Compound Zhebei granules combined with chemotherapy for the treatment of refractory acute leukemia: a randomized clinical trial

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Abstract

OBJECTIVE: To observe the effect of compound Zhebei granules (CZBG) with chemotherapy in the treatment of refractory acute leukemia.

METHODS: In this multicenter, double-blind, placebo-controlled clinical trial, we used a central (online) randomization system to assign 235 patients to two treatment groups. A total of 118 patients received chemotherapy combined with CZBG (4 g, twice daily) and 117 patients received chemotherapy plus placebo. The clinical efficacy was evaluated at the end of one chemotherapeutic cycle.

RESULTS: In the full analysis set, in which deaths due to disease progression were regarded as inefficacy, the rates of complete remission (CR) and partial remission (CR + PR) were 32.35% and 50.00%, respectively, for the chemotherapy combined with CZBG group, and 23.08% and 35.58%, respectively, for the chemotherapy plus placebo group. There was a statistically significant difference between the two groups according to a $\chi^2$ test ($P < 0.05$). In the per protocol analysis set (PPS), the CR (33.67%), CR + PR (52.04%) response rates for the chemotherapy plus CZBG group were significantly different from the response rates of the control group (CR: 24.24% and CR + PR: 37.37%), respectively ($P < 0.05$).

CONCLUSION: CZBG plus chemotherapy can improve the clinical remission rate of refractory acute leukemia after one just one therapeutic cycle.

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Key words: Refractory acute leukemia; Zhebei
granules; Chemotherapy remission rate; Randomized clinical trial

INTRODUCTION

Acute leukemia (AL) is a hematologic malignancy that is a serious hazard to health. Currently, chemotherapy remains the most important therapeutic option for AL, but 30% of patients do not respond to treatment. In addition, 40%-60% of patients become unresponsive to treatment after relapse, and are subsequently reassessed as having refractory acute leukemia (RAL). RAL has short overall survival and is a challenge in the treatment of AL. As such, developing new methods to improve the chemotherapy remission rate of RAL remains of the utmost importance.

Traditional Chinese Medicine has been used for thousands of years to treat or prevent diseases, including cancer. In recent years, it has been shown that some herbal products display anticancer properties. Compound Zhebei granules (CZBG) are an herbal medicine prepared from three herbs: Zhebeimu (Bulbus Fritillariae Thunbergii), Fangji (Radix Stephaniae Tetrandrae), and Chuanxiong (Rhizoma Chuanxiong). Previously, using in vivo and in vitro models we have shown that multidrug resistance (MDR) of leukemic cells can be reversed. The mechanism of action of CZBG is through induction of apoptosis and the inhibition of resistance-associated enzymes and drug resistance-associated membrane protein expression.

In this study, we designed a randomized, multicenter, double-blind, placebo-controlled clinical trial under good clinical practice guidelines to study the effect of CZBG plus chemotherapy on the remission rate of patients with RAL.

MATERIALS AND METHODS

Patients

The study participants were inpatients between May 2007 and December 2009 at Dongzhimen Hospital, which is affiliated with the Beijing University of Chinese Medicine, the Xiyuan Hospital, which is affiliated with the China Academy of Chinese Medical Sciences, the first affiliated hospital of Tianjin University of Traditional Chinese Medicine, the Langfang Chinese Medicine Hospital which is affiliated with Hebei Medical University, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, the Chinese Medicine Hospital of Zhejiang Province, and the First Affiliated Hospital of the Heilongjiang University of Chinese Medicine. The trial was approved by the ethics committee of all the aforementioned hospitals, and informed consent was obtained from all patients (WHOICT-Clinical trial registration number: ChiCTR-00000410). A flowchart of the clinical trial is included at appendix 1.

