Title： **Thalidomide, cyclophosphamide and prednisone in newly diagnosed Multicentric Castleman's disease: a prospective, single-center, single-arm, phase-II pilot trial**

NCT number: NCT03043105

Document date: February 2017

Specific aims:

To explore the effectiveness and safety of thalidomide, cyclophosphamide and prednisone (TCP regimen) in newly diagnosed Multicentric Castleman's disease (MCD) patients.

Significance:

Multicentric Castleman's disease (MCD) is a lymphoproliferative disorder associated with systemic symptoms including fever, night sweats, fatigue, anorexia, and cachexia. Unlike unicentric Castleman's disease (UCD) which responds well to surgical resection, there is no 'standard' treatment for MCD patients. A wide variety of medical therapies, including prednisone mono-therapy, conventional chemotherapy (eg. cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone, CHOP) [1] and targeted therapy (eg. Interleukin-6 antibody)[2], have been attempted in MCD. However, some therapies like prednisone were not potent enough to control the disease; on the other hand, some therapies like CHOP might bring safety concerns while MCD is a relatively indolent disease which waxes and wanes. Moreover, although randomized controlled studies have showed the efficacy and safety of Interleukin-6 (IL-6) targeted treatment (siltuximab)[2], and retrospective analyses have suggested the potential role of CD-20 targeted therapy (rituximab) in treating MCD[3], both drugs are very expensive, especially for patients in developing countries.

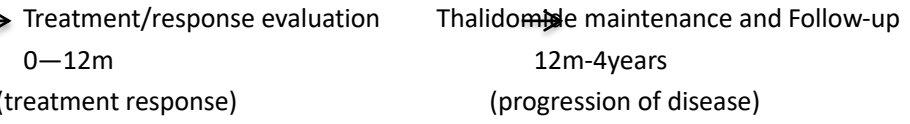
Thalidomide is a relatively inexpensive immunomodulatory drug which have been used to treat multiple myeloma, POEMS patients [4] and occasionally, MCD [1]. Multiple myeloma is a malignancy of plasma cells which might share certain pathogenesis with MCD, especially its plasma cell variant. POEMS syndrome is a disorder very closely related to MCD; 11% to 30% POEMS patients have documented diagnosis of Castleman's disease. These clues suggest a potential role of thalidomide in MCD patients. Moreover, thalidomide has anti-inflammatory properties and could reduce TNF-alpha, IL-6 and IL-10 levels [6] while elevated levels of these cytokines might contribute to the pathogenesis of Castleman's disease [7,8]. Thus, thalidomide is a promising agent in treating MCD. Cyclophosphamide and prednisone are drugs which have been commonly used to treat MCD [1] and bring fewer safety issues than other potent drugs like hydroxydaunorubicin or vincristine. Therefore, a combination of these drugs with thalidomide (TCP regimen) is very likely to be an effective and safe option in MCD patients.

In the present proposal, a prospective, single arm, phase-II pilot trial will be conducted to determine the efficacy and safety of thalidomide, cyclophosphamide and prednisone (TCP regimen). If effective, this regimen could be recommended as an economical and efficacious treatment option for patients with MCD in China and other developing countries.

Methods:

Study design: This will be a single center, open-labeled , single arm, phase-II pilot study. The treatment and the response evaluation phase will last from the time of enrollment up to 12 months (evaluation will be carried out every 12 weeks in the first 6 months and every 3 months thereafter to 12 months). The follow-up phase to assess for progression of disease will last from 12 months to 4 years after enrollment (evaluation will be carried out every 12 months)

Flow chart illustrating the time frame of our study:



Visit#	Time	Plan
Screening	**/**	●Pathological review of patients' specimen. ●To find out symptomatic patients who are willing to be treated. ●Informed consent.
Visit 0	**0 m**	●Demographic features, past medical history. ● Symptoms recorded according to MCD-related overall symptom score*. ●Physical examination, laboratory evaluations (eg, blood tests including Interleukin-6 and VEGF, bone marrow aspiration, CT scan), questionnaire (eg, ECOG performance status score, SF-36 score).
Visit 2-3	**3m** **6m**	● Symptoms recorded according to MCD-related overall symptom score*. ●Physical examination, laboratory evaluations (eg, blood tests, CT scan), questionnaire (eg, ECOG performance status score, SF-36 score). ●Adverse events.
Visit 4-5	**9m** **12m**	● Symptoms recorded according to MCD-related overall symptom score*. ●Physical examination, laboratory evaluations (eg, blood tests, CT scan), questionnaire (eg, ECOG performance status score, SF-36 score). ●Adverse events. ●Complete TCP treatment, initiation of Thalidomide maintenance.
Visit 6-9	**15m** **18m** **21m** **24m**	● Symptoms recorded according to MCD-related overall symptom score*. ●Physical examination, laboratory evaluations (eg, blood tests, CT scan), questionnaire (eg, ECOG performance status score, SF-36 score). ●Adverse events. ●Complete Thalidomide maintenance.
Visit 10-11	**36m** **48m**	● Symptoms recorded according to MCD-related overall symptom score*. ●Physical examination, laboratory evaluations (eg, blood tests, CT scan), questionnaire (eg, ECOG performance status score, SF-36 score). ●Adverse events.

