Clinical evaluation of extra-hematologic comorbidity in myelodysplastic syndromes: ready-to-wear *versus* made-to-measure tool

There is growing evidence to indicate that comorbidity has an unfavorable effect on life expectancy of patients with myelodysplastic syndromes (MDS), and significantly influences clinical decision making.[1]

Recently, Naqvi and colleagues evaluated the prognostic impact of comorbidity in MDS[2] by using the Adult Comorbidity Evaluation-27 (ACE-27) scale, a measure of comorbidity developed for assessment of patients with solid tumor.[3] They found that comorbidity significantly affects survival and improves the prognostic stratification of patients with MDS.

Despite these remarkable results, this study has potential weaknesses. ACE-27 failed to stratify the prognosis in subjects aged 65 years or older, the great majority of MDS patients, as well as in the IPSS low-risk subgroup,[2] in whom comorbidity was reported to considerably increase the risk of death.[1] In addition, the use of a general measure of comorbidity may have led to possible interactions between hematologic disease and comorbid conditions being overlooked.

The choice of the instrument to measure comorbidity is crucial to effectively capture and score the effect of comorbidity in the population of interest. Available measures can be divided into two groups: general measures, and disease-specific measures.[4] Like "ready-to-wear" clothes, general comorbidity measures are intended for use in several different populations.[3,5] These scores are widely used and have a good reliability. However, the weakness of these tools lies in the assumption that each comorbidity computed in the measure has the same impact on different diseases and patient populations.[4] Conversely, disease-specific comorbidity measures are developed and tested in a single disease population and intended for use in that specific setting. Like "made-to-measure" garments, disease-specific comorbidity measures have a conceptual advantage in that they account for specific features unique to the population of interest.

Recent data suggest that in MDS cardiac comorbidity may have not just an additive detrimental effect *per se* but interacts with anemia in worsening the course of the disease.[6] In this setting, a general comorbidity measure such as the Charlson-Comorbidity-Index failed to provide prognostic information, whereas the Hematopoietic Cell Transplantation-specific Comorbidity Index appears to be only partially effective in the general MDS patient population.[7,8] We developed an MDS-specific comorbidity index (MDS-CI) in which the comorbid conditions to be included in the score were selected on the basis of a multivariable regression accounting for possible associations between clinical conditions and interactions with MDS-specific features, such as anemia. The score obtained is a combination of five clinical conditions, and identifies three risk groups with different probabilities of survival.[8] The prognostic value of the MDS-CI was validated in two large independent cohorts of patients.[8,9]

To evaluate the effectiveness of a "ready-to-wear" *versus* a "made-to-measure" strategy in MDS, we compared the ability to capture prognostic information on comorbidity of ACE-27 and MDS-CI in 840 consecutive patients diagnosed with MDS at our institution between 1992 and 2007. When comparing MD Anderson and Pavia patient populations, no significant differences were found in age or IPSS risk distribution. A significant proportion of the MD Anderson patients (>50%) underwent treatments potentially modifying the natural history of the disease while only 17% of the Pavia patients were treated.

In our patient population, the four ACE-27 risk groups showed no significantly different probabilities of survival (P=0.11, Figure 1). In a multivariable analysis including demographic and disease-related factors, ACE-27 did not show a significant effect on survival (HR 1.01-1.35; P=0.9-0.06).

We then carried out a multivariable analysis to evaluate which comorbid conditions among those included in ACE-27 have a prognostic effect in MDS patients, and found that only myocardial infarction (HR 1.48; P=0.003), congestive heart failure (HR 1.32; P=0.05), respiratory system disease (HR 1.74; P=0.033), paralysis (HR 13.19; P<0.001), solid tumor (HR 1.47; P=0.002), leukemia/lymphoma (HR 1.894; P=0.041), and neuromuscular diseases (HR 6.24; P=0.039) showed an independent significant effect on survival.

