Clinical efficacy for the treatment of esophageal cancer with rabdosia rubescens alone and combining with chemotherapy

Rui Wang\textsuperscript{1}, Peng Cheng\textsuperscript{2}, Qingxia Fan\textsuperscript{1}, Ruilin Wang\textsuperscript{1,}\textsuperscript{*}

\textsuperscript{1}Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China; \textsuperscript{2}Department of General Surgery, Hospital of Air Force No.94600, Zhengzhou, Henan 450046, China

Received June 20, 2007

Abstract

Objective. To observe clinical efficacy of rabdosia rubescens for the treatment of esophageal cancer patients with rabdosia rubescens alone or rabdosia rubescens combined with chemotherapy. Four hundred and forty-eight patients with esophageal cancer were treated with rabdosia rubescens alone or rabdosia rubescens combined with chemotherapy. Results. For the early stage esophageal cancer patients treated with rabdosia, the survival rates of 3, 5, 10, 13 year were significantly higher than those of patients not receiving any therapy ($P < 0.001$). For the late stage esophageal cancer, the response rate of rabdosia rubescens combined with chemotherapy was significantly higher than that in PYM-BLM based chemotherapy alone ($P < 0.01$). There was no significant difference between rabdosia rubescens combined with chemotherapy and chemotherapy alone on side effects ($P > 0.05$). Conclusion. For the early stage esophageal cancer, rabdosia rubescens could control disease and prolong the survival time. Rabdosia rubescens could also enhance the effect of chemotherapy on advanced esophageal cancer patients. [Life Science Journal. 2007; 4(3): 22 – 25] (ISSN: 1097 – 8135).

Keywords: rabdosia rubescens; chemotherapy; esophageal cancer; clinical efficacy

1 Introduction

Donglingcao (rabdosia rubescens) is also called Bin-glingcao, Liuyueling, Shanxiangcao. It is one of labtea plants and produced mainly in Henan, Hebei, Shanxi, Hubei, Hubei, and so on.

Rabdosia rubescens consists of a series of terpene such as single terpene, double terpene, brass, organic acid and so on. Oridonin is one diterpenoid compound isolated from rabdosia rubescens leaves. It has been demonstrated to have anti-tumor, anti-bacteria effects and oxygen free radicals clearance\textsuperscript{[1]} and objective clinical efficacy on the treatment of esophageal cancer, gastric cardia cancer, hepatocellular cancer (HCC), pancreas cancer, prostate cancer and relapsed cystic cancer with local perfusion. The following report is about clinical efficacy of rabdosia rubescens with julep\textsuperscript{1} troche alone or combined with chemotherapy on esophageal cancer.

2 Materials and Methods

2.1 Subjects

Five hundred and six patients were enrolled and diagnosed as esophageal cancer by pathology and X-ray. Of the one hundred and thirty-four esophageal cancer patients in early stage, seventy-six from Tangyin County and Hebi City were treated with rabdosia rubescens julep and troche (treatment group), while fifty-eight patients who refused to receive any therapy were taken as control. Of the three hundred and seventy-two esophageal cancer patients in middle-late stage, one hundred sixty-seven patients were treated with rabdosia rubescens alone, and two hundred and five patients were treated with rabdosia rubescens combined with chemotherapy. All the patients were not suitable or reluctant to undergo esophagectomy, radiotherapy or receive chemotherapy alone.

2.2 Methods

2.2.1 Rabdosia rubescens alone. For the middle-late stage patients, Julep: 1 g/ml, 30 ml, tid, after meals. Troche: natural drug/troche: 4g, 5 – 8 troche, tid, after meals.
The total dosage for one course of treatment was 10000g natural drug or so. Two or three months were one course of treatment. Patients whose disease reduced or stabilized after treatment continued to receive therapy for the second or third course of treatment. The following was the sustained dosage after 3 – 4 courses of treatment: Juice: 15 – 20 ml, tid/Troche: 4 troche, tid. These two kinds of medicines were taken alternatively with each for one month. For the early stage esophageal cancer, the same dose as that of middle-late stage, but the cycle decreased to 2 courses each year. Therapy was changed to sustained dosage after 3 – 4 years.

2.2.2 Combination treatment. Rabdosia rubescens: juice 30ml, tid or 6 troche, tid, after meals, combined with chemotherapy concurrently.