Diagnosis criteria

The AL diagnostic criteria were based on the 1987 National Hematology Conference of Chinese Medical Association. These criteria include: (a) acute onset, fever, anemia, progressive bleeding, which is accompanied by tenderness of the sternum, swollen lymph nodes, hepatomegaly or splenomegaly. (b) A dramatic decrease in hemoglobin and platelet levels with leukemia cells in the peripheral blood which account for more than 30% of complete blood cells. (c) Extremely active bone marrow proliferation most of which were leukemia cells, blasts took at least 30% of bone marrow, and reduced levels of red blood cells and megakaryocytes. (d) The classification of leukemia was determined according to cell morphology, cytochemical staining, and immunological tests (subtype classification relied on "Diagnosis and standardization of response criteria for blood disease" edited by Zhang Zhi at 19)). The three subtypes of acute lymphoblastic leukemia (ALL) included: L1, L2, and L3, while the seven subtypes of acute myelocytic leukemia (AML) were: M0, M1, M2, M4, M5, M6, and M7. The RAL diagnostic criteria was based on the draft diagnostic criteria of the RAL proposal of the Second National Refractory Leukemia Workshop, held in October 1999 (the Fuzhou meeting). These criteria included: (a) Failure of the patient to obtain complete remission (CR) after two cycles of standard induction chemotherapy; (b) the patient relapsed during consolidation therapy after achieving CR during induction therapy; (c) their disease transformed from blast crisis of chronic myelogenous leukemia or from myelodysplastic syndrome; (d) the patient was diagnosed with heterozygous (hybrid) leukemia or leukemia with no less than two kinds of abnormal antigen expression that failed to obtain CR after one cycle of standard chemotherapy; or (e) their peripheral white blood cell count was > 100.0 × 10^3/L.

Inclusion criteria

To be eligible for the trial the patients were required to meet three inclusion criteria: (a) the patients met the diagnostic criteria of AL and any one condition of RAL; (b) the patients signed the informed consent form; and (c) the patients had not been treated within the previous month before the trial began with any other traditional Chinese or modern medicine.

Ineligibility criteria

Patients were excluded from the trial if they presented with any one of the following: (a) any coexisting medical condition including severe heart, brain, liver, or kidney disease; (b) mental illness; (c) glaucoma; (d) for female patients, pregnancy or currently lactating; (e) an allergy to any herbs within the CZBG formula; and (f) under 10 years of age or older than 80.

Exclusion criteria

Further exclusion criteria included: (a) the patient was unable to meet the inclusion criteria during any stage
of the trial; (b) they were unable to complete one cycle of chemotherapy; (c) the patient required a change in their treatment plan because of serious adverse events, severe complications, or disease progression.

**Response criteria**

After one cycle of treatment, clinical efficacy and safety evaluation data were collected. The response criteria were based, with modifications, on the Standard of National Leukemia Chemotherapy Symposium held by the Professional Committee of the Chinese Medical Association of Hematology in Suzhou, Jiangsu Province, in November 1987. Complete Remission (CR): (a) Bone marrow: myeloblast cell type I + II (or monoblast or lymphoblast) ≤ 5%, with normal red blood cell and megakaryocyte counts. For M2b, myeloblast I + II ≤ 5% of the neutrophil proportion in the normal range. For M4, myeloblast I + II monoblast ≤ 5%; for M6, myeloblast I + II ≤ 5% with a generally normal ratio of erythroblasts and erythrocytes, and for M7, a normal ratio of red cells and granulocytes with an absence of megakaryoblasts. (b) Blood count: hemoglobin (HGB) ≥ 1.0 × 10^9/L, platelets ≥ 100 × 10^9/L, and no leukemic cells in the peripheral blood. (c) Clinical manifestations: no signs and symptoms of tissue infiltration, and the patient could lead a normal, or near normal, life.

Morphological complete remission with abnormal blood count (CRi): Morphology of their bone marrow met the CR criteria, but with persistent neutropenia (< 1.0 × 10^9/L) or thrombocytopenia (< 100 × 10^9/L).

Partial Remission (PR): Myeloblast cell type I + II (or monoblast or lymphoblast) > 5% and ≤ 20%, clinical manifestations, or blood count that did not reach the CR standards.

