Exploring Castleman disease in China: pre-IL-6 treatment era and advancements in knowledge

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Castleman Disease (CD), which comprises various subtypes including unicentric (UCD) and multicentric (MCD) forms, is a group of heterogeneous lymphoproliferative disorders first described by Benjamin Castleman in the 1950s.[1] Clinical symptoms of CD vary by subtype with most UCD patients being asymptomatic, but MCD patients commonly exhibit systemic symptoms alongside lymph node enlargement such as fever, night sweats, fatigue, weight loss, anemia, liver and kidney dysfunction, and excessive fluid overload.[2] Misdiagnosis due to CD's rarity and the variability of its symptoms can lead to improper medication, and research on this disease are primarily sourced from case series or retrospective studies because of the limited availability of clinical and prognostic information. Continued engagement of physicians, scientists, and patients is essential for further advancements in Castleman Disease, and the Castleman Disease Collaborative Network (CDCN) has been instrumental in coordinating recent progress.[3] The China Castleman Disease Network (CCDN) was established in 2021, along with the release of the first Chinese expert consensus regarding CD treatment, highlighting the significance of the development of diagnostic criteria for CD.[4] Even so, large-scale research is needed to validate the established consensus standard and provide reliable supportive evidence for clinical physicians' decision-making.

Based on this premise, on behalf of the CCDN, Zhang et al. collaborated with 40 hospitals in China to conduct a comprehensive retrospective study involving 1634 patients from 2000 to 2021.[5] Prior to this study, the majority of research on this topic was limited to a single center and did not attain a comparable level of scale. The MCD patients were divided into two groups: HHV-8-associated MCD and HHV-8-negative MCD, with the latter subgrouped into asymptomatic MCD (aMCD) and idiopathic MCD (iMCD), the latter further divided into iMCD-TAFRO and iMCD-NOS based on the presence or absence of specific diagnostic criteria. Furthermore, iMCD patients were also classified into severe or mild/moderate/non-severe disease categories based on the CDCN definition, depending on the severity of their condition.[6] It should be noted that PEOMS was excluded in this study. The study aimed to validate the severity of iMCD and its subtypes, through an analysis of demographic and clinical characteristics, treatment modalities and overall survival.

The study identified MCD in 731 patients (44.7%), with 12 HHV-8-associated MCD positive and HIV-negative cases and 719 HHV-8-negative MCD cases, of which 80.7% (580) were iMCD, including 25.9% (150) severe cases. 41 (7.1%) iMCD patients were categorized as iMCD-TAFRO, and 539 were defined as iMCD-NOS, with 97 (18.0%) of these patients classified as iMCD-IPL. The study revealed that iMCD-TAFRO had the worst prognosis (3-year overall survival rate of 65.7%) and iMCD-IPL had the best estimated 3-year overall survival rate (98.5%) compared to other iMCD-NOS patients. These findings offered a more comprehensive and objective representation of the current status of Castleman Disease (CD) in China, expanding on and supporting previous retrospective studies.[7,8] On top of that, it revealed that severe iMCD was associated with increased mortality (75.6% estimated 3-year overall survival rate) in 418 NOS patients, validating the concept proposed by the CDCN in 2018 and demonstrating worsened outcomes in iMCD-TAFRO compared to iMCD-NOS.

CHOP or CHOP-like therapy decreased from being the primary first-line treatment option for iMCD, accounting for 66.7% of treatments before 2010, to only 5.2% since 2020, while thalidomide-based continuous therapy became the primary option, with 34.4% of patients receiving it after 2020. These findings showed that Chinese physicians have shifted from pulse combination chemotherapy towards a continuous treatment approach involving TCP or BCD regimen and IL-6 targeted therapy for CD over the past two decades. Chemotherapy involves the use of chemicals to disrupt

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cancer cell growth and division, but its toxic side effects on normal cells necessitate periodic treatment cycles and rest periods, while antibody drugs, which bind selectively to specific molecules or receptors with fewer side effects, typically require long-term continuous treatment.[9]

Anti–interleukin-6–directed therapies have shown promising results in many iMCD patients.[3] The approval of Siltuximab, an anti-IL-6-targeted therapy by the National Medical Products Administration of China, and its impending availability in China, is expected to greatly impact the iMCD treatment strategy. Even though, it does not necessarily mean that it will be the sole treatment strategy for iMCD in the future, and refractory cases still require additional treatments. At this specific time point, the importance of reviewing the treatment methods for CD over the past two decades is highlighted.

Considering that CD is a rare disease, it presents challenges to research such as small sample size, difficulty in conducting controlled studies, potential biases, and incomplete clinical data. Nevertheless, this study is currently the most extensive research on CD in China. As a multicenter study, certain challenges may still arise. Due to the variations in the number of subjects across different centers, the generalizability of the study findings may be compromised. In addition, the analysis of data may necessitate the use of more advanced statistical techniques to accommodate dissimilarities and correlations among multiple centers. To address these issues, the establishment of organizations or communities such as the CDCN is crucial in motivating patients to voluntarily enroll and enlarge the community and research dataset. Notably, in 2021, the first Chinese patient-led organization for Castleman disease, House of Castleman, was founded in 2021 and has gradually gained social influence. With the anticipated lifting of the prevention and control measures for COVID-19 in China at the beginning of 2023, there is expected to be an increase in opportunities for academic exchanges and public education on rare diseases. On the other hand, the benefits to patients are also intricately linked to the progress of China's healthcare policies.

In this study, it was also found that the delay in seeking medical care for patients with MCD ranges from at least 12 months to up to 353 months, which may be due to the rare nature of the disease. To address the issue of limited awareness about this disease, it's important for healthcare professionals and patients alike to increase their knowledge about rare diseases. The establishment of a disease concept lies in the accurate and timely diagnosis of patients who suffer from it, while a consensus on treatment is the ultimate outcome of all-encompassing research efforts. All research and initiatives aimed at rare diseases should be encouraged.

Contributors

N.-N. Zhong contributed to the conceptualisation and writing - original draft. B. Liu contributed to the supervision and writing - review & editing. L.-L. Bu contributed to the conceptualisation and writing - review & editing.

Declaration of interests

None.

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