Chemotherapy regimens:
(1) CTX-BLM:
   CTX: 400 mg, iv, for odd weeks;
   BLM: 15 mg, im, for even weeks.
   Seven weeks were one course of treatment.
(2) NOP(Nitrocaphane)-PYM
   NOP: 20 mg, iv, for odd weeks;
   PYM: 8 mg, im, for even weeks.
   Seven weeks were one course of treatment.
(3) DDP-VCR-PYM
   DDP: 20 mg, iv, day 1 – 5/week, for 1, 4, 7 weeks;
   VCR: 0.5 mg, iv, day 1, 3, 5/week 9:00 am, for No. 2, 3, 5, 6, 8 weeks;
   PYM: 8 mg, im, day 1, 3, 5/week 4:00 pm, for No. 2, 3, 5, 6, 8 weeks.
   Eight weeks were for one course of treatment.

2.2.3 Criteria for recent efficacy and the time to survival after treatment. (1) Efficacy was assessed by CR, PR, MR, SD, PD five grades for the middle-late stage esophageal cancer.

   Complete response (CR): Disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to the tumor for at least one month.

   Partial response (PR): Reduction of greater than 50 percent in the sum of the products of the largest two perpendicular diameters. No new lesions may appear and no existing lesion may enlarge for at least one month.

   Minimal response (MR): Reduction of greater than 25 percent but less than 50 percent in the sum of the products of the largest two perpendicular diameters. No new lesions may appear for at least one month.

   Stable disease (SD): Less than 25 percent reduction or less than 25 percent increase in the sum of the products of the largest two perpendicular diameters. No new lesions may appear for at least one month.

   Progressive disease (PD): Greater than 25 percent increase in the sum of the products of the largest two perpendicular diameters or the appearance of new areas of malignant disease.

   (2) The time of survival after treatment: time from the beginning of treatment to death or the last follow-up.

2.3 Statistical analysis

All experimental data were processed by SPSS11.0. Fourfold table χ² test was used to evaluate the significance. There was a statistical significance when P was less than 0.05.

3 Results

3.1 Efficacy and the time of survival after treatment

3.1.1 Result of early stage esophageal cancer patients. After 13 – 15 years’ follow-up, in treatment group the survival rates of 1, 3, 5, 10, 15 years were 100%, 98.68%, 84.02%, 63.49%, 50.13% and 44.56% respectively. In control group the survival rates of 1, 3, 5, 10 year were 100%, 51.52%, 28.62%, 11.45%, and 8.59% respectively. The survival rates in treatment group were significantly higher than those in control group except the first year (P < 0.001).

3.1.2 Efficacy and survival time of rabdosia rubescens alone. (1) Efficacy. The 167 middle-late stage esophageal cancer patients treated with rabdosia rubescens alone, CR + PR were 8.38% (14/167), and overall response (OR, CR + PR + MR) was 33.53% (56/167). The results were shown in Table 1.

   Table 1. Efficacy of the middle-late stage esophageal cancer patients treated with rabdosia rubescens alone

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Efficacy evaluation (cases, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td>CR</td>
</tr>
<tr>
<td>cancer</td>
<td>Total cases</td>
</tr>
</tbody>
</table>

3.1.3 Efficacy and survival time of combination therapy. (1) Efficacy: Table 3 showed two hundred and five patients with middle-late stage esophageal cancer were...
treated with rabdosia rubescens combined with PYM (BLM) based chemotherapy (BLM-CTX, PYM-NOP, PYM-VCR- DDP). CR + PR: 36.58% (75/205), OR (CR + PR + MR): 66.82% (137/205). One hundred and eighty-two patients were treated with the same chemotherapy regimen only. CR + PR: 20.32% (37/182), OR: 42.85% (78/182). There was significant difference between the two groups ($P < 0.01$).

(2) The time of survival: Table 4 showed the survival rates of 1, 3, 5 year in combination group were 40.13%, 11.11% and 7.27% respectively. The survival rates in chemotherapy group alone were 17.6%, 5.38% and 4.04% respectively. It was of significant difference in the first year ($P < 0.01$) and no significant difference of the third year and the fifth year ($P > 0.05$).

### 3.2 Side effect

No obvious side effects were found in patients treated with rabdosia rubescens julep and troche in this research. Only a minority of patients sometimes appeared mild abdominal symptoms, such as urging sound, diarrhea and so on. The above symptoms could disappear without treatment and be prevented and treated with MiQue and Crataegus pinnatifida bunge julep. Skin itch appeared in four patients. No liver, renal, cardiac and bone toxicity were found in patients who took long-time therapy. Symptoms caused by chemotherapy when combination of rabdosia rubescens and chemotherapy were administered.