No Remission (NR): Bone marrow morphology, blood count and clinical manifestations all failed to meet the criteria noted above.

**Randomization and blinding**

The randomization process was undertaken using the Central Randomization System of the China Academy of Chinese Medical Sciences. Randomized numbers were accessed via telephone or internet before each clinical trial center recruited their eligible patients. Patients were then assigned to either the CZBG plus chemotherapy group or the chemotherapy plus placebo group according to the randomized number of their drugs. All the participants, care providers, and outcome assessors were blinded throughout the trial.

**Treatment**

The chemotherapy regimens were determined based on results from previous clinical trials and the consensus of principal investigators from all clinical trial centers. One cycle of vincristine, daunorubicin, cyclophosphamide (VDC)/L-asparaginase, dexamethasone (LD), methotrexate, oncovin, L-asparaginase, dexamethasone (MOAD) or mesna, ifosfamide, novantrone, etoposide (MINE) was administrated to the ALL patients, while homoharringtonine, Ara-C, etoposide (HAE), mesna, Ara-C, etoposide (MAE) or cytarabine, aclacinubicin, granulocyte colony-stimulating factor (CAG) was administered to the AML patients. Patients were given CZBG (1 × 4 g bag, twice daily) or a placebo, which was started three days before chemotherapy was commenced, then given for 14 consecutive days. The placebo was designed to be exactly the same as CZBG with regards to its packaging, size, appearance, color, taste, smell, and dosage form.

Configuration method of CZBG: the daily dosage of each herb was: Zhebeimu (Bulbus Fritillariae Thunbergii) 12 g, Fangji (Radix Stephaniae Tetrandrae) 12 g, Chuanxiong (Rhizoma Chuanxiong), 6 g (all referring to the weight of original herbal pieces prepared for making the decoction). The herbal medicine ratios used for the preparation of the granules were: Zhebeimu (Bulbus Fritillariae Thunbergii) 5 : 1, Fangji (Radix Stephaniae Tetrandrae) 3.3 : 1, and Chuanxiong (Rhizoma Chuanxiong) 2.9 : 1.

The granules were prepared using the following method. The herbs were boiled in water for 2 h: 5 kg of Zhebeimu pieces (Fritillaria thunbergii Miq) in 40 L of water, 3.3 kg of Fangji pieces (Radix Stephaniae Tetrandrae) in 26.4 L of water, and 2.9 kg of Chuanxiong (Rhizoma Chuanxiong) in 19.8 L of water. The solutions were then filtered to collect the solid residues before more water was added (40 L, 26.4 L, and 19.8 L, respectively), the solutions boiled again for 1.5 h, before the solutions were filtered a second time. The filtrates from the two processes were mixed together and concentrated to produce granules. The relative daily amounts of each granule type were then weighed and mixed according to the prescribed dosage: Zhebeimu (Bulbus Fritillariae thunbergii) 2.4 g, Fangji (Radix Stephaniae Tetrandrae) 3.6 g and Chuanxiong (Rhizoma Chuanxiong) 2.0 g. This daily dose was packed into two bags, 4 g each, ready for serving. The CBZG was provided by Beijing Tcmages Pharmaceutical Co., Ltd.,

**Supportive measures**

The supportive measures for the patients included: using antibiotics from the same category and the same generation for infection or fever; red blood cell transfusion for patients with hemoglobin levels < 60 g/L or platelet levels < 30 × 10^9 g/L; and G-CSF for patients with a white blood cell count < 2.0 × 10^9 g/L. No other herbal decoction or Chinese medicine was given during the trial, nor was any other medication with a demonstrable reversal effect on multidrug resistance allowed during the study.

