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Upfront Alternative Donor Transplant versus Immunosuppressive Therapy in Patient with Severe Aplastic Anemia Who Lack Fully HLA Matched Related Donor: Systematic Review and Meta-analysis of Retrospective Studies.

Hind Alotaibi[1], Mansour Alfayez[1], Shahid Iqbal[2], Nawal Alshehry[1], Mohammed Marei[1], John DiPersio[3], Ibraheem Motabi[1].

[1] Adult Hematology Department, King Fahad Medical City, Riyadh, Saudi Arabia.[2]Manchester Royal Infirmary, Manchester, United Kingdom.[3]Washington University School of Medicine, St. Louis, Missouri, United States.

Introduction

Idiopathic aplastic anemia is a rare and life threatening disorder characterized by immune mediated hematopoietic stem cells dysfunction. The standard treatment strategy of severe aplastic anemia (SAA) has been hematopoietic stem cell transplant (HSCT) for children and adults younger than the age of 40 if an HLA matched sibling donor (MSD) is available. Immunosuppressive therapy (IST) is the mainstay of treatment for older patients or when MSD is not available. The response rate to IST with the use of horse anti-thymocyte globulin (ATG) is around 70%[1]. Despite that, many patients suffer from relapse or clonal evolution. The use of alternative donor transplant (ADT) from matched unrelated donor (MUD) or HLA haploidentical donor (HID) is not commonly used in frontline setting. We herein, conducted a systematic review and meta-analysis of retrospective studies to compare the outcome of IST versus ADT as upfront therapy for SAA.

Methods

We conducted a comprehensive search in PUBMED/MEDLINE and EMBASE (1998-2019) for retrospective studies that compared the outcome of ADT with IST as upfront therapy in patients with SAA. The study was conducting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We included the studies with 10 patients or more in each arm. Studies that included patients with inherited aplastic anemia or PNH are excluded. The primary outcome is the 5-year overall survival. Two authors independently screened the studies, extracted the data, and evaluated the quality of included studies and discrepancies were resolved by a third author. Study quality was evaluated by description of study characteristics, patients' characteristics, treatment details, and outcome. The odd ratio (OR) for 5-year survival was measured by Mantel-Haenszel test using random effect model. We also conducted another search and meta-analysis to compare upfront with salvage ADT. The meta-analyses were performed using Review Manager software version 5.3.

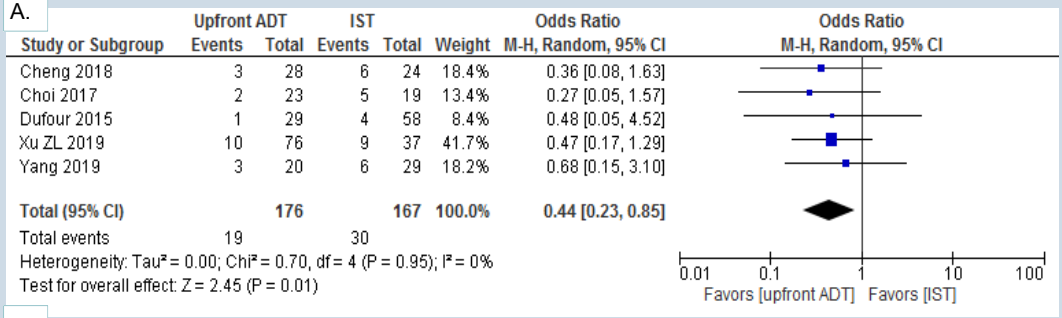
Results

We screened a total of 697 articles (506 EMBASE, 191 PUBMED/MEDLINE). Five studies met our inclusion criteria included a total of 343 patients (176 in ADT group and 167 in IST group) for upfront ADT versus IST comparison [2,3,4,5,6] and 6 studies with a total of 298 patients (198 in upfront ADT group and 100 in salvage ADT group) for upfront versus salvage ADT comparison [3,4,6,7,8,9]. Included patients were of pediatric age group in 4 out of 5 studies. Xu ZL *et al*, included adult patients with median age 28 (18-49) years in upfront ADT arm and 32 (18-62) years in IST arm. Of those, only 10 patients in ADT group and 12 patients in IST group were above age of 40. In ADT versus IST comparison, the type of transplant was HID in three studies (total of 124 patients) and MUD/MMUD in two studies (total of 52 patients). The rabbit ATG was used in three studies, horse ATG in one study, and both types were used in one study (total of 68 patients received horse ATG and 99 patients received rabbit ATG). In term of disease severity, all included patients were SAA and very SAA (VSAA). Five studies were included in meta-analysis for 5-year overall survival. The pooled OR is statistically significant at 0.44 [95% CI 0.23-0.85] in favor of upfront ADT (Fig 1-A). The survival outcome was compared between upfront versus salvage ADT in 6 studies. The pooled OR is statistically significant at 0.31 [95% CI 0.15-0.64] in favor of upfront ADT (Fig 1-B).

Conclusions

The pooled analysis of this study showed a potential survival advantage of upfront ADT over IST in patients with SAA who lack an HLA identical sibling donor. The use of ADT earlier in the disease course rather than as a salvage in young patients with severe disease, may improve survival. Data in older patients are limited, and at present, we cannot recommend ADT upfront in older patients. Given the limitations of our study including various types of IST, heterogeneity of patient population, health care systems, and retrospective nature of included studies; further studies are needed to confirm our findings.

A.



B.

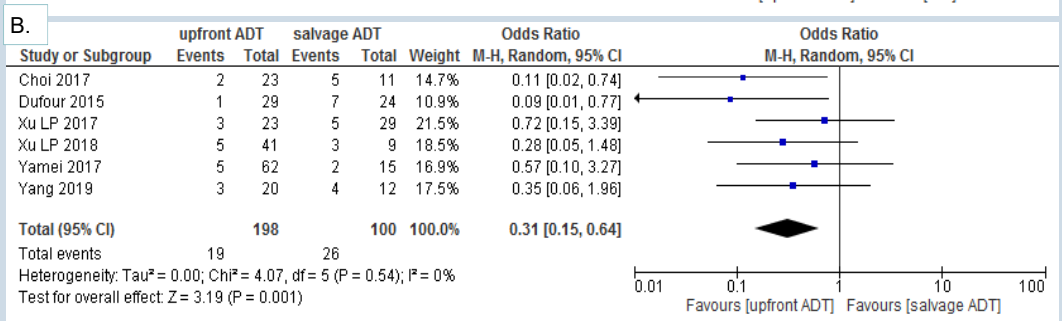


Figure 1: The pooled analysis of 5-year overall survival.

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