Variable Response Rates Across Chemotherapy Regimens for Idiopathic Multicentric Castleman Disease

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Introduction

- Idiopathic multicentric Castleman disease (iMCD) is a rare, hematologic disorder that involves diffuse lymphadenopathy, systemic inflammation, and cytopenias leading to potentially fatal multi-organ dysfunction.[1]
- Clinical manifestations vary – ranging from mild/moderate symptomatology (iMCD-NOS; Not Otherwise Specified and iMCD-IPL; Idiopathic Plasmacytic Lymphadenopathy) to most severe (iMCD-TAFRO; Thrombocytopenia, Anasarca, Fever/Elevated C-Reactive Protein, Renal Dysfunction, Organomegaly).[2]
- Though etiology remains unknown, the pro-inflammatory cytokine, interleukin 6 (IL6), has been implicated in disease pathogenesis.[1]
- Siltuximab, an IL6 antagonist, is the only FDA-approved treatment for iMCD.[3]

Objective

- For patients with severe disease (severe renal dysfunction, extravascular fluid accumulation, pulmonary compromise, +/- severe anemia) with clinical worsening after starting siltuximab, consensus guidelines recommend combination chemotherapy.
- However, limited data exist comparing different chemotherapy agents and their responses. We sought to address this knowledge gap.

Methods

- We utilized ACCELERATE, a longitudinal Castleman disease (CD) natural history registry to collect and extract complete medical history and lymph node biopsy slides.
- Each case was adjudicated on the likelihood of an iMCD diagnosis by a panel of experienced clinicians and hematopathologists.[4]
- Demographic and clinical characteristics (±90 days from pathological diagnosis) were aggregated.
- Treatment history was inventoried, and responses were determined for further analysis and comparisons. Data was extrapolated from a previous study.[5]
  - Clinical response was defined as at least 50% reduction in abnormal clinical and laboratory criteria.
- Continuous data are reported as mean (standard deviation) or median (interquartile range [IQR]), as stated. Categorical variables are reported as frequencies and percentages. Statistical testing and data visualization performed using R version 4.4.2 and tidyverse packages.

Results

Table 1. Thirty-four unique iMCD patients received 52 chemotherapy regimens.

Sex, n (%)	
Males	24 (70.6)
Females	10 (29.4)
Age at diagnosis, years	
Median (IQR)	34.7 (21.7, 46.4)
Range	1.8 - 65.8
CD Subtype, n (%)	
TAFRO	31 (91.2)
NOS	2 (5.9)
IPL	1 (2.9)
Race, n (%)	
White	20 (58.8)
Black/African American	5 (14.7)
Asian	6 (17.7)
Other/Refused to Answer	3 (8.8)
Histopathological Subtype, n (%)	
Hypervascular	24 (75.0)
Mixed	7 (21.9)
Plasmacytic	1 (3.1)
NA	2
Treatments Received	
Chemotherapy, N	52
Cyclophosphamide-Inclusive, n/N (%)	33/52 (63.5)
Etoposide-Inclusive, n/N (%)	23/52 (44.2)
Doxorubicin-Inclusive, n/N (%)	21/52 (40.4)
Bortezomib-Inclusive, n/N (%)	15/52 (28.9)
IL6 Inhibition	
Chemotherapy + IL6, n/N (%)	21/52 (40.4)
Chemotherapy – IL6, n/N (%)	31/52 (59.6)
Clinical Response	
Cyclophosphamide-Inclusive, N	33
Response, n/N (%)	19/28 (67.9)
No Response, n/N (%)	9/28 (32.1)
Not Assessable	5
Etoposide-Inclusive, N	23
Response, n/N (%)	14/22 (63.6)
No Response, n/N (%)	8/22 (36.4)
Not Assessable	1
Doxorubicin-Inclusive, N	21
Response, n/N (%)	10/18 (55.6)
No Response, n/N (%)	8/18 (44.4)
Not Assessable	3
Bortezomib-Inclusive, N	15
Response, n/N (%)	9/13 (69.2)
No Response, n/N (%)	4/13 (30.8)
Not Assessable	2
Time to Next Treatment, months	
Median (IQR)	5.5 (2, 23.3)
Range	1 – 117

