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Reduced-intensity conditioning transplantation

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Abstract

Development of nonmyeloablative and reduced-intensity conditioning regimens (RIC) has enabled older or medically infirm patients with myeloid malignancies to be treated with allogeneic hematopoietic cell transplantation (HCT). The regimens are sufficiently immunosuppressive to allow engraftment of allogeneic cells and they rely largely on graft-versus-leukemia effects rather than high-dose cytotoxic therapy to eliminate malignant cells. Overall 2–5-year survivals after allogeneic HCT in older AML/MDS patients have ranged from 25–64%. Outcomes were comparable for HLA-matched related and unrelated grafts. Best results were seen in patients transplanted in first or second remission. Relapse and progressive disease continue to be problems, particularly in patients with large tumor burdens at time of HCT. Reduction of tumor burden before HCT with targeted therapy such as radiolabeled anti-CD45 antibody may improve outcome. Despite still existing problems, early results in elderly AML/MDS have been encouraging.

Keywords

acute myelocytic leukemia; allogeneic hematopoietic cell transplantation; graft-versus-leukemia effects; myelodysplastic syndrome; reduced-intensity conditioning

Acute myelocytic leukemia (AML) and myelodysplastic syndromes (MDS) are diseases of the elderly. Median age at diagnosis, according to Surveillance, Epidemiology and End Results (SEER) statistics, is 68 years. Results with chemotherapy, even though it might be successful in inducing a first remission, have been poor, and only a few patients above the age of 55 years have become long-term survivors. Treatment with conventional allogeneic hematopoietic cell transplantation (HCT) has been limited to younger patients because high-dose cytotoxic conditioning regimens are poorly tolerated by the elderly. In order to address a clear need for alternative therapies in older patients, recent years have seen the introduction of various reduced-intensity and nonmyeloablative conditioning regimens for allogeneic HCT. The principles of this approach included reduction of regimen-related toxicities and shifting the burden of tumor cell kill from high-dose cytotoxic therapy to graft-versus-leukemia effects. The following report reviews recent results with this approach.

One study in patients with AML and MDS conducted at M.D. Anderson Hospital used two conditioning regimens, one consisting of fludarabine, Ara-C, and idarubicin (FAI), while the other combined fludarabine with melphalan either at 140 or 180 mg/m² (FM) [1]. Median ages of patients given the FAI and FM regimens were 61 and 54 years, respectively. Forty-four percent of FAI patients were in remission at HCT compared to 16% of FM patients. All FAI

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patients had sibling donors while 47% of FM patients had unrelated donors. Three-year non-relapse mortality for FAI patients was 16% compared to 39% for FM patients, relapse rates were 53% and 26%, and 3-year event-free survival rates were 31% and 35%, respectively.

A UK MDS/AML study included 76 patients conditioned with fludarabine, melphalan 140 mg/m², and alemtuzumab [2]. Two-year survival rates for AML patients in first, second, or third remissions ranged from 40–45%, MDS patients had a 35% survival, and patients with relapsed/refractory disease had a survival of approximately 30%.

A study from the Dana-Farber Cancer Center in patients with myeloid malignancies compared high-dose regimens, either cyclophosphamide and fractionated total body irradiation or busulfan 16 mg/kg, and cyclophosphamide, to a reduced-intensity regimen of fludarabine and busulfan 3.2 mg/kg [3]. Follow-up was considerably shorter for reduced-intensity patients. Two-year transplant-related mortality for reduced-intensity patients was 30% compared to 45% for high-dose patients. In turn, the relapse rate for high-dose regimens was 25% compared to 35% for the reduced-intensity regimen. Accordingly, 2-year survivals for the two treatment modalities were comparable, approximately 30% for high-dose regimens and 35% for the reduced-intensity regimen.

Five of the following six studies were presented at the American Society of Hematology meeting in December of 2008.

A large CIBMTR study analyzed results with reduced-intensity conditioning and either related or unrelated grafts in patients with AML and MDS in a first complete response (CR1) [4]. Four groups of patients were studied, aged either 40–45, 55–60, 60–64, or older than 65 years (including 220, 150, 132, and 63 patients, respectively). One-year non-relapse mortalities among the four age groups ranged from 18–30% for AML patients and 31–34% for MDS patients. The 3-year relapse mortalities ranged from 29–39% for both disease categories across all age groups. Three-year progression-free survival rates for the four AML patient groups were 43%, 41%, 27%, and 34%, and for the four MDS groups 36%, 27%, 29%, and 23%, respectively.

