DT-PACE/ESHAP chemotherapy regimens as salvage therapy for multiple myeloma prior to autologous stem cell transplantation

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Running Title: Infusional therapy as salvage regimens in multiple myeloma

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Routine use of novel agents to treat newly diagnosed and relapsed multiple myeloma(MM) produces high response rates and improved survival. However, 15-20% of patients have suboptimal responses and their management remains challenging.[1]Traditional regimens, such as DT-PACE(dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) and ESHAP(etoposide, methylprednisolone, cytarabine, cisplatin) are employed in patients with relapsed/refractory(RR) disease, and may bridge patients to autologous stem cell transplantation(ASCT).[2-4] Originally developed to improve responses to traditional chemotherapy regimens, and enable stem-cell mobilization,[5-7] the role of infusional regimens in the context of novel agents is unclear, especially as recently reported series indicate relatively poor outcomes.[8,9] These regimens can be associated with significant toxicity,[2] placing a burden on healthcare resources.[10]

We undertook a single centre retrospective analysis to assess the role of infusional regimens in RR MM patients to explore and identify features associated with clinical benefit. Relevant clinical information was obtained from electronic records. Overall response rate (ORR) and cytogenetic risk were assessed as per IMWG criteria(Table 1).[11] (Progression-free (PFS) and overall survival(OS) were estimated using Kaplan-Meier and Cox regression methods (time-dependent where appropriate).

Between 2010-2019, 63 MM patients received DT-PACE/ESHAP containing regimens: 42(67%) for primary refractory, and 21(33%) for relapsed disease including five patients who had previously received ASCT. 61(97%) patients had received novel agent therapy(Supp Table 1); a substantial proportion had adverse cytogenetics, ISS II/III and/or extramedullary disease(EMD)(Table 1). Primary refractory patients were less heavily pre-treated (71% had 1 prior line of treatment compared to 14% in refractory patients, with median prior lines of 1 and 2 respectively), otherwise were similar with regard to other characteristics. Various combinations were used with the majority receiving VDT/DT-PACE (38/63) and ESHAP (13/63), Supplementary Table 2 shows patient characteristics by regimen given and receipt of ASCT.

Infusional regimens were well tolerated with no life-threatening adverse events. Side effects included gastrointestinal toxicity (n=9), fluid overload (n=9), infections including neutropenic sepsis (n=7), renal impairment (n=4), peripheral neuropathy (n=2). All

patients developed ≥Grade 3 haematological toxicity during treatment; 3 patients had G3 neutropenia when commencing therapy. 3(5%) patients died within 60 days due to progressive disease with no treatment related deaths.

ORR was 71% for the cohort, 74% in primary refractory and 67% in relapsed patients (Supp Table 3). 14/42(33%) primary refractory patients achieved complete response/very good partial response(CR/VGPR) compared to 5/21(24%) relapsed patients. 33/35(94%) patients requiring stem-cell mobilisation pre-ASCT successfully harvested stem-cells following DTPACE/ESHAP.

After a median follow-up of 29.5 months, 35(56%) patients had died, 12(19%) had progressed and 16(25%) were alive without progression. Median PFS was 7.9 months (95%CI:3.4-12.4)(Fig 1A) and median OS was 28.9 months (95%CI:11.4-46.5)(Fig 1B).Deeper responses (≥VGPR vs SD/PD) were associated with longer PFS(15.5 vs 1.8 months, HR=0.09, 95%CI:0.04-0.20, p<0.001) but not OS(28.9 vs 10.5 months, HR=0.79, 95%CI:0.34–1.83, p=0.68). Adverse cytogenetics was associated with poorer outcomes: PFS(6.8 months vs not reached, HR=3.56, 95%CI:1.08-11.79, p=0.04) and OS(12.2 months vs not reached, HR=8.30, 95%CI:1.12-61.68, p=0.04) (Fig 1C&D). Other diagnostic disease parameters traditionally associated with inferior outcomes including CRAB criteria and EMD did not correlate with PFS or OS(Supp Fig 1).

