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Hematopoietic Cell Transplantation Outcomes in Monosomal Karyotype Myeloid Malignancies

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A B S T R A C T

The presence of monosomal karyotype (MK+) in acute myeloid leukemia (AML) is associated with dismal outcomes. We evaluated the impact of MK+ in AML (MK+AML, n = 240) and in myelodysplastic syndrome (MDS) (MK+MDS, n = 221) on hematopoietic cell transplantation outcomes compared with other cytogenetically defined groups (AML, n = 3360; MDS, n = 1373) as reported to the Center for International Blood and Marrow Transplant Research from 1998 to 2011. MK+ AML was associated with higher disease relapse (hazard ratio, 1.98; $P < .01$), similar transplantation-related mortality (TRM) (hazard ratio, 1.01; $P = .90$), and worse survival (hazard ratio, 1.67; $P < .01$) compared with those outcomes for other cytogenetically defined AML. Among patients with MDS, MK+ MDS was associated with higher disease relapse (hazard ratio, 2.39; $P < .01$), higher TRM (hazard ratio, 1.80; $P < .01$), and worse survival (HR, 2.02; $P < .01$). Subset analyses comparing chromosome 7 abnormalities (del7/7q) with or without MK+ demonstrated higher mortality for MK+ disease in for both AML (hazard ratio, 1.72; $P < .01$) and MDS (hazard ratio, 1.79; $P < .01$). The strong negative impact of MK+ in myeloid malignancies was observed in all age groups and using either myeloablative or reduced-intensity conditioning regimens. Alternative approaches to mitigate disease relapse in this population are needed.

INTRODUCTION

The presence of multiple chromosomal abnormalities, termed *complex cytogenetics*, in leukemia cells is associated with unfavorable outcome. The reported definitions of complex cytogenetics varies from ≥3 to 5 cytogenetic abnormalities in a single clone [1,2]. Breems et al. further examined this group of patients with poor-risk disease and identified autosomal monosomies to be associated with poor outcome [3]. This classification has a tighter association with poor outcome compared with other nonrandom cytogenetic changes in the poor-risk category and predicts a subset of patients with dismal outcome. The *monosomal karyotype* (MK) is defined as the presence of at least 2 autosomal monosomies or 1 autosomal monosomy associated with any other structure abnormality (MK+). Cytogenetic abnormalities have similar prognostic impact in myelodysplastic syndrome (MDS), where the number of chromosomal abnormalities is also associated with poor outcomes [4,5] and in MDS, MK+ is strongly associated with shorter survival, as it is in acute myeloid leukemia (AML) [6]. In both AML and MDS, abnormalities in chromosome 7, including deletion and monosomy, are common single abnormalities associated with poor prognosis. The prognostic effect of MK+ could be due to single most common monosomy.

Hematopoietic cell transplantation (HCT) is the treatment of choice for patients with cytogenetic-defined poor-risk AML in first complete remission (CR1), which may lead to 30% to 40% 5-year survival, compared with <10% with nontransplantation approaches [1,7,8]. However, these data are mostly from patients younger than 60 years receiving allogeneic transplantation with myeloablative (MA) conditioning. Reduced-intensity conditioning (RIC) is commonly used in AML patients older than 60 years [9]. This reduction in intensity decreases toxicity and early transplantation mortality, allowing older or compromised patients to receive an allogeneic HCT. However, when compared with MA approaches, this benefit is offset by increase in relapse rates [10]. Additionally, a retrospective analysis done by the European Group for Blood and Marrow Transplantation demonstrated that poor-risk cytogenetics at diagnosis is associated with higher relapse and shorter leukemia-free survival in patients with AML in CR1 receiving RIC compared with those receiving MA conditioning [11].

Older AML patients more often have increased cytogenetic abnormalities including unfavorable risk and MK [3,12,13]. MK+ AML may increase the risk of relapse after transplantation [14-18]; however, it is unclear whether MA conditioning may mitigate this increased relapse risk. We analyzed the effect of MK+ AML in patients undergoing HCT in CR1 and explored the prognostic impact of the MK+ in transplantations for MDS.

MATERIALS AND METHODS

Data Sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantation to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program coordinating center in Minneapolis. Participating centers are required to report all transplantations consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule [9].

Patients

All patients with AML in CR1 who received a first allogeneic HCT from 1998 to 2011 from HLA-matched or single HLA locus–mismatched donors