Another CIBMTR analysis studied 3731 myeloablative patients with AML/MDS and a median age of 42 years and 1500 reduced-intensity/nonmyeloablative patients with a median age of 55 years [5]. Longest follow-up for myeloablative patients was 58 months compared to 40 months for reduced-intensity/nonmyeloablative patients. Non-relapse mortalities were 34% for myeloablative and 34–37% for reduced-intensity/nonmyeloablative patients. Relapse rates were 32% for myeloablative and 39–43% for reduced-intensity/nonmyeloablative patients. Event-free survivals were 33% for myeloablative and 24–30% for reduced-intensity/nonmyeloablative patients.

A French multi-center study focused on 2-year survivals in patients with AML in first remission who were given human leukocyte antigen (HLA)-identical sibling grafts [6]. Their median age was 55 years, and multiple reduced-intensity regimens were used. Twenty-one patients with good cytogenetic risk had 64% survival, 304 patients with intermediate-risk cytogenetics had 57% survival, and 53 patients with poor-risk cytogenetics had 38% survival.

A German multi-center study analyzed results in 172 patients with AML/MDS with poor-risk cytogenetics [7]. Median patient age was 53 years. Conditioning consisted of a FLAMSA-reduced-intensity regimen. Related and unrelated donors were used. Seventeen percent of patients were treated up front without preceding chemotherapy, 33% had primary induction failure, 22% were in CR1, and 28% were in relapse. The overall 4-year relapse rate was 30%, non-relapse mortality was 21%, and event-free survival was 32%.

Another German AML study analyzed 3-year survivals in 103 patients with AML given myeloablative regimens and 265 given reduced-intensity regimens [8]. Median patient age was 57 years. Among patients with standard-risk cytogenetics and transplanted in first remission, survival for HLA-matched sibling recipients was 60% compared to 45–50% for unrelated recipients. In patients with standard-risk cytogenetics transplanted in >1st remission, survivals both among unrelated and related recipients were 20%. Among patients in first remission with high-risk abnormalities, survival after unrelated grafts was 40% compared to 30% after HLA-matched sibling grafts. High-risk sibling recipients transplanted in >CR1 had an approximately 5% survival compared to 20% for unrelated recipients.

A multi-center study from the Seattle Consortium included 259 patients with a median age of 59 years who either had de novo AML in first (n=95) or second (n=57) remission, were not in CR1 or 2 (n=26), or had secondary AML (n=81) [9]. One hundred twelve patients had HLA-identical sibling donors, 116 had HLA-matched unrelated donors, and 31 had HLA-mismatched donors (unrelated: n=30). Five-year outcomes were evaluated. Ninety-six percent of patients had durable engraftment following a truly nonmyeloablative conditioning regimen of fludarabine, 30 mg/m²/day × 3 days, and 2 Gy of total body irradiation. All patients received postgrafting immunosuppression with mycophenolate mofetil and either cyclosporine or FK506. Non-relapse mortality, which was significantly influenced by comorbidities, was 25% for patients in CR1, 27% for those in CR2, 35% for those not in CR1 or CR2, and 28% for those with secondary AML. Relapse mortalities for the four patient groups were 36%, 36%, 42%, and 46%, respectively. When analyzing results by origin of hematopoietic cell grafts, non-relapse mortality was 18% among patients with HLA-matched sibling donors, 31% among those with HLA-matched unrelated donors, and 55% among those with HLA-mismatched donors. No statistically significant differences in non-relapse mortalities were seen among patients aged 60–64 (n=166; 28%), 65–69 (n=90; 22%), and 70–74 (n=24; 29%) years. Among patients with AML in CR1, those with minimal residual disease at HCT, detected either by flow cytometry, cytogenetics, or molecular probes, had significantly increased relapse mortality in multivariate analysis with HR=4.60 (*P* = 0.007). Survivals of patients with *de novo* AML in CR1 or CR2 were 40% and approximately 25% among AML patients not in CR1 or CR2 and secondary AML patients.

Conclusion

Taken together, the available data showed 2–5-year survival rates of 25–64% after allogeneic HCT for older AML/MDS patients. Survival was similar for recipients of related and unrelated HLA-matched grafts. Major issues included non-relapse mortalities ranging from 16–39%, which, in part, resulted from complications of graft-versus-host disease including infections and, in part, were caused by comorbidities preceding HCT. Relapse rates ranged from 16–53%, and were influenced both by disease burden and cytogenetic risk at HCT. Attempts to reduce relapse have included targeted anti-leukemic therapy added to conditioning regimens, such as radiolabeled monoclonal antibody directed at CD45. Future work focuses on gaining a better understanding of minor histocompatibility antigen disparities between donors and recipients, which might help in distinguishing between targets of adverse immunological reactions, such as graft-versus-host disease, and beneficial graft-versus-leukemia effects. Nevertheless, despite still existing problems, outcomes of allogeneic HCT in older AML/MDS patients have been encouraging, especially in those who were transplanted beyond first remission.

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