Lenalidomide and dexamethasone for Rosai-Dorfman disease: a single arm, single center, prospective phase 2 study

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eClinicalMedicine
2024;73: 102685
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102685

Summary

Background Rosai-Dorfman disease (RDD) is a rare heterogeneous histiocytic disorder lacking standardized first-line treatment.

Methods This single-center, phase 2 prospective study enrolled 13 newly diagnosed and 10 recurrent RDD patients from June 2021 to March 2023 at Peking Union Medical College Hospital (Beijing, China). Lenalidomide 25 mg days 1–21 plus dexamethasone 40 mg days 1, 8, 15, 22 was administered in 28-day cycles, totaling 12 cycles. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR) to lenalidomide and dexamethasone (RD) regimen, toxicity, and overall survival (OS) measured from RD start to death or last follow-up. OS and PFS were estimated according to Kaplan–Meier survival analysis and compared with the log-rank test. For OS and OR rate, 95% confidence limits were obtained using the Clopper-Pearson method, with standard methods used for PFS. $p < 0.05$ was considered statistically significant. The trial was registered with ClinicalTrials.gov (NCT04924647).

Findings The median age was 44 years (IQR 35–54). All patients had extranodal RDD. MAPK pathway alterations occurred in 6/18 (33%). Elevated IL-6 and TNF-α were found in 39% (n = 9) and 70% (n = 16), respectively. All patients received ≥6 cycles (median 12, range 6–12, IQR 10–12). The ORR was 87% (20/23, 95% CI 66%–97%), 30% (n = 7) complete remission, 57% (n = 13) partial remission). Treatment with RD significantly decreased median serum levels of both IL-6 (from 5.9 (IQR 4.2–8.7) to 2.9 (IQR 2.1–5.9) pg/mL, p = 0.031) and TNF-α (from 12.2 (IQR 8.6–17.9) to 8.3 (IQR 6.1–10.5) pg/mL, p = 0.0012). With a median 26 months follow-up (range 6–28, IQR 16–28), 4 patients relapsed and none died. Two-year OS and PFS were 100.0% (95% CI 85%–100%) and 69.0% (95% CI 51%–94%), respectively. No grade 3–4 adverse events or discontinuations due to adverse events occurred. Twelve patients (n = 12, 52%) had grade 1–2 hematological toxicity. Other toxicities included constipation (n = 2, 9%), glucose intolerance (n = 2, 9%), edema (n = 2, 9%), insomnia (n = 1, 4%), and tremor (n = 1, 4%).

Interpretation Lenalidomide and dexamethasone regimen is an effective and safe regimen for newly diagnosed and recurrent RDD.

Funding National Natural Science Foundation of China, Beijing Natural Science Haidian frontier Foundation Funding, and the National High Level Hospital Clinical Research Funding.

Keywords: Rosai-Dorfman disease; Treatment; Lenalidomide; Dexamethasone

Introduction

Rosai-Dorfman Disease (RDD) is a rare, heterogeneous histiocytic disorder that remains poorly characterized.[1] The natural history can be variable–some patients with single system disease are asymptomatic with an indolent course, while others have aggressive multisystem disease requiring systemic therapy. Corticosteroids, immunomodulatory drugs (IMiDs), purine analogs,

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Research in context

Evidence before this study

We searched PubMed using the terms "Rosai-Dorfman Disease" [medical subject heading terms] AND "treatment" [title/abstract] for papers published in English between January 1, 2000 and September 30, 2023. We excluded review articles and case reports. We did not identify any prospective studies. One retrospective study showed MEK inhibitors had an 88% overall response rate in RDD patients with MAPK alterations, but only 38% in those without. We concluded that a major unmet need existed for prospective studies for RDD.

Added value of this study

To our knowledge, this study is the first prospective therapeutic trial in Rosai-Dorfman Disease. Our study showed lenalidomide and dexamethasone regimen is highly effective in newly diagnosed and recurrent RDD, with acceptable toxicity. The overall response rate was 87%, and the 2-year overall survival and progression-free survival were 100% and 69.0%, respectively.