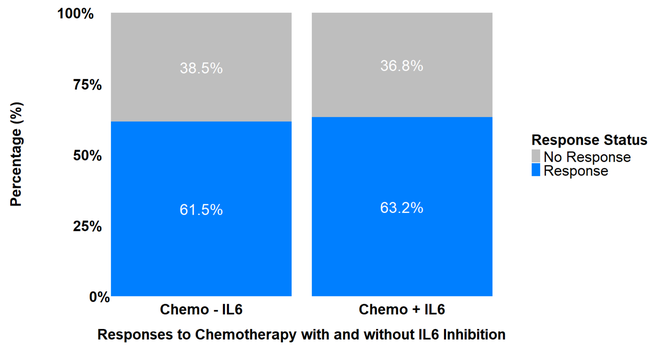

Figure 1. Clinical responses between patients who received chemotherapy (N = 52) with and without IL6 inhibition (siltuximab and/or tocilizumab).

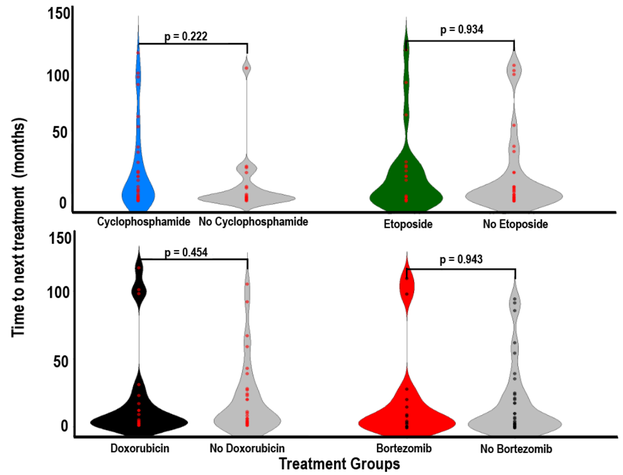

Figure 2. Time to next treatment measured for patients receiving regimens containing individual chemotherapies vs. regimens lacking that particular chemotherapy. Patients without a next/additional treatment were censored at last day of available medical records.

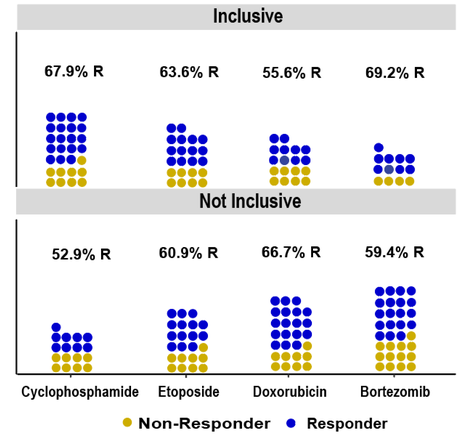

Figure 3. Response rates observed between different chemotherapy regimens that contain (or do not contain) a particular medication.

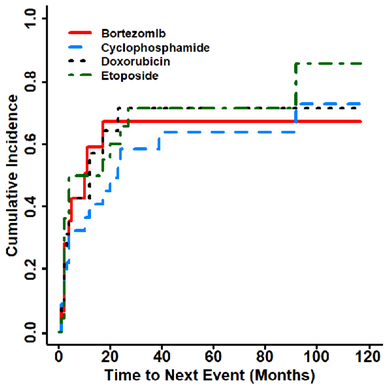

Figure 4. Cumulative incidence plot showing time to next event analysis by each chemotherapy category. “Event” is defined as initiation of a new regimen or death.

Conclusions

- This is the first investigation aimed at characterizing specific chemotherapy regimens for iMCD patients.
- We observed comparable clinical responses when we categorized chemotherapy regimens into four distinct groups.
- Similarly, we found comparable responses for patients who receive IL6 inhibition in conjunction with their chemotherapy than those who do not.
- Median time to next event of 5.5 months aligns with data in the literature for the treatment of other neoplasms.
- Considering the vulnerability of these patients, further research is need to identify optimal treatment approaches.

References

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