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P1140 TIME TO TUMOR, SYMPTOMATIC AND LABORATORY RESPONSES FOLLOWING SILTUXIMAB TREATMENT IN IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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Background: Idiopathic multicentric Castleman disease (iMCD) is a rare, heterogeneous disorder involving multicentric lymphadenopathy, systemic inflammation, and cytokine-driven organ dysfunction. Siltuximab—a monoclonal antibody against interleukin-6—is the only FDA- and EMA-approved treatment for iMCD. A phase 2, randomized, double-blind, placebo-controlled trial of siltuximab for the treatment of iMCD (NCT01024036) showed that 18/53 patients (34%) responded to treatment, compared with 0% in the placebo group, but it is not known how long patients should be maintained on siltuximab before deciding whether the treatment is beneficial.

Aims: To determine the time to and sequence of normalization of laboratory, clinical, and lymph node responses in patients who responded to siltuximab.

Methods: The phase 2 trial enrolled adults with symptomatic iMCD who were human immunodeficiency virus seronegative and human herpesvirus 8 negative. In this post hoc analysis, we aimed to determine the sequence of and time to normalization of laboratory, clinical, and lymph node responses in patients who responded to siltuximab. The Kaplan–Meier and cumulative incidence with competing risks methods with corresponding log-rank tests were produced to estimate and compare the progression-free survival (PFS), overall survival, time to treatment failure, time to lymph node response, time to durable symptomatic response, and time to normalization of laboratory values.

Results: Seventy-nine patients were enrolled in the trial (n=53 siltuximab, n=26 placebo; all patients received best supportive care). The median duration of follow-up was 422 days (range 55–1051). Siltuximab treatment improved PFS compared with placebo (p=0.0001). The median PFS was 14.5 months (95% CI 13.6–upper bound not reached) for patients on placebo, whereas it was not reached for patients on siltuximab. The 2-year estimates for overall survival were 93% (95% CI 85–100%) for the siltuximab arm and 77% (95% CI 55–98%) for the placebo arm (p=0.11). Time to treatment failure in the placebo arm was 4.8 months and was not reached with siltuximab (p=0.005). In the 18 siltuximab-treated patients who achieved the primary endpoint of durable tumor (radiologic) and symptomatic response, most first achieved rapid normalization of various laboratory parameters and symptomology (median of 0.8 months to normalization based on a 34-point MCD symptom score) (Table 1). Lymph node responses occurred later (median of 4.1 months to normalization).

Image:

Table 1. Time to normalization of parameters in siltuximab responders

Parameter (in order of time to normalization)	Rate of incidence of primary endpoint responders	Median time to normalization, months (95% CI)
Platelet numbers ("normal" defined as ≤ULN)	84% at 3 months 94% at 12 months	0.7 (0.7–2.1)
Symptomatic response (≥50% reduction in a 34-point symptom score from baseline)	94% at 3 months 94% at 12 months	0.8 (0.4–1.4)
CRP (surrogate measure of IL-6) ("normal" defined as ≤ULN)	53% at 3 months 60% at 12 months	2.1 (0.7–NR)*
Albumin ("normal" defined as ≥LLN)	67% at 3 months 83% at 12 months	2.8 (0.7–NR)
Hemoglobin ("normal" defined as ≥LLN)	47% at 3 months 87% at 12 months	3.5 (1.4–11.4)
Lymph node response (≥50% decrease in the sum of the product of the diameters from baseline)	24% at 3 months 88% at 12 months	4.1 (3.7–9.2)
Durable symptomatic response (symptomatic responses maintained for at least 18 weeks)	33% at 3 months 89% at 12 months	6.9 (3.4–NR)
IgG ("normal" defined as ≤ULN)	33% at 3 months 56% at 12 months	10.6 (2.1–NR)*
Fibrinogen ("normal" defined as ≤ULN)	31% at 3 months 58% at 12 months	6.9 (3.4–NR)*

CRP, C-reactive protein; IgG, immunoglobulin G; LLN, lower limit of normal; NR, not reached; ULN, upper limit of normal.
*Times to normalization were not significantly different between the two treatment arms.

Summary/Conclusion: Significant improvements in biochemical parameters such as platelet count, albumin, and symptomatic responses occur within 3 months in the majority of responders, showing them as early indicators of response. Lymph nodes were slower to show an improvement in response to treatment, and so involution of these should not be used to drive early therapeutic decisions in iMCD patients following siltuximab. The present study shows the recovery sequence of different parameters over time following initiation of treatment with siltuximab.