Background: POEMS (Polyneuropathy, Organomegaly, Endocrinopathies, Monoclonal protein, Skin changes) syndrome is a rare paraneoplastic syndrome and therapies are directed against plasma cells that produce the proteins that cause this syndrome. Novel therapies are widely used in multiple myeloma aiming for plasma cell eradication. However, data on their use in POEMS syndrome are lacking.

Aims: To provide the Mayo Clinic experience in treating 16 patients with relapsed POEMS syndrome with novel agents (daratumumab, carfilzomib, pomalidomide, and elotuzumab).

Methods: We identified all POEMS patients seen at Mayo Clinic Rochester, Minnesota using a prospectively maintained database of patients seen at our center between June 1979 and May 2021. Of these patients, we identified all the patients that were treated with a “novel” agent, defined as daratumumab, carfilzomib, pomalidomide, and elotuzumab.

The primary endpoints were response to therapy (hematological, PET, VEGF and clinical, which will be referred to as responseH, P, V, C, respectively), and time to next therapy (TTNT), defined as time from institution of regimen of interest to next therapy. The secondary outcome was safety.

Results: The median age at POEMS diagnosis was 57 years (range 39-79) and 15 patients (93%) were men. Among all patients at diagnosis, 10 (63%) had skin changes, 15 (94%) had signs of extravascular volume overload, and 15 (94%) patients had endocrine disorders. Ten and six patients had IgA and IgG isotypes, respectively, and all the patients had lambda light chain isotype. Radiological evidence for sclerotic lesions were found in 13 (81%) patients.

The median time from diagnosis to novel agent’s first dose administration was 50 months (IQR 23-122) and the median lines of therapy prior to novel agent was 2 (range 1-4). Twelve patients (75%) underwent prior autologous stem cell transplantation (ASCT), and 5 patients had prior lenalidomide. The median age at novel agent administration was 63 years (IQR 51-70) and 4 patients (24%) were 70 years or older.

The patients were treated with a a doublet including dexamethasone (N=5) (31%) or in various combinations with other agents: DRd (N=6), DC(V)d (N=3), KRd (N=3), KPd (N=1), DP(V)d (N=5), and EloRd (N=1).

The outcomes with novel agent therapies were favorable (Table 1). Among patients treated with daratumumab based therapies (N=17), 9 patients achieved CR/VGPRH, 7 patients achieved CR, and 5 patients achieved CRp. Among patients treated with carfilzomib-based therapies (N=6), 3 patients achieved CR/VGPRH and one achieved PRH. Only one patient treated with carfilzomib-based therapies achieved a clinical response.

Neither patient who received pomalidomide and dexamethasone or elotuzumab with lenalidomide and dexamethasone responded. At a median follow-up of 38 months since starting of the novel agent (IQR 24-57), 15 of the patients (94%) are still alive, and the median TTNT was not reached.
None of the patients discontinued therapy due to adverse events and no deaths occurred on therapy. Novel therapies were safe with 7 events of hospitalization due to pneumonia (4 in daratumumab-based therapies and 3 on carfilzomib-based therapies), and 4 patients were hospitalized due to volume overload (all received dexamethasone with therapy). Three patients experienced infusion-related reactions (IRR) to the first dose of IV daratumumab.

| PR ID | Regimen | Prior lines of Rx, N | Dx to novel Rx, mo | Duration of therapy, mo | Time to next therapy, mo | Hematologic | VEGF | PET | Clinical |
|-------|---------|----------------------|-------------------|-------------------------|--------------------------|-------------|------|-----|----------|
| 1     | Dara-VG | 1                    | 22                | 3                       | 1                        | VGPR        | NE   | NE  | CR       |
| 2     | Dara-PD | 2                    | 26                | 16                      | 1                        | VGPR        | CR   | CR  | CR       |
| 3     | DCG    | 1                    | 27                | 56-                     | 1                        | VGPR        | CR   | CR  | CR       |
| 4     | DCD    | 1                    | 19                | 31-                     | 1                        | NE          | CR   | NE  | CR       |
| 5     | Dara-DC | 2                   | 35                | 3                       | 1                        | SD          | NE   | NE  | PD       |
| 6     | DCG    | 1                    | 28                | 16-                     | 1                        | CR          | NE   | NE  | SD       |
| 7     | DCD    | 3                    | 47                | 35                      | 1                        | CR          | CR   | NE  | CR       |
| 8     | DCD    | 1                    | 53                | 46                      | 1                        | CR          | CR   | NE  | SD       |
| 9     | DCG    | 1                    | 100               | 12-                     | 1                        | NE          | CR   | CR  | NE       |
| 10    | DCG    | 3                    | 135               | 112-                    | 1                        | VGPR        | NE   | PR  | SD       |
| 11    | DCG    | 3                    | 129               | 42-                     | 1                        | VGPR        | NE   | PR  | NE       |
| 12    | DCG    | 3                    | 138               | 57                      | 1                        | CR          | CR   | PR  | PR       |
| 13    | DCG    | 2                    | 319               | 3                      | 1                        | PD          | PD   | PD  | PD       |
| 14    | DCG    | 4                    | 341               | 57-                     | 1                        | CR          | CR   | NE  | CR       |
| 15    | Krd    | 1                    | 22                | 2                       | 1                        | NE          | PD   | NE  | PD       |
| 16    | DCG    | 2                    | 24                | 30                      | 1                        | CR          | CR   | NE  | CR       |
| 17    | Krd    | 1                    | 125               | 12-                     | 1                        | CR          | CR   | NE  | NE       |
| 18    | Krd    | 1                    | 165               | 14-                     | 1                        | NE          | NE   | PR  | SD       |
| 19    | Krd    | 2                    | 51                | 3                       | 5                        | PR          | NE   | PD  | PD       |
| 20    | DCG    | 5                    | 36                | 4                       | 3                        | SO          | SO   | SD  | SD       |
| 21    | DCG    | 5                    | 42                | 3                       | 2                        | SO          | SO   | SD  | SD       |

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Summary/Conclusion: Response rate was high and the responses were deep. Novel agent therapies were safe, and no death case occurred on therapy. Future studies are needed to clarify the optimal sequence of novel agents and the best combination.