Implications of all the available evidence

The available evidence suggests that lenalidomide plus dexamethasone may provide disease control in RDD patients. The current study further supports these observations. The data from this study are potentially practice-changing for management of RDD patients.

chemotherapy and targeted agents have been used with variable efficacy.[2] However, no standard treatment exists owing to the lack of prospective clinical trial data.

Recent studies have identified mutations in mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway genes in RDD patients.[3] Small retrospective analyses have demonstrated variable response rates to MEK inhibitors such as cobimetinib and trametinib.[4,5] However, patients without MAPK pathway alterations generally exhibited poorer responses.

Prior studies have demonstrated elevated levels of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) in RDD, with strong macrophage colony-stimulating factor (M-CSF) expression in RDD cells, implicating aberrant immune-mediated processes.[6] IMiDs like thalidomide and lenalidomide reduce TNF-α and IL-6 and are widely used to treat plasma cell diseases.[7] We previously showed IMiDs combined with dexamethasone were effective in treating relapsed/refractory Langerhans cell histiocytosis in adult patients.[8] More recently, lenalidomide has demonstrated excellent responses in cases of multifocal recurrent RDD.[9,10] However, reports on lenalidomide for RDD remain limited. Therefore, it is imperative to define the outcomes of lenalidomide-based regimens in a prospective study of RDD patients.

This phase 2, prospective, single-center study was designed to evaluate the efficacy and safety of a lenalidomide and dexamethasone (RD) regimen in adult patients with newly diagnosed or relapsed/refractory RDD.

Methods

Study design and participants

This single-center, single-arm, phase 2 study was conducted at Peking Union Medical College Hospital (Beijing, China), recruiting patients nationally. Eligible patients were ≥18 years with 1) histological diagnosis of RDD per World Health Organization criteria,[1] confirmed by two independent pathologists; 2) Eastern Cooperative Oncology Group performance status 0–2; and 3) newly diagnosed or recurrent/refractory RDD. Adequate renal, hepatic, and bone marrow function was required, defined as absolute neutrophil count ≥1500/mm^3, platelets ≥100,000/mm^3, creatinine clearance ≥60 mL/min (Cockcroft formula), aspartate/alanine aminotransferases ≤2.5× upper limit of normal (ULN), and total bilirubin ≤2.5× ULN or ≤10× ULN with known liver involvement. Exclusion criteria were: concurrent malignancies, uncontrolled cardiovascular disease, and pregnant/breastfeeding women.

RDD was classified as unifocal (single lesion), single-system multifocal (>1 lesion in one organ), or multi-system (MS, >1 organ/system involved).[3]

Ethics statement

Informed consent was obtained from all patients, and the protocol was approved by the Peking Union Medical College Hospital Ethics Committee. This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Procedures

Patients received oral lenalidomide 25 mg on days 1–21 and dexamethasone 40 mg on days 1, 8, 15, 22, in 28-day cycles for 12 total cycles. All patients received aspirin thromboprophylaxis during RD treatment. Supportive care including antibiotics, platelet transfusions, and granulocyte colony-stimulating factor (G-CSF) prophylaxis was provided if needed. Treatment was discontinued for disease progression, unacceptable toxicity, withdrawal of consent, or investigator-determined lack of further benefit.

Patients underwent monitoring during treatment for adverse events and safety assessments including complete blood counts and chemistries. Toxicities were recorded and graded using National Cancer Institute

Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Safety data collection continued for 30 days after the final RD cycle, except for secondary primary malignancies which were captured throughout follow-up. Secondary primary malignancies were defined as any new malignancy diagnosed after initiation of RD therapy.

