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722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Impact of Early Anti-Cytomegalovirus Therapy on the Incidence of Chronic Graft-Versus-Host Disease

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Introduction: Cytomegalovirus (CMV) infections are associated with poor outcomes in recipients of allogeneic hematopoietic stem cell transplants (HSCTs). Therefore, preventive therapy or preemptive treatment have been developed. Ganciclovir (GCV) and foscarnet (FCN) are essential intravenous anti-CMV agents. A previous regional multicenter study revealed a significantly lower risk of chronic graft-versus-host disease (GVHD) in patients who received preemptive FCN therapy. To validate this observation and to investigate the mechanism or target, we executed a comprehensive nationwide study.
Patients and Methods: We defined the early anti-CMV therapy as administration within 180 days after transplantation without evidence of target therapy for CMV infections. We retrospectively analyzed patients who received FCN or GCV as early anti-CMV therapy, and who are not received any anti-CMV agents (no anti-CMV) between June 2005 and December 2019. We excluded patients who received FCN, GCV, valganciclovir, or letermovir as prophylactic therapy; those who began anti-CMV therapy before the day of transplantation; those who received both FCN and GCV; those who underwent T cell-depleting treatment.
Results: A total of 19536 adults with hematological malignancies who received their first allogeneic HSCT were included. We compared patients who received FCN (n = 1555) or GCV (n = 7335) as early anti-CMV therapy, and no anti-CMV recipients (n = 10646). FCN or GCV recipients showed higher incidence of acute GVHD than no anti-CMV recipients. The cumulative incidence of acute GVHD 200 days after transplantation were 46% (95% confidence interval [CI], 41%-51%), 47% (95% CI, 45%-50%), and 26% (95% CI, 25%-28%) for FCN, GCV, and no anti-CMV recipients, respectively ($P < 0.001$). The cumulative incidence of chronic GVHD three years after transplantation were 28% (95% CI, 26%-31%), 37% (95% CI, 36%-38%), and 29%

(95% CI, 28%-30%) for FCN, GCV, and no anti-CMV recipients, respectively (P < 0.001). The cumulative incidence of extensive chronic GVHD three years after transplantation were 17% (95% CI, 15%-19%), 22% (95% CI, 22%-23%), and 16% (95% CI, 15%-26%) for FCN, GCV, and no anti-CMV recipients, respectively (P < 0.001) (Figure A). In multivariate analyses adjusted for acute GVHD or other important variables, the risks of extensive chronic GVHD among GCV recipients was higher than FCN recipients (hazard ratio [HR], 1.17; 95% CI, 1.01-1.34; P = 0.031), whereas no-anti CMV recipients and FCN did not showed statistically significance. In further investigations, we performed stratified analyses and revealed that the incidence of extensive chronic GVHD was significantly lower among the FCN recipients than among the GCV recipients only in stratifications that involved male recipients of female donor HSCT (according to sex compatibility). Comparing with GCV, the incidence of extensive chronic GVHD was significantly reduced among male recipients of female donor HSCTs who were taking FCN (HR, 1.63; 95% CI, 1.19-2.23; P = 0.002), but FCN did not affect the incidence of extensive chronic GVHD for other sex compatibility-based stratifications (HR, 1.05; 95% CI, 0.90-1.23; P = 0.51). Among male recipients of female donor transplants, the incidence of extensive chronic GVHD three years after transplantation were 13% (95% CI, 10%-17%), 27% (95% CI, 25%-29%), and 20% (95% CI, 18%-21%) for FCN, GCV, and no anti-CMV recipients, respectively (P < 0.001; Figure B). FCN and no anti-CMV recipients showed similar risk of extensive chronic GVHD (HR, 1.22; 95% CI, 0.89-1.66; P = 0.21). The incidence of extensive chronic GVHD was significantly reduced among FCN recipients who received HSCT from female donors, regardless of stem cell source, GVHD prophylaxis, or previous acute GVHD incidence, in male recipients.

Conclusions: In this study, patients requiring early anti-CMV therapy were at a high risk of chronic GVHD, primary due to their increased incidence of acute GVHD. Remarkably, FCN could potentially mitigate the incidence of chronic GVHD for them. Especially, FCN would be beneficial for male recipients of female donor transplants who are typically at high risk for chronic GVHD. These findings pave the way towards a deeper understanding of the mechanism underlying chronic GVHD and overcome the unmet needs of allogeneic HSCT recipients.