Patients with primary refractory disease had superior outcomes compared to those with relapsed disease(median PFS 15.5 vs 6.1 months, HR=0.37, 95%CI:0.19-0.70,p<0.01; median OS 46.1 vs 8.9 months, HR=0.36, 95%CI:0.18-0.71, p<0.01; Fig 1E). There was no significant difference in PFS (p=0.66) or OS (p=0.09) between DT-PACE or ESHAP. 46(73%) patients proceeded to consolidation with ASCT (second ASCT, n=2) and had longer PFS and OS compared to those who did not(median PFS 15.5 vs 2.0 months, time-dependent HR=0.25, 95%CI:0.10-0.61, p<0.01; median OS 46.1 vs 7.3 months, HR=0.32, 95%CI:0.15-0.68,p<0.01)(Fig 1F). Of these, 23/32(72%) had adverse cytogenetics, and 34(74%) had primary refractory disease. 17(27%) patients did not proceed to ASCT due to inadequate response (≤PR)(n=5),

rapid relapse post infusional treatment(n=8), or ASCT not planned (n=4). ASCT treatment related mortality was low (1/63, <2%).

In multivariable analyses (Supp Fig2), adjusting for each of the other factors, consolidation with ASCT remained significant for PFS (all p values <0.01) and for OS (all p values <0.05). Depth of response to ESHAP/DT-PACE was strongly associated with PFS(p<0.001) but not OS(p=0.73).

Patients refractory to novel agent containing induction regimens have inferior outcomes, with significantly shorter PFS/OS. One series reports that those able to receive ASCT fared better, suggesting that these patients still benefit from ASCT.[12] Our data show a clear distinction in outcomes between patients who were consolidated with ASCT post DTPACE/ESHAP (mostly primary refractory), versus the rest. Patients who were consolidated with ASCT following ESHAP/DT-PACE had a PFS of 15.5 months without maintenance, hence with maintenance would expect to fare even better. The benefit of consolidating infusional therapy with ASCT is consistent with published series[2,8,13] and highlights the continued importance of ASCT as consolidation therapy in patients with disease refractory to novel agents. As previously reported, adverse cytogenetics was associated with shorter PFS and OS.[2,8]

Compared with other recently published series, our cohort had longer PFS and OS outcomes and, in contrast to regimen related mortality rates of 9.7-14.8% in other series,[8,9,13-15] we had only one death (during ASCT).This may relate to several factors. In our series, more patients had primary refractory disease and/or were ASCT naïve, whilst other published series included more heavily pre-treated patients with relapsed disease. This could partly explain the lower regimen related toxicity and mortality. Most patients were treated in an ambulatory care setting, with growth-factor support and prophylactic antimicrobials. A number of factors associated with poor outcomes, such as EMD or CRAB criteria, were not significantly associated with PFS or OS; however, a limitation of our study is the relatively small sample size and number of events, hence our findings remain to be confirmed in larger series.

This is the largest UK dataset of MM patients treated with DTPACE/ESHAP reported to date, and confirms that even with current novel therapy, traditional infusional

regimens retain a role in patients with high risk disease and are well tolerated. We demonstrate benefit for patients with primary refractory disease who can be successfully consolidated with ASCT. Patients with relapsed disease, or unable to proceed to ASCT, have poorer outcomes and alternative strategies including emerging immunotherapies such as antibody-drug conjugates, bi-specific T-cell engagers or chimeric-antigen receptor (CAR) T cells should be explored. Within the limitations of a retrospective analysis, our results suggest that DTPACE/ESHAP regimens should be reserved for patients where ASCT consolidation is planned.

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LA/SJC/FN/JH collected the data
LA/SJC/NC analysed the data
LA/SJC/KY wrote the manuscript
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