***MCD-related overall symptom score:** a published symptom score [2] calculated as the sum of the toxicity grades of the NCI-CTCAE (National Cancer Institute Common Toxicity Criteria for Adverse

Events version 4.0) terms.

Patients:

Target population: Adult patients with MCD in China.

Accessible population: Adult patients who have been first diagnosed as MCD (proven by biopsy and confirmed by pathologists' review) in Peking Union Medical College Hospital, which is one of the largest centers for hematological diseases in China and attracts patients from almost all over the country.

Inclusion Criteria: 1. Demography: ≥18 years, all race/ethnic groups in China; 2. Newly diagnosed and previously untreated (patients are allowed to have received oral prednisone for up to 1 week before enrollment) **symptomatic** MCD patients (symptomatic disease is defined by the presence of clinical symptoms with the NCI-CTCAE grading $\geqslant$1 that are attributable to the disease, and for which treatment is indicated); 3. Eastern Cooperative Oncology Group (ECOG) Performance Status $\leqslant$2; 4. Clinical laboratory values meeting these criteria at screening: absolute neutrophil count $\geqslant$ 1·0 x 109/L, Platelets $\geqslant$ 50 x 109/L, Alanine aminotransferase (ALT) within 2·5 x upper limit of normal (ULN); total bilirubin within 2·5 x ULN; estimated glomerular filtration rate (according to MDRD formula) <15ml/min;5. Women of childbearing potential must agree to use birth control measures during the study and for at least 3 months after receiving the last dose of study agent, and must have a negative pregnancy test at screening period. Men must agree to use birth control measures during the study and for at least 3 months after receiving the last dose of study agent; 6. Informed consent must be signed.

Exclusion Criteria: 1.age under 18 years; 2. ECOG (eastern cooperative oncology group) status above 2; 3. Immunosuppressive or anti-neoplastic drugs within the last 3 months; 4. serious diseases including malignancy; 5. Plan to have babies within 1 year after enrollment (for women and men), or pregnancy / breast-feeding (for women); 6. Known hypersensitivity to study agents; 7. Active infection requiring systemic treatment; 8. Other severe concurrent disease (eg. uncontrolled diabetes, symptomatic coronary heart disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study; 9. Unwilling or unable to provide informed consent; 10. Unwilling to return for follow-up at PUMCH.

Sampling: **A consecutive sample** of eligible and consenting patients will be enrolled into the study. All adult patients with newly diagnosed and previously untreated MCD admitted or transferred to our center would be seen as potential eligible subjects. Symptomatic patients (defined as above) would be interviewed, those who agree to give informed consent to participate the trial would be enrolled. Patients with laboratory abnormalities in the absence of clinical symptoms do not qualify in this study.

Sample size calculation:

Null hypothesis: For newly-diagnosed symptomatic Chinese MCD patients, the response rates of TCP regimens were lower than those of IL-6 targeted treatment.

Alternative hypothesis: For newly-diagnosed symptomatic Chinese MCD patients, the response rates of TCP regimens were not lower than those of IL-6 targeted treatment.

Statistical analysis: Chi-square tests were used for the primary endpoint.

Effect size: as MCD is a rare disease, there is only one randomized controlled trial which evaluates the response rate of IL-6 targeted therapy[2]; according to our experience using TCP regimens for

MCD, the response rate was about 57.1%. With alpha=0.05; beta=0.20 & power=0.80, the sample size was calculated with PASS 2008 software: the estimated sample size was 50 patients (single-arm) which was closed to the sample size of prior randomized controlled trial (n=53). Assuming a lost follow-up rate of 10%, the estimated number of patients enrolled was 55.

Our center now enrolls about 20 newly-diagnosed MCD patients each year which allows us to complete the enrollment within 3-5 years.