Clinical evaluation and imaging were performed after cycles 6 and 12 of RD, then every 6 months thereafter for disease assessment. Imaging modalities included 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), thoracic and abdominal computed tomography (CT), and cerebral magnetic resonance imaging (MRI). Treatment response was evaluated using PET Response Criteria in Solid Tumors (PERCIST 1.0). The overall response rate (ORR) was defined as the cumulative proportion of patients attaining either a complete response (CR) or partial response (PR) following RD therapy.

Outcomes

The primary endpoint was progression-free survival (PFS) defined as the time from RD initiation to first documented disease progression, relapse after RD, death from any cause, or last follow-up. Secondary endpoints were ORR to RD, toxicity, and overall survival (OS) measured from RD start to death or last follow-up. The final follow-up was October 1, 2023.

Laboratory tests

In patients with available samples, next-generation sequencing (NGS) of 183 genes was performed as previously described.[10] Cereblon immunohistochemical staining was done on diagnostic tissue specimens as described in prior studies.[11] Serum level of the cytokines interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α were measured by the electrochemiluminescence immunoassay (SIEMENS Immulite 1000).

Statistical analysis

This exploratory trial aimed to provide response and toxicity estimates rather than formal hypothesis testing. A sample size of 20 was deemed adequate for this purpose. In practice, some patients were in the process of being enrolled when 20 patients were reached, and there was an overshoot to 23 patients. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Clinical and molecular data were analysed using descriptive statistics. Continuous variables were summarised as medians and IQRs, categorical variables as frequencies and proportions. The p-value from Fisher's exact one-tailed test was doubled to obtain two-tailed tests used for the comparison of treatment response. The pre- and post-therapy serum cytokine levels were compared using Wilcoxon signed rank test for paired samples. OS and PFS were estimated according to Kaplan–Meier survival analysis and compared with the log-rank test. For OS and OR rate, 95% confidence limits were obtained using the Clopper-Pearson method, with standard methods used for PFS. $p < 0.05$ was considered statistically significant. This study is registered at ClinicalTrials.gov, number NCT04924647.

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis or writing of the report. The corresponding author had full access to all data in the study and had full responsibility for the decision to submit for publication.

Results

From June 2021 to March 2023, 13 newly diagnosed and 10 recurrent RDD patients were included. The baseline characteristics of the 23 patients are summarized in Table 1. The median age was 44 years (IQR 35–54

Characteristic	N = 23
Age, years (median, IQR)	44 (35–54)
Age >60, n (%)	3 (13%)
Male sex, n (%)	15 (65%)
Newly diagnosed, n (%)	13 (57%)
Extranodal RDD, n (%)	23 (100%)
Unifocal	2 (9%)
Single-system multifocal	3 (13%)
Multisystem	18 (78%)
Organs involved, n (%)	
Subcutaneous tissue	12 (52%)
Bone	11 (48%)
Sinus	9 (39%)
Laryngopharynx	9 (39%)
Lymph node	8 (35%)
Central nerve system	4 (17%)
Gland[a]	4 (17%)
Orbit	3 (13%)
Kidney	3 (13%)
Heart and major vessels	2 (9%)
Muscle	2 (9%)
Lung	1 (4%)
Inflammatory markers	
IL-6, pg/mL (median, IQR)/Elevated, n (%)	5.3 (3.2–8.9)/9 (39%)
IL-8, pg/mL (median, IQR)/Elevated, n (%)	12.2 (10.3–38.3)/1 (4%)
IL-10, pg/mL (median, IQR)/Elevated, n (%)	5.0 (3.1–11.4)/1 (4%)
CRP, mg/L (median, IQR)/Elevated, n (%)	6.0 (2.1–12.3)/8 (35%)
TNF-α, pg/mL (median, IQR)/Elevated, n (%)	9.3 (8.0–15.1)/16 (70%)

IQR, interquartile range; RDD, Rosai-Dorfman disease; IL, interleukin; CRP, C reactive protein; TNF, tumor necrosis factor. [a]Gland refers to the parotid gland in 3 patients and the thyroid gland in 1 patient.

