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POSTER ABSTRACTS

731.AUTOLOGOUS TRANSPLANTATION: CLINICAL AND EPIDEMIOLOGICAL

Patient Recorded Outcomes from a Randomized, Controlled Phase 2 Trial of E-Selectin Inhibition with Uproleselan Vs Placebo to Reduce GI Toxicity during Melphalan-Conditioned Autologous Hematopoietic Cell Transplantation for Multiple Myeloma

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Background:
The use of high-dose melphalan conditioning followed by autologous hematopoietic cell transplant (AHCT) continues to be a key component in the treatment of patients with multiple myeloma (MM). However, high-dose melphalan is associated with a high rate of GI toxicity (>90%), which adversely impacts clinical outcomes and negatively influences patient quality of life (QoL). Indeed, it has been reported that AHCT leads to short-term deterioration of health-related QoL in patients with MM, and QoL typically improves by 2-3 months post-AHCT. Pre-clinical and clinical data suggest that E-selectin inhibition may play a role in reducing immune-mediated GI epithelial injury following cytotoxic chemotherapy. We hypothesized that uproleselan (upro), a synthetic, competitive E-selectin antagonist, may improve health-related QoL by reducing risk of chemotherapy-induced diarrhea in patients undergoing AHCT.
Methods:
We conducted a Phase 2, single-center, randomized, double-blind, placebo-controlled trial in patients with MM receiving high-dose melphalan (200 mg/m2) as conditioning for AHCT for MM. Patients were randomized 1:1 to receive prophylactic upro+standard of care (SoC) vs placebo+SoC. Uproleselan was given in 6 doses of 800 mg IV starting on day-3 through day 0. The primary endpoint was diarrhea severity as assessed by CTCAE v5.0 (secondary endpoint - Bristol Stool Scale). In addition, a key secondary endpoint was patient reported outcomes (PRO) of GI-related QoL using the National Cancer Institute (NCI) PRO-CTCAE Measurement System, a validated PRO tool developed to evaluate symptomatic toxicities in patients with cancer in clinical trials. Significance level of $p<0.2$ was pre-specified for all endpoints, per protocol. Patients were surveyed during the peri-transplant period at day-3 (baseline), day+8, and day+14 or day of discharge (DoD). Responses were graded on a scale of 1-5, with 1 indicating absence of symptoms or zero interference with daily activities and 5 indicating very severe symptoms or very significant interference with daily activities. GI-specific domains assessed included swallowing, mouth sores, appetite, nausea, vomiting, heartburn, bloating, abdominal pain, flatulence, and incontinence.
Results:
Fifty adult patients with MM were enrolled from 5/2021-10/2022. Baseline PRO symptoms were similar between the upro+SoC and placebo+SoC arms at baseline (day-3). By day+8 post-AHCT patients in the upro+SoC arm reported a significant improvement in severity of GI-related symptoms across 30% (6/20) of domains surveyed vs placebo+SoC ($p=0.07$-0.14). Furthermore, improvement in mouth sore-related symptoms continued to day+14 post-AHCT in the upro+SoC arm vs placebo+SoC ($p=0.17$). The remaining GI-related symptoms returned to baseline by D+14 or DoD ($p>0.20$). Also of note, a numerically lower mean diarrhea severity score and lower incidence of Grade 3 diarrhea (by CTCAE v5.0) was observed favoring upro+SOC which did not meet the pre-specified significance threshold ($p=0.34$, $p=0.26$, respectively). However, a significant reduction in severe diarrhea (by Bristol Stool Scale) was observed favoring upro+SoC ($p=0.10$) vs placebo+SoC, with improvement in the upro+SoC arm to mild diarrhea ($p=0.02$).
Conclusions:
Upro+SoC resulted in a clinically significant improvement in GI-toxicity related symptoms as assessed via PRO-CTCAE in patients with MM undergoing melphalan-conditioned AHCT, when compared to placebo+SoC. These improvements in patient reported outcomes are further supported by data from the primary and additional secondary endpoints of the study. Taken together, these results suggest prophylactic E-selectin inhibition may represent a promising strategy to mitigate chemotherapy-

associated GI-toxicity. Further studies are needed to verify these findings and to further define the optimal dosing of upro in the peri-AHCT period.

