Of great importance regarding the recommendation to switch therapy is the potential trade-off regarding toxicity. In the Hughes *et al.* study,[4] the authors note adverse events with switch from imatinib to nilotinib were in line with prior phase II studies, including approximately 10% discontinuation for AEs. In the ENESTcmr study,[10] however, with 36 mos of follow up, authors noted that for those patients switching to nilotinib, rates of AEs and related treatment discontinuation were higher in addition to a numerically higher amount of cardiovascular events observed with nilotinib.

What have we learned from this experience? Clearly we have the option and the means to intervene at several time points to optimize response and rescue treatment failure. Given the increasing amount of data on the benefit of early molecular response and the increased risk associated with non-intervention, guidelines[1,3] encourage intervention in order to recuperate missed milestones. Based on available data, we still cannot fully judge the benefit of correcting failure to achieve early molecular response. From the ENESTnd data,[4] there is confirmation of excellent salvage of imatinib-treated patients with switch to achieve missed cytogenetic response milestones and relevant molecular response (MMR), and the merits of dose escalation of nilotinib for similar missed milestones.

Coupled with data from the ENESTcmr study, we now can expect improvement with switch to nilotinib across the spectrum of missed cytogenetic and molecular milestones, from initial cytogenetic response to complete molecular response (more aptly termed MR4.5). The additional improvement in response observed with dose escalation of nilotinib is consistent with a very subtle difference in primary response and earlier evidence of survival advantage seen in the 400 mg BID nilotinib arm compared to the 300 mg BID arm within the core ENEST trial. However, reflecting the caution advised in the report of the 36-month ENESTcmr data, benefits of switch must be weighed against any risks of new toxicity. Certainly, adjusting to an alternative TKI can be tumultuous for patients and typical toxicities requiring management must not be overlooked. Late toxicities such as cardiovascular/vascular AEs must be carefully considered, as early gains may be offset by subsequent complications. Of course, as we continue to actively pursue the possibility of 'treatment-free remission', the attraction of defined treatment duration may increase our focus on short-term gains assuming long-term risk may be reduced or eliminated.

Philosophically speaking, one may increasingly feel that a double major in biology as well as economics is needed to best help CML patients nowadays navigate these issues of so-called 'risk management'…

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Hematologic malignancies in elderly patients

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Over recent decades, global life expectancy has increased remarkably, and further increases are anticipated.[1] Current estimates suggest that the most important changes in world population over the next 40 years will occur within the oldest age groups; the number of people aged 65 years and over worldwide is expect-

ed to double by 2050.[2] Since almost half the cancers diagnosed in 2002 developed in people aged 65 years and over, an aging population will have a definite impact on the incidence and treatment of cancers, in particular hematologic malignancies (HMs).[2,3]

Hematologic malignancies are a diverse group of blood cancers with various etiology, incidence, prognosis and survival.[4,5] In population studies, HMs are grouped into four broad categories including leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma and myeloma.[3] In recent years, the World Health Organization (WHO) has developed a consensus-based classification in which HMs are basically categorized according to their lineage (myeloid and lymphoid) and cell maturity.[6] This classification also utilizes morphology, immunophenotype, and genetic and clinical criteria to further subdivide each category.[6]

Several recent studies have used the WHO classification to evaluate population-based features of the entire spectrum of HMs in different countries worldwide.[5,7-10] In light of this, results from the HAEMCARE project, which collected the incidence of HMs in Europe during the period 2000-2002,[5] demonstrate that, in general, the incidence of both myeloid (acute myeloid leukemia, myeloproliferative neoplasms, myelodysplastic syndrome, and unknown myeloid neoplasms) and lymphoid malignancies (Hodgkin lymphoma, mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, and unknown lymphoid neoplasms) increases with age, peaking at 75-99 years.[5] In contrast, the incidence of lymphocytic leukemia/acute lymphoblastic leukemia (LL/ALL) peaks at 0-14 years, while Hodgkin lymphoma and Burkitt lymphoma/leukemia cases mainly occur at 15-44 years.[5] Another network-based study from the UK found that the majority of myeloid and lymphoid malignancies are diagnosed in patients approximately 70 years old.[9] Again, the precursor B-cell and T-cell lymphoblastic leukemias tend to occur at a median age of 12.7 and 18.5 years, respectively.[9]

Results from a recent study on the incidence of acute leukemia (WHO classification) in the US also reveal that in adulthood, most acute myeloid malignancy subtypes increase with advanced age (>70 years), whereas B-cell and T-cell lymphocytic leukemia/lymphoma occur predominantly in childhood/youth (age 1-14 years).[7] A previous report on the lymphoma incidence patterns in the US according to WHO subtype also demonstrates that the total number of lymphoid neoplasms increases unilaterally with age in all ethnic and sex subgroups. Furthermore, steep increases in incidence with age are observed for most subtypes, with some exceptions.[11] For instance, Burkitt lymphoma/leukemia and mixed cellularity/lymphocyte-depleted Hodgkin lymphoma rates increase more gradually with age. As shown in other studies,[7,9] B-cell and T-cell lymphoblastic lymphoma/leukemia are diagnosed predominantly in children.[11] Moreover, nodular lymphocyte predominant Hodgkin lymphomas were diagnosed predominantly in persons aged 15-34 and 15-64 years, respectively.[11]

