative to revise these criteria. We believe that the modifications (IWG 2016) will be crucial and will allow for more individualized pre- and on-study assessment and, therefore, provide the MDS community with an improved tool in terms of response evaluation.

Summary

MDS is a moving target with maximum innovation in the understanding of the complex molecular pathways during the last decade. Compared to other “chronic” hematological malignancies like myeloma or CLL this has, unfortunately, not yet been translated into novel treatment options. Given the actual developments in the field, we are optimistic that recent frustrations will be overcome and that new treatment opportunities will soon be available for our patients.

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Innovative approach to older patients with malignant hemopathies

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Introduction

Aging represents a significant health problem since nobody can escape this natural process.

Though not a disease *per se*, aging progressively leads to organ dysfunctions and represents a major risk factor for most cancers and diseases. Indeed, with the aging of the population, a 50% increase in new cancer cases is expected over the next 20 years.

Since adult stem cells are responsible for maintaining tissue homeostasis, an attractive theory is that age-related degenerative changes may be due to alterations in tissue stem cells, particularly in the hematopoietic stem cells (HSCs). Extensive research is currently underway; it demonstrates a progressive waning in our immune defenses and concomitantly, genetic and epigenetic modifications of the hematopoietic stem cells and their microenvironment.

In addition, older patients of a similar age are an extremely heterogeneous population in terms of fitness. Thus, chronological age does not adequately guide clinicians in choosing their treatment.

A better understanding of the cellular and molecular changes involved in the aging process, combined with a better assessment of the “fitness” status of older patients, will definitely help optimize and personalize therapeutic approaches in this older population in order to achieve the primary objective: healthy aging and not only prolonged survival.

Assessment of Immunosenescence

Cellular “senescence” refers to the specific phenomenon wherein a proportion of competent cells undergoes permanent growth arrest in response to various cellular stresses, translating in a replicative limit in culture, while being metabolically very active.

The definition of “immunosenescence” is still a controversial issue, but is commonly accepted as the decrease in immune function associated with aging; it combines immune deficiencies (changes in innate immune functions, shrinking of naïve T- and B-cell compartments, reduced T- and B-cell receptor diversity, decreased T-cell receptor sensi-

tivity to stimuli) and an age-related pro-inflammatory state (excess production of inflammatory cytokines such as IL-6 and TNF; the production of autoantibodies). This leads to an increased sensitivity to infections, autoimmune disorders, chronic inflammatory diseases and cancer development.^{1,2}

Due to their impaired immune defenses, older cancer patients are more vulnerable to life-threatening side effects of hematotoxic and immunosuppressive drugs. A comprehensive care program, including vaccinations, nutritional supplements, primary prophylaxis with granulocyte colony-stimulating factors and IV immunoglobulins, if required, constitutes the current recommended approach to this population.³

Genetic and epigenetic changes in HSCs

The functional decline in hematopoiesis in the elderly, which involves a progressive reduction in the immune response and an increased incidence of malignancies, is partly linked to HSC aging. Understanding the molecular processes controlling hematopoietic stem cell survival, self-renewal and commitment to specific differentiated cell lineages is indeed crucial to determine the drivers and effectors of age-associated stem cell dysfunction, which remain poorly elucidated to this day.

The aging phenotype is partly explained by damages in DNA integrity resulting in poor DNA repair, telomere shortening, chromosomal instability, altered intercellular communication and senescent environment, and loss of apoptosis-regulating genes. Moreover, recent observations suggest that small changes in the epigenetic landscape can lead to significant alterations in the expression patterns (either directly by loss of regulatory control, or through indirect additive effects, ultimately leading to transcriptional changes of the stem cells). These changes can also play a key role in modulating the functional potential of HSCs. The two best characterized epigenetic changes are DNA methylation and histone modifications. However, non-coding RNAs could also play a role in regulating HSC function in aging.⁴

The aging of HSCs has long been thought to be an intrinsic irreversible process. Mouse model studies have shown that aging is associated with elevated activity of the Rho GTPase Cdc42 in HSCs which causes loss of polarity. This results in a symmetric distribution of epigenetic markers that is responsible for functional deficits of aged HSCs, whereas in dividing young HSCs, distribution is mainly asymmetric. This work suggests that the inhibition of Cdc42 activity in aged HSCs may reverse a number of phenotypes associated with HSC aging. These findings support the hypothesis that the functional decline of aged HSCs may be reversed by pharmacological intervention of age-altered signaling pathways and epigenetic modifications.⁵⁻⁶ Such restorative interventions hold promise for the treatment of many diseases, including sarcopenia, heart failure and neurodegeneration.

Besides the molecular mechanisms associated with the aging of hematopoietic stem cells, poor homing capacity and the aging of stem cell niches are currently being further investigated.⁷

Such knowledge will be essential to develop therapies to slow, and perhaps reverse, age-related degenerative changes and to enhance the regenerative capacity of organs, thus favoring healthy aging.⁸

Table 1.