Tabel 1: **Characteristics of the 23 Rosai-Dorfman disease patients at the time of initiation of Lenalidomide and dexamethasone therapy.**

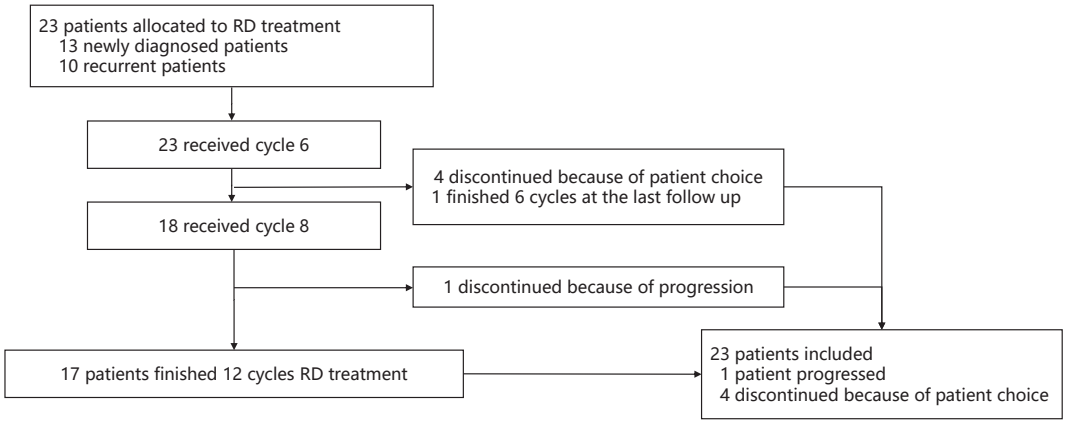

Fig. 1: **Study diagram of 23 patients administrated the lenalidomide and dexamethasone regimen. RD, lenalidomide and dexamethasone**.

years), 65% (n = 15) were male. The median duration from symptom onset to diagnosis was 8 months (range 1–101, IQR 4–35). All had extranodal disease (2 unifocal, 3 single-system multifocal, 18 MS). Median number of involved organs was 3 (range 1–7, IQR 2–5). The most common involved sites were subcutaneous tissue (n = 12, 52%), bone (n = 11, 48%), sinus (n = 9, 39%), laryngopharynx (n = 9, 39%), lymph nodes (n = 8, 35%), central nervous system (CNS, n = 4, 17%), gland (n = 4, 17%, parotid gland in 3 patients and the thyroid gland in 1 patient), orbit (n = 3, 13%), and kidney (n = 3, 13%). Among the four patients with CNS involvement, two patients present as intracranial mass proximal meninges (1 in occipital lobe, 1 in parietal lobe), one presents as a sellar mass and one presents as masses in parietal lobe and medulla oblongata region. Eleven patients had bone involvement. Among them, long bones and metaphyseal involvement were found in only 2 of them. Both of these patients present as osteolytic lesions rather than osteosclerosis which is usually found in Erdheim-Chester disease (ECD). Among three patients who had kidney involvement, two presented as multiple masses with soft tissue density in the kidney and one presented as multiple peri-kidney stripes. Elevated C reactive protein (CRP, normal range < 3 mg/L, median 6.04 mg/L, IQR 2.1–12.3) occurred in 8 patients (35%). Nine patients (39%) had elevated IL-6 levels (normal range < 6.5 pg/mL), with a median level of 5.3 pg/mL (IQR 3.2–8.9). Sixteen patients (70%) had elevated TNF-α levels (normal range < 8.1 pg/mL), with a median level of 9.3 pg/mL (IQR 8.0–15.1). Among 10 patients who received RD in the subsequent therapy, the median prior lines of therapy were 2 (range 1–3, IQR 1–2), including corticosteroids (n = 4), surgery (n = 4), chemotherapy (n = 3), and thalidomide (n = 2).

