Validation of the Freiburg Comorbidity Index in 466 Multiple Myeloma Patients and Combination With the International Staging System Are Highly Predictive for Outcome

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Abstract

Although the prognosis and therapy options have improved substantially in multiple myeloma (MM), clinical outcome might vary considerably. Because a standardized comorbidity risk index is lacking, we developed the Freiburg Comorbidity Index (FCI) and validated this in an independent cohort of 466 MM patients. This FCI stratifies patients in specific risk groups with significantly different outcomes.

Background: The outcomes of MM patients vary considerably and depend on a variety of host- and disease-related risks. As yet, a comorbidity risk index in MM patients has neither been standardized nor validated. **Patients and Methods:** We conducted an initial analysis in 127 MM patients and developed the FCI, validating it in an independent cohort of 466 MM patients. The FCI includes patients' Karnofsky Performance Status, renal and lung disease status. We compared the prognostic information of this validated FCI with established comorbidity indices (Hematopoietic Cell Transplantation-Specific Comorbidity Index and Kaplan Feinstein), the International Staging System (ISS), MM therapy, and age. **Results:** Our validation confirmed that patients with 0, 1, or 2 to 3 FCI risk factors display significantly different overall survival (OS) of not reached, 86, and 39 months, respectively ($P < .0001$). Via multivariate analysis including the FCI, ISS, therapy, and age, the FCI retained its independent prognostic significance ($P < .0015$). The combination of the FCI and ISS allowed definition of 3 distinct subgroups with low-risk (FCI 0 and ISS I-II), intermediate-risk (all remaining), and high-risk (FCI 1-3 and ISS III) with OS probabilities at 5-years of 85%, 74%, and 42%, respectively ($P < .0001$). **Conclusion:** Our validation analysis demonstrated that the FCI remains a reliable comorbidity index, is simpler to generate than other available comorbidity scores, and contributes valuable information to the ISS. Their combination allows the definition of low-, intermediate-, and high-risk patients. These results advocate use of the FCI in future prospective studies and might guide personalized treatment strategies.

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Introduction

Treatment concepts and survival of multiple myeloma (MM) patients have changed considerably because of better understanding of the disease, the implementation of sensitive tests, risk-adapted therapies, and improved supportive care.[1-3] The simultaneous presence of 2 or more other diseases might, however, complicate MM treatment.[4,5] Therefore, with growing numbers of elderly patients,[6,7] reliable tools are needed to assess their vulnerability expressed in chronic conditions and limitations in daily activity, which would offer a major guidance in therapeutic decisions. Such measures are also essential when accounting for drug-induced side effects, treatment compatibility, and mortality.[7]

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The growing awareness that treatment strategies in elderly MM patients can be optimized necessitates a more detailed definition of patients' clinical status.[5,7-9] Historically, treatment decisions in symptomatic MM patients have been largely based on age. Today, disease biology and patient fitness, defined by the Karnofsky Performance Status (KPS), are also considered when assessing therapeutic options.[10] However, because the KPS does not reflect the entire functional status of cancer patients, advances in defining patient fitness more precisely are warranted. Prognostic indices have thus been proposed[11-14] and used in different cancers.[15] Nevertheless, there are too little data on comorbidities in MM patients and their outcomes.[7] In addition, MM patients with comorbidities are often excluded from clinical trials. Thus, results from various trials are not necessarily transferable to elderly patients. In this context, the European Myeloma Network and our group have recommended to consider the patient age, physical condition, and comorbidities to assist in therapy decisions and to advance to personalized therapies.[7,9] We have previously demonstrated the relevance of comorbidities in MM patients and have provided an initial step for the use of an easily assessable comorbidity score.[9,16] We developed the Freiburg Comorbidity Index (FCI), consisting of the most relevant multivariate risk factors in our initial MM cohort. This FCI enabled us to clearly define risk groups with substantially different progression-free survival (PFS) and overall survival (OS).[9] To verify the FCI's applicability, we validated this score in a much larger, independent MM cohort from our University Center, comparing its value with other established comorbidity scores. Moreover, we evaluated the prognostic information of the FCI in addition to the International Staging System (ISS),[1] therapy strategies, and different age groups. We hypothesized that the FCI would add patient-related characteristics to the prognostic value of the ISS, and therefore assessed, whether the combined use of the FCI and ISS would add to the prognostic information in MM. Our study aimed to elucidate the effect of comorbidities in MM and to generate data on a simple prognostic tool reflecting patient diversity. We did not seek to examine myeloma-specific variables or treatment effects on outcome in this study.