**Statistical analysis**

The trial data were processed using SAS (version 9.1.3,
SAS Institute, Beijing, China). Rank sum tests were used to compare the response rates between the two groups, while χ² tests were used to control the multicenter effect when determining the chemotherapy efficacy. All statistical analyses were two-sided tests. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Clinical data
Patient Characteristics: between May 2007 and December 2009, 269 patients were diagnosed with RAL after screening from seven first-level, first-grade Chinese hospitals; a total of 238 patients were enrolled in our study. Three patients were excluded before the trial: one patient did not meet the age criteria (82 years old), one was missing baseline data, and another withdrew their consent. In total, 21 patients were excluded after the trial began due to: loss during follow up, leaving the clinical trial, seriously lacking baseline data, and refusing to provide clinical evidence for efficacy evaluation. During the trial there were 20 deaths, eight of which had clinical evidence of disease progression (elevated leukemia cells in peripheral blood count), while the other 12 died of complications during treatment. In accordance with the statistical analysis plan, 235 patients entered the full analysis set (FAS) with 118 in the chemotherapy with CZBG group (treatment group) and 117 in chemotherapy plus placebo group (control group). There were 197 patients entered in the per protocol analysis set (PPS) with 98 patients in the treatment group and 99 in the control group (Figure 1). There were nine deaths in the treatment group, and 11 in the control group. None of the deaths were related to treatment with CZBG, and there was no significant difference of in the number of deaths between the two groups. The relative information for the patients is given in Table 1. A comparison of two groups’ baseline information showed that there was no statistical significance with regard to sex (P = 0.6511), age (P = 0.57), type of AL (P = 0.784), etiological classification of RAL (P = 0.743) or chemotherapy regimen (P > 0.05) (Table 2).

Clinical efficacy
As was shown in Tables 3 and 4, the FAS and PPS CR rates of the treatment (32.35%, n = 33 for FAS;
The main active ingredients of CZBG are peimine, tetrandrine, and tetramethylpyrazine. Our previous research showed that CZBG-containing serum can inhibit the proliferation of L1210/CDDP cells, inhibit the efflux of anticancer drugs from K562/A02 cells, and induce apoptosis of K562/A02 cells, and in- it the proliferation of L1210/CDDP cells, inhibit the expression of resistance-associated enzymes (e.g. GSH, TopoII) and membrane proteins (e.g. P-gp, MRP) of K562/A02 xenograft tumor tissue. Moreover, both the FAS and PPS CR + PR rates were significantly higher (P = 0.0328 for FAS and P = 0.038 for PPS) in the treatment group (50.00%, n = 51 for FAS; 52.04%, n = 51) than those in the control group (35.58%, n = 37 for FAS; 37.37%, n = 37 for PPS). The above results indicated that the treatment group had higher chemotherapy-related remission rates compared with the control group after just one cycle of treatment.

**DISCUSSION**

The main active ingredients of CZBG are peimine, tetrandrine, and tetramethylpyrazine. Our previous research showed that CZBG-containing serum can inhibit the proliferation of L1210/CDDP cells, inhibit the efflux of anticancer drugs from K562/A02 cells, and induce apoptosis of K562/A02 cells.\(^6,7\) We have also shown that high and medium doses of CZBG can enhance the inhibitory effect of doxorubicin on K562/A02 tumor xenografts, and reduce the expression of MDR, genes in transplanted tumor tissue.\(^6,7\) CZBG can also increase the apoptosis-inducing effect of doxorubicin on K562/A02 breast xenograft tumors, reduce the high expression of BCL-2 proteins, and up-regulate BAX protein expression.\(^8,9\) Finally, it has been shown that CZBG works synergistically with doxorubicin to inhibit the expression of resistance-associated enzymes (e.g. GSH, TopoII) and membrane proteins (e.g. P-gp, MRP) of K562/A02 xenograft tumor tissue.\(^6,9,10\) To demonstrate the clinical efficacy of CZBG, we designed this randomized, multi-center, double-blind, placebo-controlled clinical trial and chose chemotherapy remission rates, which is the internationally recognized

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### Table 1 Number of patients for all trial centers