Disclosures Miyao: *Chugai Pharmaceutical:* Speakers Bureau; *Janssen Pharmaceutical:* Speakers Bureau. **Doki:** *Novartis Pharma K.K.:* Honoraria; *Janssen Pharmaceutical K.K.:* Honoraria. **Tanaka:** *Kyowa-Kirin:* Speakers Bureau; *Chugai Pharmaceutical:* Speakers Bureau; *Daiichi Sankyo:* Speakers Bureau; *Sumitomo Pharma:* Speakers Bureau; *Astellas Phrama:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Asahi Kasei Pharma:* Speakers Bureau; *MSD:* Speakers Bureau; *Pfizer:* Speakers Bureau; *Otsuka Pharmaceutical:* Speakers Bureau. **Kanda:** *Saitama Hokeni Kyokai:* Speakers Bureau; *MSD:* Speakers Bureau; *Kyowa Kirin:* Research Funding, Speakers Bureau; *Janssen Pharmaceutical:* Speakers Bureau; *Sanofi:* Speakers Bureau; *Pfizer:* Speakers Bureau; *Shionogi Pharma:* Research Funding; *Towa Pharma:* Speakers Bureau; *Taiho Pharmaceutical:* Research Funding; *Meiji Seika Pharma:* Speakers Bureau; *Takeda Pharmaceutical:* Research Funding, Speakers Bureau; *Japan Blood Products Organization:* Research Funding, Speakers Bureau; *Alexion Pharma:* Speakers Bureau; *AbbVie:* Research Funding, Speakers Bureau; *Human Life CORD:* Speakers Bureau; *Novartis:* Speakers Bureau; *Eisai:* Research Funding, Speakers Bureau; *Precision:* Speakers Bureau; *Wakunaga Pharmaceutical:* Speakers Bureau; *Sumitomo Pharma:* Research Funding, Speakers Bureau; *Bristol Myers Squibb:* Speakers Bureau; *Amgen:* Speakers Bureau; *Chugai Pharmaceutical:* Research Funding, Speakers Bureau; *Daiichi Sankyo:* Research Funding, Speakers Bureau; *AstraZeneca:* Speakers Bureau; *Otsuka Pharmaceutical:* Research Funding, Speakers Bureau; *CSL Behring:* Speakers Bureau; *Asahi Kasei Pharma:* Research Funding, Speakers Bureau; *FUJIFILM Wako Pure Chemical:* Speakers Bureau; *Nippon Shinyaku:* Speakers Bureau; *Nippon Kayaku:* Research Funding; *JCR Pharmaceuticals:* Research Funding. **Atsuta:** *JCR Pharmaceuticals Co., Ltd.:* Consultancy; *CHUGAI PHARMACEUTICAL CO., LTD.:* Speakers Bureau; *Otsuka Pharmaceutical Co., Ltd:* Speakers Bureau; *Novartis Pharma KK:* Speakers Bureau; *Meiji Seika Pharma Co, Ltd.:* Honoraria. **Kanda:** *Amgen:* Ended employment in the past 24 months, Honoraria; *Janssen Pharmaceutical K.K.:* Honoraria; *Novartis Pharma K.K.:* Honoraria; *Sanofi K.K.:* Honoraria; *AbbVie Pharma:* Honoraria; *Megakaryon Co.:* Honoraria; *Eisai Co.:* Research Funding.

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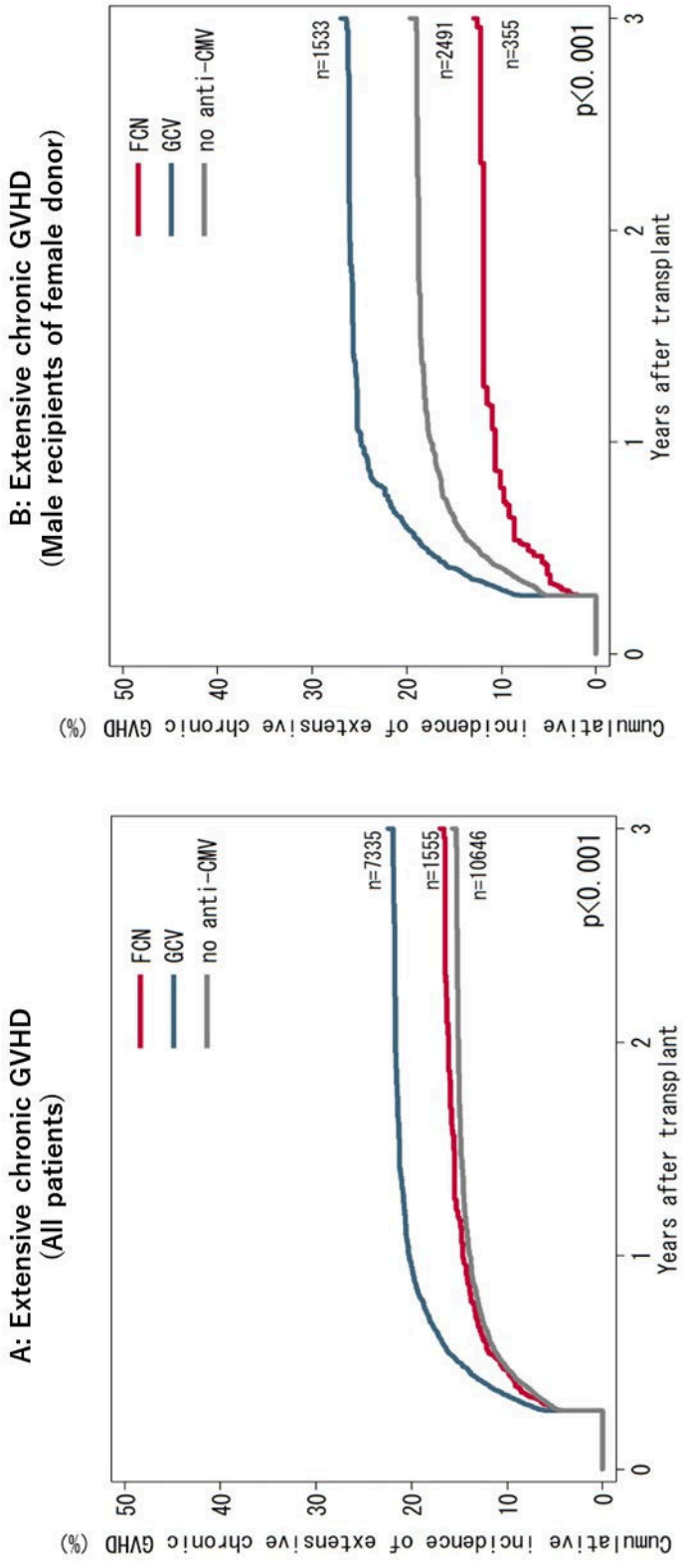

Figure 1