TAKE HOME MESSAGES

Older patients are an extremely heterogeneous population requiring a deep and multidimensional evaluation of physiological reserves

Unsuspected cognitive impairment deserves specific attention because of its significant impact on survival

Geriatric assessment should take into account the reversible (disease-related) character of the complaints and wishes of the patient

Reliable biomarkers of frailty are urgently needed

Assessment of "physiological" age

The older population with cancer is a heterogeneous cohort in terms of physical performance, physiological functions, psycho-cognitive functions and socio-economic environment. Chronological age does not adequately guide physicians in proposing optimal therapeutic approaches. In contrast with younger populations, the management of these older patients deserves a multi-step procedure: besides the accurate assessment of the tumor's prognosis and the patient's risk of dying from it, clinicians have to take into account the biological reserves, the patient's life expectancy and their capacity to tolerate the treatment. Additionally, the patient's wishes and their capacity to understand the therapeutic approach should be fully integrated in the geriatric assessment.⁹

A modern approach thus consists in the assessment of the patient's physiological age.¹⁰ In this setting, geriatricians are essential collaborators, proposing various tools to evaluate physical performance (PS, Up and Go test, ADL, IADL, etc.), physiological status (Comorbidity index, polypharmacy, nutritional status, etc.), psycho-cognitive functions (GDS, MMSE, MOCA, etc.) and socio-economic environment (income, caregivers, etc.). A test which could be used to evaluate the dynamic physiological reserve would be a helpful tool in this approach.

Although clinicians can reliably evaluate physical fitness, it has now been demonstrated that depression and cognitive impairment are completely underestimated and the socio-economic environment is also poorly explored. Yet, poor cognitive functions and a disadvantaged socio-economic environment are correlated with worse survival, and deserve specific attention in "clinically fit" patients.

Thus, geriatric assessment not only helps to identify older patients with a higher risk of morbidity/mortality, but also allows for better management of their vulnerabilities.¹¹⁻¹² However, such a comprehensive geriatric assessment is not applicable on a routine basis outside centers with oncogeriatric nurses.¹³ Additional simple tools are still needed to further assess the risk/benefit ratio for a specific patient receiving a specific anticancer therapy that could potentially compromise their long-term functionality and quality of life.¹⁴

Attention should be drawn to very old patients. Few reports and even fewer randomized trials are published in this population which, despite a significant reduction in treatment posology, experiences early life-threatening grade 3/4 toxicities. A prephase treatment has been demonstrated to significantly reduce the first chemotherapy cycle's toxicity, and is now recommended in frail patients suffering from diffuse large B-cell lymphoma.¹⁵⁻¹⁶

The G8 questionnaire represents a simple screening test to rapidly identify oncological patients requiring a full geriatric assessment.¹⁷⁻¹⁸ However, nutritional and psychological problems have a major impact on the total G8 score, and since these issues may be disease-related in patients with malignant hemopathies, some authors propose delaying this screening test in order to eliminate the bias due to these problems, which could be reversible after a few days of treatment.¹⁹

Furthermore, the increased mortality in elderly patients is not only related to their frailty and poor tolerance to chemotherapy. Indeed, oncologists tend to reduce the doses of treatment in older patients in order to avoid potentially fatal side effects such as febrile neutropenia, thereby decreasing the chances of therapeutic success. Additionally, patients and their families, fearing a loss of autonomy, will also push physicians to cut back on the doses of treatment. These patients in poor physical or psychological conditions are too often excluded from prospective studies, even though they represent the population we most often have to face in our daily practice.

Biomarkers of frailty

In addition to age and diagnosis, the most frequently reported "clinical" items correlated with shortened overall survival are impaired functional and nutritional status.¹² For "clinically fit" patients receiving chemotherapy, a mild cognitive impairment is correlated with worse overall survival.²⁰⁻²¹

Besides shorter overall survival, unacceptable outcomes in the eyes of clinicians, patients and their relatives, are early toxic death, loss of autonomy and unexpected hospitalization. In recent large retrospective analyses, early toxic deaths (within 6 months of treatment) are correlated with poor nutritional status (MNA<24) and low physical performance (Up and Go test >20s).¹⁷ Loss of autonomy is correlated with psychological distress (GDS>5) and abnormal daily functioning (IADL<8), and the increased risk of hospitalization is correlated with poor nutritional status (MNA<24).²²⁻²³

Biological cellular or molecular biomarkers of frailty are still currently under investigation (CRP, IL-6, IL-10, etc.), and require validation in hematological malignancies based on a large series in the general population which tend to show their potential predictive value.²⁴ The expression of p16 in circulating T lymphocytes, a known biomarker of senescence, not only correlates with age²⁵ but also with chemotherapy-related aging.²⁶

However, despite using the best available geriatric assessment, some clinically fit patients, referred to receive full-dose chemotherapy, presented unexpected treatment-related, and sometimes life-threatening side effects, whereas some patients deemed clinically vulnerable tolerated full-dose treatment. Thus, more accurate biomarkers that dynamically test the physiological reserve are urgently needed to better identify the patients who will benefit from standard treatment.

Conclusion

Although the multidisciplinary approach brings together the concerns of scientists, geriatricians, home practitioners and onco-hematologists (Table 1), the additional involvement of the patients themselves should result in optimized

and personalized patient care, focusing not only on overall survival, but also on improved qualitative survival.

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