In total, 17 patients (74%) completed the protocol, 1 ongoing after 6 cycles, while 5 (22%) went off protocol due to patient decision (n = 4) or disease progression (n = 1) (Fig. 1). All patients received at least 6 courses of RD therapy, with a median number of RD regimen cycles being 12 (range 6–12, IQR 10–12).

Among 18 patients undergoing NGS, 18 single nucleotide variations, insertions and deletions were detected in 10 (56%), with a median of 1 somatic mutation per patient across candidate genes (range 0–5, IQR 0–2). The most common aberrations were KRAS (n = 3, 17%), BRAF (n = 2, 11%), and MAP2K1 (n = 2, 11%). Two *BRAF* non-V600 alterations, p. Y472C and p. Q366X, were identified. MAPK pathway alterations occurred in 6 (33%). Detailed genomic profiles are displayed in Table S1.

Each patient had PET-CT scan at baseline and after therapy for evaluation. Everyone had at least one PET-evaluable lesion according to PERCIST 1.0. The ORR was 87% (20/23, 95% CI 66%–97%), with 7 patients (30%) achieving a CR, 13 patients (57%) achieving a PR and three patients (13%) had stable disease (SD) for best response. Response dynamics and survival are shown in Fig. 2 and Table S2. Four patients who had CNS involvement presented as intracranial hypermetabolic PET evaluable mass by PERCIST 1.0. According to the CNS lesion, 2 had CR, 1 had PR and 1 had SD. For these patients, we also evaluated the response by MRI using RECTST 1.1, which was consistent with PERCIST 1.0. One patient with heart involvement had PR. ORR was non-significantly higher in newly diagnosed patients vs recurrent patients (100% (13/13) vs 70% (7/10), p = 0.14). And CR rates were similar, 38% (5/13) in newly diagnosed patients and 20% (2/10) in recurrent patients (p = 0.63). Five of ten recurrent patients were treated with steroids. The ORR in these patients was 80% and 60% in patients who never got steroids, without significant difference. Two patients who were exposed to thalidomide as prior therapy had PR on RD. ORR was 100% (6/6) in patients with MAPK pathway alterations and 83% (10/12) in others. ORR did not