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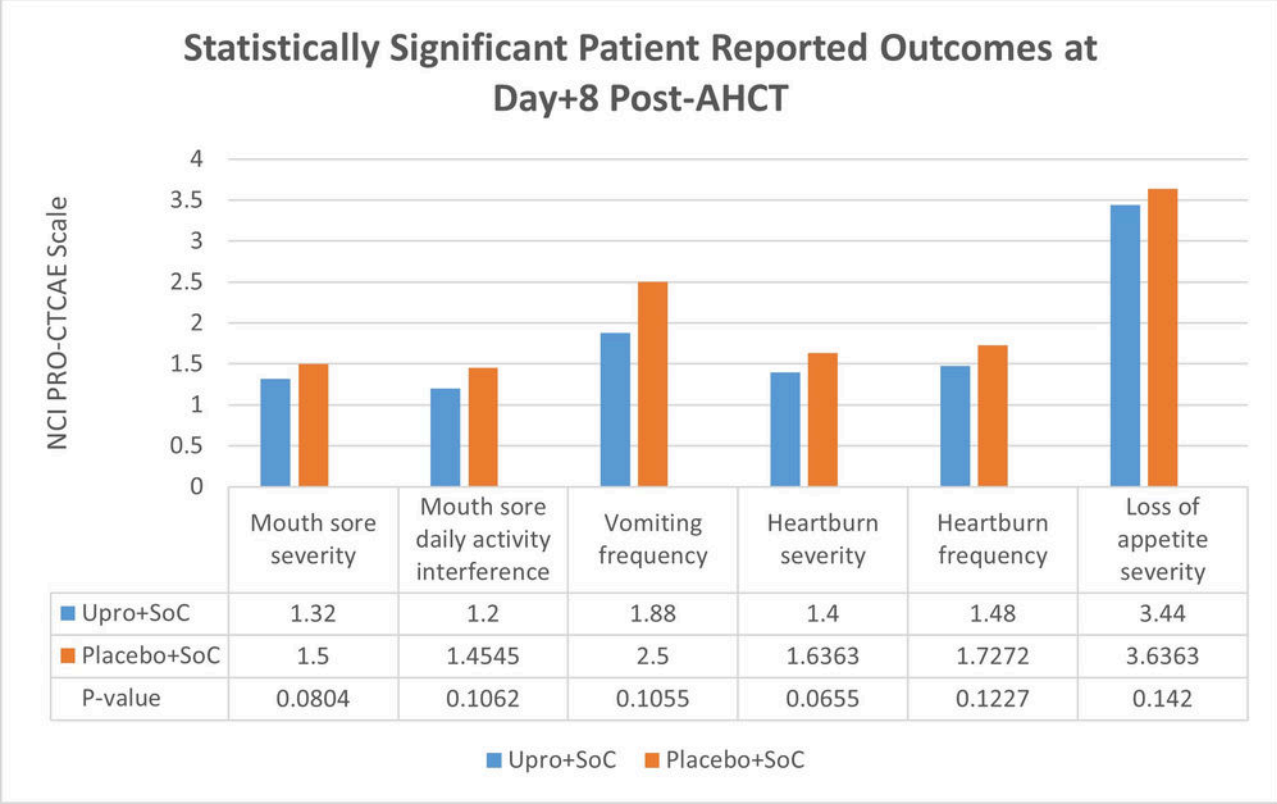

	Mouth sore severity	Mouth sore daily activity interference	Vomiting frequency	Heartburn severity	Heartburn frequency	Loss of appetite severity
Upro+SoC	1.32	1.2	1.88	1.4	1.48	3.44
Placebo+SoC	1.5	1.4545	2.5	1.6363	1.7272	3.6363
P-value	0.0804	0.1062	0.1055	0.0655	0.1227	0.142

Figure 1

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