### 4 Discussion

It has been demonstrated that Rabdosia rubescens exerts anti-tumor activity taken orally or by injection. Natural diterpenoid oridonin was purified from rabdosia rubescens by high-performance liquid chromatography. It can exert anti-tumor effect\[^2\]–\[^4\]\ and induce apoptosis\[^5\]–\[^7\]\ on human liver cancer cell BEL-7401, human esophageal cancer cell EC109, lung cancer cell SPC-A-1, human breast cancer cell MDA-MB-231 and so on. It has been proven by animal experiment that extracted rabdosia rubescens solution can obviously inhibit the precancer-

### Table 2. The survival time for the middle-late stage esophageal cancer patients treated with rabdosia rubescens alone

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases (begining)</th>
<th>Cases (end)</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>156</td>
<td>48</td>
<td>30.77</td>
</tr>
<tr>
<td>2</td>
<td>156</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>21</td>
<td>13.46</td>
</tr>
<tr>
<td>4</td>
<td>156</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>16</td>
<td>10.26</td>
</tr>
<tr>
<td>6</td>
<td>136</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>127</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>126</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>96</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>8</td>
<td>8.89</td>
</tr>
</tbody>
</table>

* vs. combination, $P < 0.05$

### Table 3. Efficacy of the middle-late stage esophageal cancer patients treated with rabdosia rubescens and chemotherapy or chemotherapy alone

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cases</th>
<th>Efficacy evaluation (cases, %)</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>PR</td>
<td>MR</td>
</tr>
<tr>
<td>Combination</td>
<td>205</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>182</td>
<td>5</td>
<td>32</td>
</tr>
</tbody>
</table>

* vs. combination, $P < 0.05$

### Table 4. Survival time of the middle-late stage esophageal cancer patients treated with combination therapy and chemotherapy alone

<table>
<thead>
<tr>
<th>Year</th>
<th>Group</th>
<th>Cases (begining)</th>
<th>Cases (end)</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first</td>
<td>Combination</td>
<td>129</td>
<td>52</td>
<td>40.3</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>125</td>
<td>22</td>
<td>17.6*</td>
</tr>
<tr>
<td>The third</td>
<td>Combination</td>
<td>63</td>
<td>7</td>
<td>11.11</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>103</td>
<td>6</td>
<td>5.83*</td>
</tr>
<tr>
<td>The fifth</td>
<td>Combination</td>
<td>55</td>
<td>4</td>
<td>7.27</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>99</td>
<td>4</td>
<td>4.04*</td>
</tr>
</tbody>
</table>

* vs. combination, $P < 0.05$
ous lesion developing to cancer. Wang’s researches also proved that the rabdosia rubescens can treat esophageal cancer, gastric cardia cancer and so on[8, 9].

For the esophageal cancer patients in early stage, the survival rates of 3, 5, 10, 13 years in treatment group were significantly higher than that in control group ($P < 0.001$). The average time of 83 months from diagnosis to death was significantly longer that of 53.2 months in previous report[10]. Excluding various factors affecting the survival time, it has been demonstrated that rabdosia rubescens can control disease progression and survival time for the early stage esophageal cancer.

For the esophageal cancer patients in middle-late stage treated with rabdosia rubescens, CR + PR was 8.38%. The survival rates of 1, 3, 5 years were 30.77%, 13.46% and 10.26%. Compared with esophageal cancer patients treated with chemotherapy alone: CR + PR: 20.32% and the survival rates of 1 year, 3 years and 5 years are 17.6%, 5.83% and 4.04%, indicating poorer recent efficacy and longer survival time[11].

For patients treated with rabdosia rubescens combined with PYM (BLM)-based chemotherapy regimen, clinical efficacy is significantly better than that of patients treated with chemotherapy alone ($P < 0.01$). The result proves rabdosia rubescens can enhance the chemotherapy effect when combined with PYM (BLM)-based chemotherapy regimen[12]. Research[13] has demonstrated that the inhibitory rate of oridonin + PYM (83%) is significantly higher than that of oridonin (52%) alone or PYM (44%) ($P < 0.05$). Its mechanism is that oridonin can prevent the mitosis of cell and result in cells in G2 + M phase to pileup and lead to partial synchronization[14]. Due to cell pileup in G2 + M phase, rabdosia rubescens can exert an enhancement effect when combined with the drugs sensitive to cells in G2 + M phase such as PYM or BLM by blockage of cells in M phase.

5 Conclusion

For the early stage esophageal cancer, rabdosia rubescens could control disease and prolong the survival time. When it was used combing with chemotherapy, Rabdosia rubescens could enhance the effect of chemotherapy on advanced esophageal cancer patients. No obvious side effects were found in patients treated with rabdosia rubescens.

References