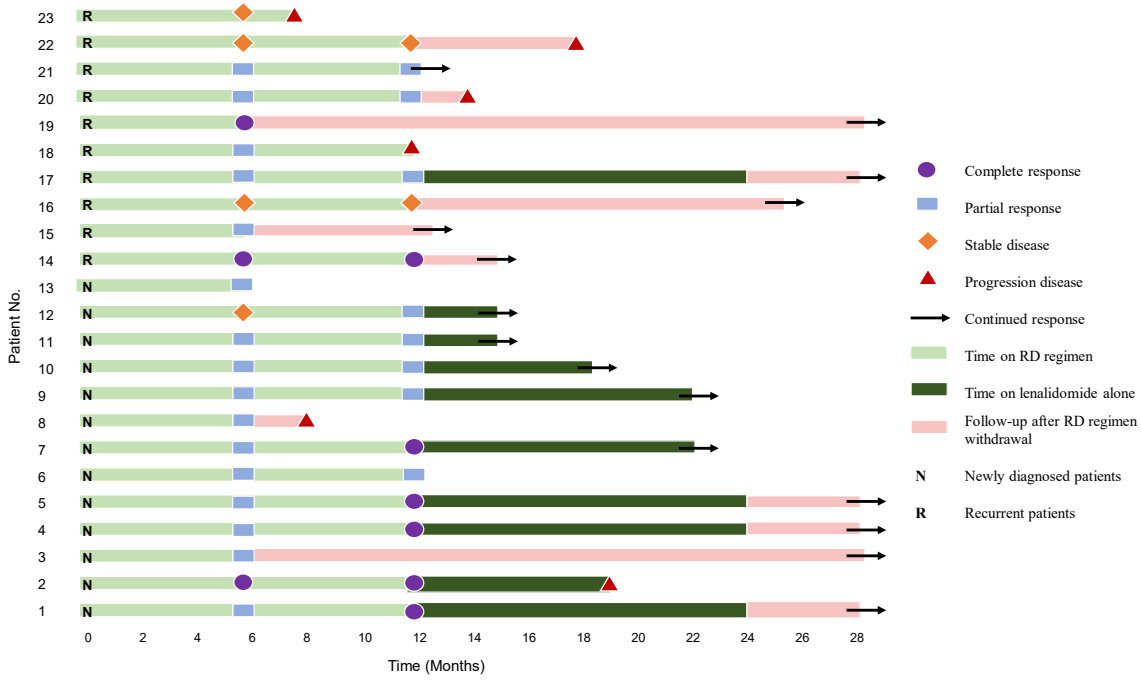

Fig. 2: **Swimmer plot showing duration of treatment and best tumor response achieved for each of 23 patients receiving the lenalidomide and dexamethasone regimen. RD, lenalidomide and dexamethasone.**

differ significantly by organ involvement. A variety of RDD imaging findings was shown in Figure S1.

Treatment with RD significantly decreased median serum levels of both IL-6 (from 5.9 (IQR 4.2–8.7) to 2.9 (IQR 2.1–5.9) pg/mL, p = 0.031) and TNF-α (from 12.2 (IQR 8.6–17.9) to 8.3 (IQR 6.1–10.5) pg/mL, p = 0.0012) in RDD patients (Figure S2). There was not any significant difference in ORR based on high or low CRP/TNF-a/IL-6 levels.

After a median 26 months follow-up (range 6–28, IQR 16–28), 6 patients (26%) had disease progression (PD), including 4 reactivated after the initial response (3 PR, 1 CR) and 2 were refractory (1 had SD after 6 cycles and progressed after 8 cycles then went off the protocol, 1 had SD after 12 cycles and progressed 6 months after RD withdrawal. Besides, one patient had ongoing SD and did not progress. Therefore, 3 patients had refractory disease in total. The median duration of response was not reached as 15 responders have ongoing responses. Progressions were limited to single sites–1 subcutaneous, 2 laryngopharyngeal, 1 sinus, and 2 CNS. Salvage treatments included surgery (n = 2), targeted therapy (n = 2), and chemotherapy (n = 2), with no deaths observed. Two-year OS and PFS were 100.0%

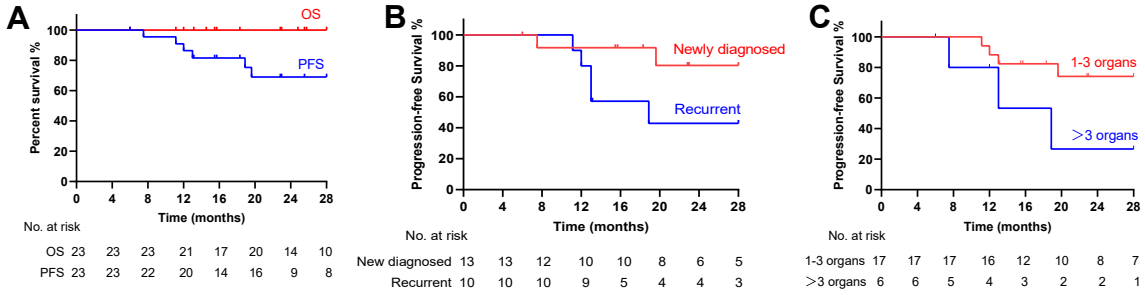

Fig. 3: **(A) Overall survival and progression-free survival (PFS) of 23 patients administered the lenalidomide and dexamethasone regimen. PFS according to newly diagnosed patients and recurrent patients (B) numbers of organ involvement at baseline (C). OS, overall survival; PFS, progression-free survival.**

(95% CI 85%–100%) and 69.0% (95% CI 51%–94%), respectively (Fig. 3A). Univariate prognostic analyses for PFS showed newly diagnosed patients tended to have better PFS than recurrent (not reached vs 18.9 months, p = 0.078) (Fig. 3B), and those with 1–3 involved organs tended to have better PFS than >3 organs (not reached vs 18.9 months, p = 0.069) (Fig. 3C). No significant PFS differences were seen based on specific organ involvement, high or low CRP/TNF-a/IL-6 levels or MAPK alterations.