Patients and Methods

Patient Description, Data Source, and Patient Selection

Consecutive patient data were retrieved from our institution's electronic medical record (EMR) and an innovative research data warehouse called the University of Freiburg Translational Research Integrated Database Environment. This acquires and stores all patient data contained in the EMR at our hospital and provides immediate advanced text-searching capacity.[17,18] Here we used an independent validation set of 466 MM patients treated at our institution between 2003 and 2009. An initial analysis was comprised of 127 symptomatic MM patients and was used as a learning set.[9] The FCI was generated by assessing individual patient comorbidities and potential risk factors, namely, age, KPS, cardiac function, hypertension, diabetes, secondary malignancies, pain, and liver, heart, lung, and renal impairment.[9]

The KPS, extracted from a detailed review of the EMR, was defined as either normal at 100%, negligibly impaired at 80% to 90%, or moderately to substantially impaired at $\leq$ 70%, summarizing their ability to perform daily activities.

According to the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI),[12] we defined pulmonary comorbidities via the lung function test or clinical aspects (scoring lung impairment by severity of dyspnea on different levels of activity). Lung impairment was scored as mild with dyspnea on intense activity or a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of $<$ 70% and FEV1 $\geq$ 80% (FEV1 percentage predicted), as moderate with dyspnea on moderate activity or FEV1/FVC $<$ 70% and FEV1 50% to $<$ 80%, and as severe with dyspnea at rest or a few steps taken and/or the need for oxygen and/or noninvasive ventilation or FEV1 $<$ 50%.[12,13]

Renal function was determined via estimated glomerular filtration rate (eGFR assessed using the Modification of Diet in Renal Disease [MDRD]).[9,16,19] Moreover, both eGFR equations, MDRD and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI), were compared.[20] Prognostic factors showing an univariate $P < .1$ were entered in a multivariate Cox model.

Univariate analysis from the initial study revealed that pulmonary-, renal-, KPS-impairment, and age were significant risk factors for PFS and OS. Relevant multivariate factors for OS after variable selection were a KPS of $\leq$ 70%, moderate or severe lung disease, and an eGFR via MDRD $<$ 30 mL/min/1.73 m^2. Interestingly, our systematic analysis of other variables revealed that hepatic or cardiac disease, hypertension, pain or diabetes were not significant risk factors for PFS and OS.[9] Based on these uni- and multivariate results, a prognostic model was generated, combining the KPS, lung impairment, and eGFR in a sum score, termed FCI.[9]

Genetic abnormalities were determined using fluorescence in situ hybridization as described.[9,21] The analysis was carried out according to the guidelines of the Declaration of Helsinki and good clinical practice. All patients gave their written informed consent for institutional-initiated research studies and analyses of clinical outcome studies conforming to our institutional review board guidelines.

Treatment Schedule of the Validation Set

Patients underwent standard chemotherapy, autologous stem cell transplantation (ASCT) or allogeneic stem cell transplantation (allo-SCT) according to our institutional MM pathway.[22-25] ASCT was recommended for medically fit, symptomatic patients up to the age of 70 years. Induction usually consisted of CTD (cyclophosphamide, thalidomide and dexamethasone) or bortezomib-based regimens such as VCD (bortezomib, cyclophosphamide, dexamethasone). Mobilization (IEV; ifosfamide 2500 mg/m^2 on days 1-3, epirubicin 100 mg/m^2 on day 1, etoposide 150 mg/m^2 on days 1-3) and conditioning (melphalan 200 mg/m^2 or 140 mg/m^2 with serum creatinine values $>$ 2.0 mg/dL) were performed as described.[22-25] Patients ineligible for ASCT received either melphalan, prednisone and thalidomide, or melphalan, prednisone and bortezomib.[22-25] Novel agent-based therapies included thalidomide, lenalidomide, and bortezomib according to the approved indications.

Statistical Analysis

Data were analyzed using SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC). OS was defined as the time from diagnosis to death from any cause and PFS as the time from diagnosis to death from any cause (without censoring at the day of allo-SCT) or cancer