In Asia, the majority of mature lymphoid neoplasms are found in adults aged 43-54 years.[8,10] Furthermore, Asian patients with mature T/NK-cell and mature B-cell neoplasms are significantly younger than patients in the West (age 43.7-46.5 and 54.4-54.8, respectively),[8,10] while B-cell and T-cell lymphoblastic lymphoma/leukemia affect slightly older individuals than those in the West (19.7-22.7 and 22-25.1, respectively).[8,10] In all studies, it has been shown that males are more prone to develop HMs than females.[5-11]

Treatment strategy

Acute lymphatic leukemia

Few trial data to guide personalized therapy for acute lymphatic leukemia (ALL) in the elderly are available. ALL differs biologically from other malignancies in that it has a reduced male/female ratio, more B-cell-related disease, and more co-expression of myeloid antigens. The number of patients expressing Philadelphia positivity may also rise with age. Due to chemotherapy treatment, acute confusion, infection, and sometimes metabolic disturbances are observed. In elderly ALL patients, little improvement in survival has been achieved during the last 20 years; 30-70% of patients achieve remission, but survival is brief and the early death rate is as high as these percentages. Generally, vincristine, steroids, and L-asparaginase cause more toxicity in elderly patients, and anthracyclines may be hard to administer in those with impaired cardiac function. Liposomal vincristine and anthracycline are being tested in randomized trials on elderly ALL patients. Nearly all older patients with Philadelphia chromosome disease should be treated with a tyrosine kinase inhibitor, vincristine, steroid, and reduced dose anthracycline. If they achieve complete remission (CR), subsequent therapy should be individually tailored depending on toxicity, comorbidities, and possibly minimal residual disease (MRD) status. B-cell antibodies also deserve to be tested formally in this age group; rituximab is well tolerated.[12]

B-cell lymphoma

Peyrade *et al.* reported that reduced-miniCHOP consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone offers a good compromise between efficacy and safety in diffuse large B-cell lymphoma patients aged over 80 years with (OS) survival of approximately 60% for two years, and stated that R-miniCHOP should be considered as the new standard treatment in this patient subgroup.[13]

Acute myeloid leukemia

The prognosis of acute myeloid leukemia (AML) worsens every decade starting at 30-40 years of age. Traditionally, poor outcome is the result of less intensive therapy in elderly patients, due to comorbidities, higher possibility of other hematopoietic disorders, and biologically poor risk prognosis. Anthracycline and cytarabine, with or without other agents, is considered the standard induction therapy for patients under 60 years of age, followed by consolidation therapy (high-dose cytarabine). As noted previously, the use of the standard regimen in elderly patients does not yield results similar to those seen in younger patients.[14] Recent studies of gemtuzumab, as well as studies of interleukin-2 as post remission therapy, did not show any benefit for these patients. Although high-dose cytarabine is beneficial as post remission therapy in younger patients, it was shown to be far too toxic in the

elderly. The overall view in the majority of the studies is that results of intensive therapy in elderly patients remain poor. Although CR rates of 40-80% can be achieved in highly selected populations, long-term survival is poor. With the introduction of reduced-intensity conditioning (RIC) regimens, allogeneic stem cell transplantation (SCT) has become a valid option. Recent reports suggest that age, at least up to 70 years, does not impact outcome of reduced-intensity SCT; thus, it may be a better option than chemotherapy in patients aged 60-70 years. A recent study of patients over 50 years of age at MD Anderson who underwent SCT with RIC-conditioning showed a superior relapse free survival (RFS) and OS when compared with those who received post remission chemotherapy.

Chronic myeloid leukemia

Although age is still considered an important prognostic factor in chronic myeloid leukemia (CML), few data are available about the long-term outcome of older patients treated with imatinib (IM) frontline. A recent study showed that response to IM is not affected by age and that the mortality rate linked to CML is similar in patients over 60 years and patients under 60 years.[15] Furthermore, IFN treatment of elderly patients in chronic phase showed the same survival rate as in younger patients at lower dosage.[16] RIC conditioning followed by SCT emphasized the benefit of early transplantation resulting in stable engraftment, low relapse rates and encouraging OS in this high-risk CML patient group.[17]