<table>
<thead>
<tr>
<th>Name of Site</th>
<th>Patients screened</th>
<th>Patients enrolled</th>
<th>Patients excluded</th>
<th>Patients lost</th>
<th>Number of deaths</th>
<th>Complete patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine</td>
<td>46</td>
<td>40</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>35</td>
</tr>
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<td>Xiyuan Hospital Affiliated to China Academy of Chinese Medical Sciences</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine</td>
<td>41</td>
<td>40</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Langfang Chinese Medicine Hospital Affiliated to Hebei Medical University</td>
<td>42</td>
<td>40</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>First Affiliated Hospital of Guangzhou University of Chinese Medicine</td>
<td>62</td>
<td>40</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Chinese Medicine Hospital of Zhejiang Province</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>First Affiliated Hospital of Heilongjiang University of Chinese Medicine</td>
<td>18</td>
<td>18</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>269</strong></td>
<td><strong>238</strong></td>
<td><strong>3</strong></td>
<td><strong>21</strong></td>
<td><strong>17</strong></td>
<td><strong>197</strong></td>
</tr>
</tbody>
</table>

### Table 2 Baseline characteristics of treatment group and control group (\(\bar{x} \pm s\))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group ((n = 117))</th>
<th>Treatment group ((n = 118))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.22 ± 18.59</td>
<td>44.57 ± 17.41</td>
</tr>
<tr>
<td>Male [(%)]</td>
<td>67 (57.26)</td>
<td>71 (60.70)</td>
</tr>
<tr>
<td>Acute leukemia types [(%)]</td>
<td>AML</td>
<td>91 (77.78)</td>
</tr>
<tr>
<td>ALL</td>
<td>26 (22.22)</td>
<td>28 (23.73)</td>
</tr>
<tr>
<td>Sub-types of RAL [(%)]</td>
<td>NR2</td>
<td>28 (23.93)</td>
</tr>
<tr>
<td>Relapse</td>
<td>50 (42.74)</td>
<td>42 (35.59)</td>
</tr>
<tr>
<td>Blast crisis of CML</td>
<td>5 (4.27)</td>
<td>7 (5.93)</td>
</tr>
<tr>
<td>MDS transformation</td>
<td>20 (17.09)</td>
<td>22 (18.64)</td>
</tr>
<tr>
<td>Heterozygous leukemia</td>
<td>5 (4.27)</td>
<td>5 (4.24)</td>
</tr>
<tr>
<td>WBC &gt; 100 (\times 10^9)/L</td>
<td>9 (7.69)</td>
<td>6 (5.08)</td>
</tr>
</tbody>
</table>

Notes: compound Zhebei granules (treatment group) or placebo (control group) was given for 14 consecutive days, starting three days before chemotherapy, with patients taking one bag (4 g) twice a day. The placebo was designed to be exactly the same as CZBG with regard to packaging, size, appearance, color, taste, smell, and dosage form. AML: acute myelocytic leukemia; ALL: acute lymphoblastic leukemia; RAL: refractory acute leukemia; NR2: no remission 2, refers to no remission after two cycles of standard chemotherapy; CML: chronic myelocytic leukemia; MDS: myelodysplastic syndrome. Chemotherapy regimens were determined based on consensus of principal investigators from all clinical trial centers. There were no significant differences in the age \((P = 0.57)\), sex \((P = 0.6511)\), and of type of AL \((P = 0.784)\) between the treatment and control groups.

33.67%, \(n = 33\) for PPS) were both higher than those in the control groups (23.07%, \(n = 24\) for FAS; 24.24%, \(n = 24\) for PPS). The difference between the two groups was both statistically significant (\(P = 0.0444, Z = -2.01\) for FAS and \(P = 0.0476, Z = -1.9795\) for PPS). Moreover, both the FAS and PPS CR + PR rates were significantly higher (\(P = 0.0328\) for FAS and \(P = 0.038\) for PPS) in the treatment group (50.00%, \(n = 51\) for FAS; 52.04%, \(n = 51\)) than those in the control group (35.58%, \(n = 37\) for FAS; 37.37%, \(n = 37\) for PPS). The above results indicated that the treatment group had higher chemotherapy-related remission rates compared with the control group after just one cycle of treatment.
 complications for which efficacy information is not available. For the PPS analysis, deaths are regarded as unresponsive to treatment. Loss cases refer to the natural shedding cases and deaths due to