The most common non-hematologic adverse events were rash (n = 6, 26%), fatigue (n = 5, 22%), and anorexia (n = 4, 17%). Other toxicities included constipation (n = 2, 9%), glucose intolerance (n = 2, 9%), edema (n = 2, 9%), insomnia (n = 1, 4%), and tremor (n = 1, 4%). All the toxicities were managed successfully with supportive care. Hematologic toxicity occurred in 12 (52%), including grade 2 neutropenia in 2 (9%) and grade 1 in 8 (35%). Grade 1 anemia and thrombocytopenia occurred in 2 (9%) each. Neutropenia led to dose reduction in 1 patient. No prophylactic antimicrobials, transfusions, or febrile neutropenia occurred. There were no grade 3–4 events or treatment discontinuations due to toxicity. Adverse events are summarized in Table 2. No secondary primary malignancies were observed during the follow-up period.

Immunohistochemical staining for cereblon was performed on available samples from 5 patients. All 5 patients showed CRBN expression, with 4 patients (80%) achieving CR or PR after RD treatment and 1 patient having SD (Figure S2).

Parameter	N = 23
Efficacy of best response	
Complete response rate	7 (30%)
Partial response rate	13 (57%)
Stable disease	3 (13%)
Safety	
Non-hematological toxicity	
Fatigue	
Grade 1	5 (22%)
Rash	
Grade 1	5 (22%)
Grade 2	1 (4%)
Anorexia	
Grade 1	4 (17%)
Constipation	
Grade 1	2 (9%)
Insomnia	
Grade 2	1 (4%)
Tremor	
Grade 1	1 (4%)
Edema	
Grade 1	2 (9%)
Glucose intolerance	
Grade 1	1 (4%)
Grade 2	1 (4%)
Hematological toxicity	
Neutropenia	
Grade 1	8 (35%)
Grade 2	2 (9%)
Anemia	
Grade 1	2 (9%)
Thrombocytopenia	
Grade 1	2 (9%)

Table 2: **Outcomes and side effects of adult patients with Rosai-Dorfman disease treated with Lenalidomide and dexamethasone therapy.**

Discussion

To our knowledge, this is the first prospective phase 2 study in RDD patients. Most prior data is from small retrospective case series given the rarity and heterogeneity of RDD. Reports on recurrent disease treatment are even more limited. Initial therapy selection is largely guided by clinical presentation. Surgery can be curative for some isolated cases but about 30% of patients relapse.[12] Systemic therapy should be considered for multisystem disease. Cladribine has shown efficacy in case reports and series, as has prednisone combined with other immunosuppressants or anti-CD20.[12] We previously reported durable remission with thalidomide in 3 refractory laryngeal RDD cases.[13] Lenalidomide induced excellent response in recurrent RDD cases, appearing better tolerated than thalidomide with less rash and neuropathy despite more myelosuppression.[10,14]

In this study, we demonstrate the efficacy and safety of RD in newly diagnosed and recurrent/refractory RDD, with 100% ORR in newly diagnosed and 70.0% in recurrent disease which was higher than reported for prednisone or cladribine monotherapy. Our prior retrospective analysis found 76.9% and 90% ORR for prednisone alone and chemotherapy in newly diagnosed RDD but with a high relapse rate.[3] Nearly 70% maintained response after 2 years follow-up without deaths observed in the current study. We also identified >3 involved organs and recurrent disease as potential PFS risk factors warranting further evaluation in larger cohorts. Here, we also found RD regimen was effective in two patients who were exposed to thalidomide in prior therapy, suggesting that lenalidomide may be more efficient than thalidomide.