Multiple myeloma

Conventional treatment for patients over 65 years of age suffering from multiple myeloma (MM) has been a combination of oral melphalan and prednisone (MP). Improvement in progression-free survival was reported in patients receiving melphalan as part of the induction treatment (dexamethasone or prednisone), but not in those receiving high-dose dexamethasone only. These findings suggest the need to incorporate an alkylating agent in combination regimens including new drugs. Recent studies showed that thalidomide/dexamethasone resulted in a higher proportion of partial response compared to MP in 72-year old patients. MP plus thalidomide or bortezomib can be regarded as standard care for elderly MM patients. The combination of conventional chemotherapy or low-dose dexamethasone with new drugs has substantially changed the treatment paradigm of MM patients.[18] Several studies have shown that elderly patients who are not eligible for transplantation benefit from regimens with proteasome inhibitors, immunomodulatory drugs (IMiDs), corticosteroids or alkylating agents in different combinations. In elderly unfit patients, a mild approach using a 2-drug regimen and lower doses should be adopted to avoid toxicity. The new proteasome inhibitor carfilzomib and the 3rd-generation IMiD pomalidomide showed great efficacy in patients who had relapsed or who were refractory to induction treatments.[18] Patients over 65 years of age are generally not considered candidates for transplantation. However, since biological age can differ from chronological age, biological age should determine whether transplantation is a treatment option. For patients aged 65-75 years, full-dose conventional therapy is recommended, while milder treatment should be used for patients over 75 years or those who have significant comorbidities.

Myelodysplastic syndrome

The International Prognostic Scoring System is used to assess the risk of transformation from myelodysplastic syndrome (MDS) to leukemia and to guide treatment decisions. Induction chemotherapy used to treat AML may be used to treat patients with higher-risk MDS with excess blasts. The main MDS treatment goal in the elderly is prolonging OS and the time to progression to AML in order to improve quality of life. For this reason, supportive care is essential. IMiDs such as lenalidomide and DNA methyltransferase inhibitors, can reduce transfusion requirements and reverse cytological and cytogenetic abnormalities in MDS patients with chromosome 5q deletion. Elderly patients with high-risk MDS can benefit from 5-azacitidine (5-AZA), with efficacy and safety profiles comparable with those found in patients under 75 years of age.[19] SCT using RIC has had an impact on the use of transplantation as an alternative treatment for elderly patients. A recent study showed that 4-year OS in patients aged over 50 years who underwent SCT using RIC was similar to those transplanted using myeloablative conditioning.[20]

Conclusion

Despite treatment difficulties in the elderly, therapy for these patients could be improved to enhance their quality of life and functional performance. Elderly patients generally have multiple medical issues and are treated with multiple pharmaceutical agents. These circumstances contribute to an increased risk of drug interactions and the consequent management of toxicities. Manifestations of common toxicities or severe side-effects may increase both morbidity and mortality in the elderly due to age-associated functional deficits in multiple organ systems. One important factor in the elderly patient is the age-related decline in immunity, including the diminished capacity of response to stimulus such as infection or myelosuppressive treatments.

Individualized treatment based on evaluation of functional and physical status, biological age, capability of tolerating treatments, comorbidities, disease stage, general overall health, and the expected toxicity profile of different regimens is the strategy necessary to achieve maximum treatment efficacy and minimum toxicity in the elderly.

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Anemia in the elderly: clinical implications and new therapeutic concepts

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Anemia in the elderly (defined as people aged > 65 years) is common and increasing as the population ages. In older patients, anemia of any degree contributes significantly to morbidity and mortality and has a significant effect on the quality of life. Despite its clinical importance, anemia in the elderly is under-recognized and evidence-based guidelines on its management are lacking.

Part of the problem here relates to its definition, which is based on WHO-criteria established in 1968.[1] The WHO definition of anemia is hemoglobin (Hb) less than 130 g/L in men, Hb less than 120 g/L in non-pregnant women, and less than 110 g/L in pregnant women. Hemoglobin levels decline with age, and there has been a debate as to whether these values are applicable to older people, although there is no accepted alternative definition of anemia in this age group. Most clinicians, however, accept this definition and are of the opinion that the normal hemoglobin range should not be lowered for older people because of its association with morbidity, mortality and hospitalization. The challenge of defining a normal hemoglobin range lies in part in finding a cohort of 'healthy' elderly subjects confounded by the high prevalence of comorbidities and impairments in parallel with advancing age. In the analysis of Cheng *et al.*,[2] an important proportion (60%) of the older adults were excluded due to frequent diseases including obesity, arterial hypertension, diabetes, recent treatment for anemia, or recent surgery or hospitalization. Thus, the introduction of selection bias limits the practical applicability of this approach. Another approach is based on the definition of Hb concentrations that are optimal for the clinical outcome of elderly subjects. Based on the distribution of Hb levels, the elderly can be grouped into quartiles or quintiles, revealing inverse J-shaped correlations with unfavorable outcome. An increased mortality was found in the lower quintile (<137 g/L for men; <126 g/L for women) as defined in the Cardiovascular Health Study cohort.[3] Similarly, anemia correlated with increased hospitalization[4] and mortality.[4,5] Thus, a suggested optimal