Recruitment and Consent: All potential subjects will receive a thorough overview of the study protocol and will review the consent form with study staff. Each potential subject will be advised that a decision not to participate in the study will not affect the quality of care he/she can receive at our center. Each subject will also be advised that he/she can stop participating in the study at any time for any reason, and that this will not impact the services he/she receives.

Retention: Patients will be followed with a regular interval at clinic or during hospitalization. At the time of enrollment, researchers will collect all available contact information from participants including address, home phone, cell phone, email, and contact information for at least 2 relatives or friends. Repeated efforts will be made to contact participants if they do not show up in their regular follow-ups.

Measurements:

Primary predictors (interventions): Group 1 (single-arm study): Thalidomide, Cyclophosphamide and Prednisone (TCP regimen):

-Thalidomide: 100mg QN for 1 year; And maintained with 100mg QN for the second year;

-Cyclophosphamide: 300mg/m^2 on Day 1, 8, 15, 22 every month for 1 year;

-Prednisone: 1mg/kg on Day 1-2, 8-9, 15-16, 22-23 every month for 1 year.

Outcome variables: Patients will undergo a detailed examination at each visits.

Primary Outcome: **Durable tumor and symptomatic response** [2] ,which is assessed by radiologic imaging and disease evaluations, is the primary outcome of this study. Durable tumor and symptomatic response was defined as **one of the following** sustained for at least 24 weeks:

- Complete response (CR): complete disappearance of all measurable and evaluable disease (eg, pleural effusion) and resolution of baseline symptoms attributed to MCD.
- Partial response (PR): a ≥50% decrease in sum of the product of the diameters (SPD) of index lesion(s), with at least stable disease (SD) in all other evaluable disease in the absence of treatment failure.

Note: this outcome is composed of two parts, the tumor response part and the symptom response part, which are listed below:

Tumor response is based on the assessment of index lesions (measurable) and non-index lesions (nonmeasurable). Index lesions: greatest transverse diameter (GTD) ≥ 16 mm, or short axis ≥ 11 mm; non-index lesion: all other lesions which do not meet the above criteria and those which cannot be accurately measured.

- Tumor CR: complete disappearance of all index lesions and evaluable disease (eg, pleural effusion)
- Tumor PR: a ≥ 50% decrease in SPD of index lesion(s), with at least SD in all other evaluable disease
- Tumor SD: failure to attain CR or PR, without evidence of progressive disease (PD)
- Tumor PD: a ≥50% increase in SPD of index lesion(s) compared to nadir, or at least 1 new lesion that has been confirmed and measures > 15 mm in longest dimension. Malignant transformation

in a previously defined mass will also be considered tumor PD.

Symptomatic response: MCD-related Overall Symptom Score [2] will be used to evaluate symptomatic response.

- Durable symptomatic response (partial and complete): Defined as a ≥50% reduction in overall MCD-related Overall Symptom Score sustained for at least 24 weeks prior to **treatment failure**.
- Durable complete symptomatic response: Defined as a 100% reduction in the baseline MCD-related Overall Symptom Score sustained for at least 24 weeks prior to **treatment failure**.

Treatment failure: defined as sustained increase in grade ≥2 disease-related symptoms persisting ≥12 weeks; new disease-related grade ≥3 symptoms; sustained >1 point increase in ECOG-PS persisting for ≥12 weeks; radiological progression; or initiation of another treatment for MCD.

Secondary Outcomes:

Progression-free survival (PFS): defined as the time to tumor PD;

Overall survival (OS): defined as the time to patients' death;

Change in SF-36 score [9]: SF-36 score is a self-administered scoring system which contains several aspects and reflects a patient's general health status.

Safety issues: Adverse events during and after the treatment period would be recorded according to NCI-CTCAE (National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0).

Statistical analysis plan

Analyses will be performed with SPSS 22 (SPSS, Inc, Chicago, IL). The independent samples Student t test (for parameters with normal distribution) and Mann-Whitney test (for parameters that are not normally distributed) will be used for comparison of baseline characteristics between responders and nonresponders. The Wilcoxon signed-rank test will be used to compare parameters before and after the TCP regimen. For patients who are evaluated as treatment failure, the time of treatment failure is considered as the end of treatment. OS and PFS are calculated from the date of treatment. For PFS analyses, death or treatment failure are considered as events. Survival curves will be plotted with the Kaplan-Meier method. $P<0.05$ is considered statistically significant.

Reference:

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