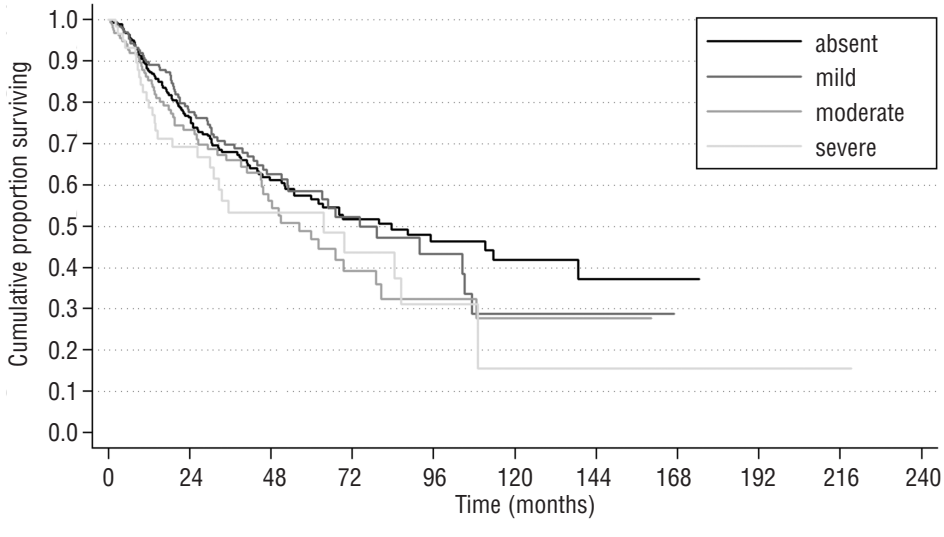

Figure 1. Probability of overall survival according to ACE-27 risk at diagnosis in all 840 MDS patients (P=0.11). There was no significant difference in cumulative probability of survival between patients with no comorbidity and those with ACE-27 mild risk (P=0.68), or between patients with moderate and severe risk (P=0.11), whereas OS was significantly lower in patients with both moderate and severe risk compared to those without comorbidity (P=0.044 and P=0.019, respectively).

As a further step, we focused on the clinical definition of these items and the grading of severity adopted in MDS-CI and ACE-27, and evaluated their goodness of fit in the MDS patient population. To this purpose, Akaike information criterion (AIC) was employed which allows the evaluation of a model by combining goodness of fit and complexity (among different models, a lower AIC indicates a better trade-off between fit and complexity, while models with an AIC difference of 4 or more with respect to the reference model have considerably less support).[10] For all comorbid conditions considered in the analysis, clinical definition and grading of severity by MDS-CI had greater goodness of fit for capturing the prognostic information of these comorbid conditions in MDS patients compared to ACE-27 (AIC for ACE 27 *vs.* MDS-CI cardiac disease 2929 *vs*. 2925, hepatic disease 2932 *vs.* 2930, pulmonary disease 2931 vs. 2928, renal disease 2930 *vs.* 2926, and solid tumor 2929 *vs.* 2926). Taken together, these data strengthen the importance of not basing definition of the prognostic value of comorbidity in the clinical setting of MDS patients exclusively on the severity of the comorbid condition *per se*, but also taking MDS-specific features into account.

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Low frequency of type-I and type-II aberrations in myeloid leukemia of Down syndrome, underscoring the unique entity of this disease

We recently published in this journal an overview of the currently known genetic events required for the development of pediatric acute myeloid leukemia (AML).[1] These aberrations can be subdivided into type-I aberrations that result in uncontrolled proliferation, and type-II aberrations that lead to the impaired differentiation of the leukemic cells.[1-2]

Recent advances in technology have allowed many novel genetic and molecular abnormalities to be detected, including cryptic translocations (such as *NUP98-NSD1*), and single gene mutations, occurring for instance in the *NPM1*, *CEBPA*, *WT1* and *MLL*-gene (MLL-PTD) which are predominantly found in patients with cytogenetically normal (CN)-AML.[1,3] Newly discovered mutations identified by whole genome sequencing include mutations in the genes encoding for *IDH1/ IDH2* and the DNA methyltransferase (*DNMT3A*) gene, which are rare in pediatric AML.[4-5]

Children with Down syndrome have an increased risk of developing acute myeloid leukemia (ML-DS).[6] ML-DS is a unique disease entity, and differs in clinical characteristics and biology from AML in non-DS children. It is characterized by somatic mutations in the *GATA-1* gene[7] which are unique for every patient. The role of the well-known and newly discovered type-I/II aberrations in myeloid leukemia of Down syndrome (ML-DS) has not yet been systematically investigated.

Therefore, we screened 34 newly diagnosed ML-DS patients for the presence of the above mentioned type-I and type-II aberrations. Samples were provided by the Dutch Childhood Oncology Group, the AML-'Berlin-Frankfurt-Munster' Study Group, and the Nordic Society for Pediatric Hematology and Oncology. Of the 34 patients, 12 ML-DS patients had a normal karyotype; this is important to note since some of the novel aberrations in non-DS AML are highly associated with a normal karyotype.

Screening of gene mutations was carried out according to availability of material. Mutation analysis was performed for the hotspot regions of the *NPM1*, *CEPBA*, *MLL* (i.e. partial tandem duplications, PTD), *WT1*, *FLT3* (i.e. internal tandem duplications, ITD) and tyrosine kinase domain mutations (TKD), *N-RAS* and *K-RAS*, *PTPN11*, *KIT*, *IDH1/ IDH2*, and the *DNMT3A* genes, as previously described.[1,5] In addition, we investigated the presence of the cryptic translocation *NUP98/NSD1* by reverse transcriptase-polymerase chain reaction (RT-PCR).[3] A complete list of investigated regions, primers and PCR condi-