Recent studies have identified MAPK/ERK pathway mutations in RDD, suggesting clonal histiocytic proliferation.[15] No genotype–phenotype correlation was observed. Retrospective data showed MEK inhibitors had 88% ORR in RDD patients with MAPK alterations, but only 38% in those without.[5] Although ECD overlaps with RDD has been reported before,[16] typical

manifestations of ECD (long-bone osteosclerosis, coated large vessels, interstitial lung disease and retroperitoneal infiltration) and BRAFV600E, the most common alteration in LCH and ECD, were not detected in this study. Here, over 75% underwent NGS, revealing MAPK pathway mutations in one third of patients. ORR was 100% in those with and 83% without MAPK alterations without significant difference. Thus, 12-month RD provides an attractive limited treatment achieving durable remissions while avoiding long-term targeted therapy exposure, especially for those without MAPK abnormalities.

IMiDs have diverse mechanisms including inhibition of angiogenesis inhibition, anti-inflammatory effects, reduced cell–cell interactions, osteoclast growth reduction and activating proapoptotic signals. Previous studies proposed lenalidomide decreases TNF-α and IL-6 expression, and the decrease is augmented by dexamethasone.[7] In this study, nearly 40% and 70% of patients had elevated baseline IL-6 and TNF-α, respectively, with significant decreases in both cytokines after RD treatment. Cereblon, part of an E3 ubiquitin ligase complex, and a direct IMiDs target, mediates proapoptotic, antiproliferative, antiangiogenic, and immunomodulatory effects.[17,18] To further investigate the high ORR, cereblon immunohistochemistry performed on tissues from 5 RDD patients, revealed cereblon expression in all diseased samples. Further studies are needed to clarify the precise mechanism and relationship between cereblon expression, clinical response and survival.

The RD regimen demonstrated a favorable safety profile in newly diagnosed and recurrent RDD. No grade ≥3 adverse events occurred, with no severe infections or bleeding observed. Thrombosis, a common IMiDs toxicity, was prevented with antiplatelet prophylaxis. The oral administration facilitated adherence and avoided hospitalization. At $500 monthly cost, RD is also far more affordable and accessible than MEK inhibitors like trametinib, particularly for patients in developing countries.

This single-center trial in a single ethnic population has limitations including referral bias. However, national referrals were required given the rarity of adult RDD. The lack of a control arm limits comparative effectiveness assessments, although randomization is difficult without an established first-line standard. Disentangling the individual contributions of each medication of RD is difficult given the study design. The follow-up duration may be insufficient to capture late relapses, so extended observations are needed to determine durability of benefit. Despite limitations, this prospective study provides valuable evidence for RD in RDD, but larger collaborative trials are warranted to definitively establish efficacy.

In summary, this study shows that the lenalidomide and dexamethasone treatment may provide a novel effective and safe option for both newly diagnosed and recurrent RDD patients.

Contributors

LC and ML contributed to data analysis and patient follow-up; TL, HC and DBZ retrospectively reviewed patient records; HL and ZZL contributed to data collection; LC and XXC wrote the paper; and all authors revised the paper and approved the submitted version.

Data sharing statement

Individual participant data will not be available. The study protocol will be available beginning 9 months and ending 36 months following article publication at caoxinxin@126.com.

Declaration of interests

The authors declare that they have no competing interests.

Acknowledgements

The authors thank all the patients and their families for their trust, respect and support. They also acknowledge all clinicians for their help in accomplishing this work. This study was supported by National Natural Science Foundation of China (Grant No. 82370179), Beijing Natural Science Haidian frontier Foundation (L222081) and the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-046).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102685.

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