<table>
<thead>
<tr>
<th>Group</th>
<th>Case number (n)</th>
<th>Loss case (n)</th>
<th>CR (including CRi) [n (%)]</th>
<th>PR [n (%)]</th>
<th>NR [n (%)]</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>117</td>
<td>13</td>
<td>24 (23.07)</td>
<td>13 (12.50)</td>
<td>62 (59.62)</td>
<td>− 2.01</td>
<td>0.0444</td>
</tr>
<tr>
<td>Treatment group</td>
<td>118</td>
<td>16</td>
<td>33 (32.35)</td>
<td>18 (17.65)</td>
<td>47 (46.08)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Comparison of the clinical remission rates between the treatment and control groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case number (n)</th>
<th>Loss case (n)</th>
<th>CR (including CRi) [n (%)]</th>
<th>PR [n (%)]</th>
<th>NR [n (%)]</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>99</td>
<td>18</td>
<td>24 (24.24)</td>
<td>13 (13.13)</td>
<td>62 (62.63)</td>
<td>− 1.9795</td>
<td>0.0476</td>
</tr>
<tr>
<td>Treatment group</td>
<td>98</td>
<td>20</td>
<td>33 (33.67)</td>
<td>18 (18.3)</td>
<td>47 (47.96)</td>
<td></td>
<td></td>
</tr>
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</table>

Notes: either Compound Zhebei granules (treatment group) or placebo (control group) was started three days before chemotherapy for 14 consecutive days, with patients taking one bag (4 g) twice a day. The placebo was designed to be exactly the same as the CZBG with regard to packaging, size, appearance, color, taste, smell, and dosage size. CR: complete remission; PR: partial remission; NR: no remission. Chemotherapy regimens were determined based on consensuses of principal investigators from all clinical trial centers. Morphological complete remission with abnormal blood count (CRi) is defined as when the morphology of the bone marrow met CR criteria but the patient maintained persistent neutropenia (< 1.0 × 10⁹/L) or thrombocytopenia (< 100 × 10⁹/L). For our datasets, CRs include all CRi patients. For the PPS analysis, deaths are regarded as unresponsive to treatment. Loss cases refer to the natural shedding cases and deaths due to complications for which efficacy information is not available. golden standard for AL clinical efficacy evaluation, as our primary indicator. From our results, we have shown that when CZBG is combined with chemotherapy, it can improve the remission rate of RAL after just one chemotherapy cycle. From the FAS analysis, the CR + PR rates of the treatment and control groups were 48.11% and 34.26% respectively. The difference between the two groups was statistically significant (P = 0.02). From the PPS analysis, the CR+PR rates of the treatment and control groups were 52.04% and 37.37% respectively. There was a significant difference between two groups (P = 0.038). Compared with the control group, the CR (CRi) and CR+PR rates of the treatment group increased by 9.22% and 14.42% for FAS, and 9.43% and 14.67% for PPS, respectively. The above results show that CZBG in combination with chemotherapy can significantly improve the remission rate just after one treatment cycle and shows good prospects for clinical application. There are however problems that may compromise the results. First, the course of therapy in our treatment period was 14 days, which is a relatively short period, so it may affect our findings regarding the treatment efficacy. Second, an ideal chemotherapy remission rate for the initial treatment of AL cannot always be achieved by one cycle of chemotherapy; multiple cycles of chemotherapy are usually required. For RAL, additional cycles of chemotherapy are needed because RAL is generally non-responsive to chemotherapy. Although this clinical trial shows a relatively high rate of remission, there is still a lower CR rate compared with some other targeted agents with a CR rate of 42%-50%. To address these limitations, we recommend further trials that include more than one cycle of chemotherapy, and that the observation period be extended.

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