A multicentre retrospective analysis of toxicity in 6 weekly vs 3 weekly Pembrolizumab dosing

Michael Rowe, Leonie Eastlake, Timothy Norris, Timothy Farley, Toby Talbot. Corresponding Author: michael.rowe2@nhs.net

BACKGROUND

Pembrolizumab is an anti-PD1 immune checkpoint inhibitor (ICI) licenced across a variety of tumour sites. The dosing schedule was 200mg 3 weekly (q3w). In April 2019 the European Commission approved 400mg 6 weekly (q6w) dosing based on simulation of dose/exposure relationships and predicted no difference in toxicity.[1] The lack of clinical data supporting this has, however, raised concern amongst clinicians. We therefore retrospectively analysed toxicity data for the q3w and q6w schedules.

METHODS

All patients who received Pembrolizumab for any indication between March-December 2019 were included across three regional centres. Patients receiving q3w were selected as the standard of care group. All of these patients subsequently switched to q6w with toxicity data collected separately for both schedules. Patients who started de-novo on q6w were assigned to the comparator group. Toxicity data was collected retrospectively using Common Terminology Criteria for Adverse Events v5.0. Clinically significant immune-related adverse events (CSirAE) were defined as immune-related events and ≥grade 3 rash. Data was analysed using incidence (Poisson distribution) and incidence ratio. Incidence rates for the q3w group prior to switching were calculated from first dose of 200mg pembrolizumab to the last dose given prior to switching to the q6w regimen. Incidence rates for the q6w group were calculated from the first dose of 400mg of pembrolizumab administered to the last documented follow-up episode.

RESULTS

63 patients started on q6w and 110 patients received q3w. Group characteristics are summarised in Table 1.

There were a total of 11 grade 3-5 CSirAE (3 for q6w and 8 for q3w) and 44 grade 1-2 CSirAE (13 for q6w and 31 for q3w). Some patients experienced more than one CSirAE. The incidence of any-grade CSirAE per 100 patient-months (95% CI) was 4.09 (1.77-5.68) for q6w and 3.32 (2.36-4.54) for q3w with an incidence ratio of 1.23 (0.64 – 2.26). The incidence of grade 3-5 CSirAE was 0.77 (0.16-2.24) in q6w and 0.68 (0.29-1.34) in q3w with an incidence ratio of 1.13 (0.19 – 4.70). Breakdown of frequency of each CSirAE encountered is summarised in Figure 1.

In the q3w group all patients switched to q6w. There was a low proportion of new CSirAE (5% Grade 1-2, 8% Grade 3-5). Figure 2 summarises CSirAEs encountered when switching from q3w to q6w. Median number of cycles given following switch was 5 with toxicity occurring after a median of 1 (range 1-6).

Both groups had a high proportion of patients with low grade toxicity (fatigue, pruritus, rash; q6w 46%, q3w 42%). Figure 3 summarises the frequency of non-immune related toxicity encountered in our patient cohort.

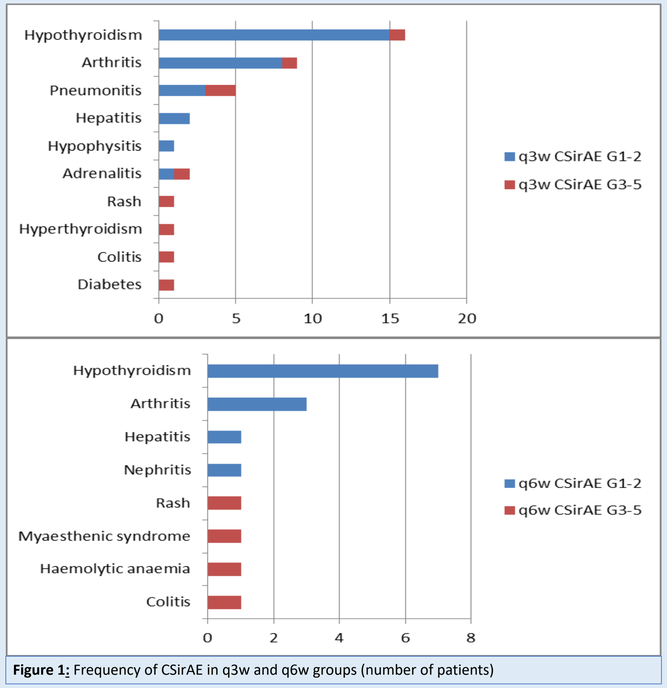

Figure 1: Frequency of CSirAE in q3w and q6w groups (number of patients)

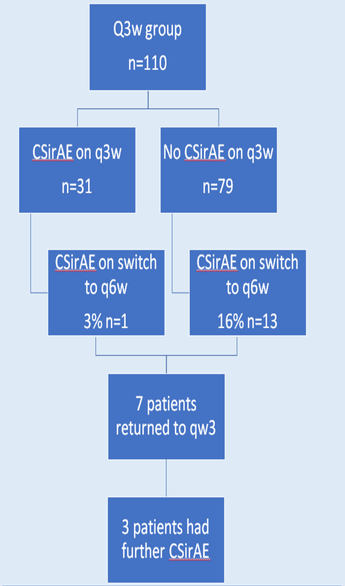

Figure 2: Frequency of CSirAE in q3w group switching to q6w

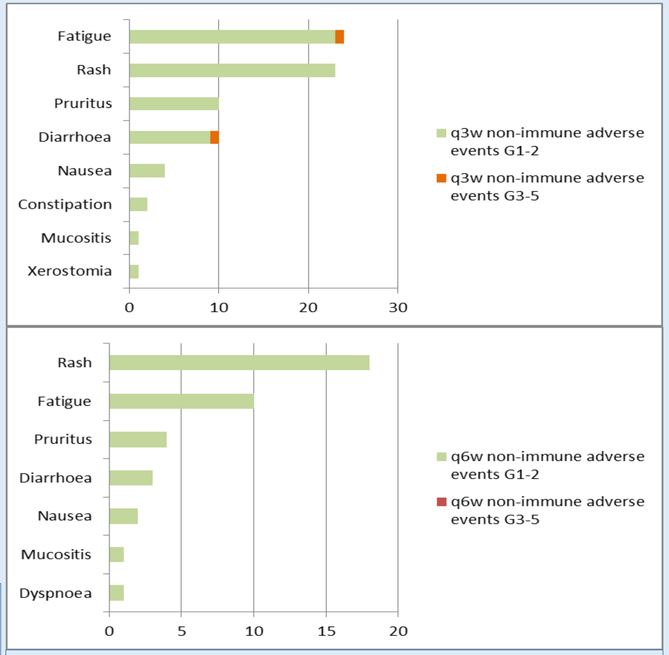

Figure 3: Frequency of non-immune adverse events in q3w and q6w groups (number of patients)

	q6w (n=63)	q3w (n=110)
Age (yr)	72 (33-90)	72 (42-91)
Follow-up time (months)	6.2 (0.1-11)	13.2 (2.5-44)
Treatment cycles given	4 (1-10)	14 (3-57)
Total treatment duration (patient-months)	391	1175
Tumour histology		
Non-small cell lung cancer	72%	44%
Melanoma	25%	54%
Urothelial	3%	2%
Treatment line		
1st line	82%	86%
2nd line	18%	14%
Reason for stopping treatment		
Ongoing treatment	46%	38%
Progressive disease	17%	15%
Toxicity	11%	9%
Death	19%	8%
Treatment complete	2%	26%
Comorbidities	5%	4%

Table 1: Group characteristics.

DISCUSSION AND CONCLUSION

To our knowledge, this is the first analysis of real-world toxicity data for a q6w Pembrolizumab regime.

Incidence of CSirAEs, particularly G3-5 toxicity was low. A large meta-analysis looking at >12000 patients treated with anti-PD1/PDL-1 agents found an incidence of 6.1%, similar to G3-5 toxicity in q3w group (7.2%).[2] Endocrinopathies and arthritis were most commonly seen. Low grade non-CSirAE toxicity was common and could impact quality of life with extended treatment.

There was a trend towards slightly higher incidence of toxicity in the q6w group but the incidence ratio was not statistically significant. Patients switching to q6w from q3w were more likely to develop CSirAE if they hadn't experienced toxicity whilst on q3w. However ICI toxicity can present after stopping treatment therefore it is not certain that switching to q6w caused the CSirAE.[3,4]

Reverting back to q3w did not prevent further CSirAE (43% developed further toxicity). It is possible that, in line with the seminal trials looking at doses of 2mg/kg-10mg/kg, pembrolizumab immune-related toxicity may be linked to mechanism of action of immunotherapy and patient pre-disposition, rather than dose.[5]

Despite limited number of events, the q6w schedule does not appear to lead to significantly higher toxicity and should be used in view of the reduced burden to patients and health services.

References: [1]Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. European Journal of Cancer. 2020;131:68-75.
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Conflict of interest statement: MR, LE, TN and TF have no conflict of interest to declare. TT has received travel and speaking honoraria from Merck, Sharpe and Dohme.