A Clinical Study on Safety and Efficacy of Aidi Injection® Combined with Chemotherapy

Hong-Xia Xu¹, Xin-En Huang¹*, Ying Li¹, Cheng-Guang Li¹, Jin-Hai Tang²*

Abstract

Objective: To observe the efficacy, side effects and impact on the quality of life of Aidi Injection® combined with leucovorin calcium/ 5-fluorouracil/ oxaliplatin (FOLFOX4 regimen) in the treatment of advanced colorectal cancer patients. Methods: A consecutive cohort of 100 patients were divided into two groups: the experimental group was treated with Aidi injection and FOLFOX4 while the control group was only administered FOLFOX4. After more than two courses of treatment, efficacy, quality of life and side effects were evaluated. Results: The response rate of experimental group was not significantly different with that of control group (P>0.05), but differences were significant in clinical benefit response and KPS score. In addition, gastrointestinal reaction and the incidence of leukopenia were lower than that of control group (P<0.05). Conclusions: Aidi injection combined with FOLFOX4 is associated with reduced toxicity of chemotherapy, enhanced clinical benefit response and improved quality of life of patients with advanced colorectal cancer. Aidi injection deserves to be further investigated by randomized control clinical trails.

Keywords: Aidi injection - chemotherapy - advanced colorectal cancer
Table 1. Comparison of Treatment Efficacy in Two Groups Treated with FOLFOX4 Alone or Aidi Injection* combined with FOLFOX4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>CR+PR(%)</th>
<th>CR+PR+SD(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFOLFOX4 and Aidi Injection*</td>
<td>50</td>
<td>0</td>
<td>24</td>
<td>16</td>
<td>10</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>50</td>
<td>0</td>
<td>22</td>
<td>16</td>
<td>18</td>
<td>44</td>
<td>64</td>
</tr>
</tbody>
</table>

N, number cases; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; FOLFOX4, Leucovorin calcium Fluorouracil/Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acantropanacis Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng).

Table 2. Karnofsky Performance Status Score in Two Groups Treated with FOLFOX4 and Aidi Injection* Combined with FOLFOX4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increased</th>
<th>Stable</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4 and Aidi Injection*</td>
<td>30</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>12</td>
<td>27</td>
<td>11</td>
</tr>
</tbody>
</table>

FOLFOX4, Leucovorin calcium Fluorouracil/Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acantropanacis Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng); KPS, score; increased, ≥10 after treatment; stable, <10; decreased, ≥10

m² and continuous iv 5-FU at a dose of 600 mg/m² on day 1, day2, Oxaliplatin 85 mg/m² repeated every 2 weeks. Treatment was biweekly administered until PD or unacceptable toxicity, withdrawal of consent, and physicians decision or treatment interruption for ≥2 weeks. The control group received FOLFOX-4 regimen, the experimental group received Aidi Injection 60-80ml intravenous infusion on iv, once daily, for 7 days and FOLFOX4. Antiemetic treatment was granisetron 3mg by intravenous bolus infusion prior to chemotherapy. Routine blood test, blood biochemistry and tumor markers were reviewed during and after chemotherapy weekly.

Efficacy Observation
Treatment efficacy was evaluated after two months treatment. Complete Remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST criteria (Therasse et al., 2000). Quality of life was evaluated in accordance with the Karnofsky Scale, designated increasing if the score increased by 10 after treatment, decreasing if the score decreased by 10 and otherwise stable.

Toxicity Assessment
Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1991).

Statistical analysis
The study data were analyzed by t and enumeration data by χ² test. Statistic significance was determined if p<0.05.

Results
Efficacy
All 100 patients had completed at least 2 cycles of treatment. Total treatment cycle was 303 and average cycle was 3. No CR was observed in both two groups. The response rate of experimental group (CR+PR) was 48%, while that in control group was 44%. The differences were not statistically significant (p>0.05). The disease control rates of two groups (CR+PR+SD) were 80% (experimental group), 64% (control group) respectively, with statistical significance (p<0.05) (Table 1).

Quality of life before and after treatment
KPS score of experimental group increased in 30 cases (60%), 13 cases stable and 7 cases decreased, while that of control group increased in 12 cases (24%), 27 cases stable and 11 cases decreased. The difference between two groups was statistically significant (p<0.05) (Table 2).

Table 3. Toxicity in Two Groups Treated with FOLFOX4 and Aidi Injection* Combined with FOLFOX4

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>FOLFOX4 and Aidi Injection*Number (%)</th>
<th>FOLFOX4 Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10(20)</td>
<td>8(16)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5(10)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Nausea,vomiting</td>
<td>15(30)</td>
<td>10(20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4(8)</td>
<td>2(4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10(20)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>3(6)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4(8)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6(12)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>2(4)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>8(16)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Elevated Cr</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>

FOLFOX4, Leucovorin calcium Fluorouracil/Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acantropanacis Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng); ALT, alanine aminotransferase; Cr, creatinine
Toxicity

All patients underwent toxicity assessment. Treatment related side effects were reversible, and no termination of chemotherapy or death caused by adverse events occurred. In Table 3, the main adverse effects were myelosuppression and gastrointestinal reactions. In experimental group, leukopenia rate was 46%, 10% of them with grade III-IV and none with infection; 16% patients showed grade I-II thrombocytopenia and 2% with grade III thrombocytopenia; grade I-II gastrointestinal toxicity rate was 50%, and grade III-IV 10%. In control group, leukopenia rate was 72%, 24% of them with grade III-IV; 30% patients with grade I-II thrombocytopenia and 8% with grade III thrombocytopenia; grade I-II nausea and vomiting was 70%, and 6% with grade III-IV. No statistically significant difference was detected in hand-foot syndrome or peripheral neuropathy. Both of two groups were tested mild liver damage, but recovered without dose modification on chemotherapy. Additionally, there was no apparent renal damage. In experimental group, 2 cases demonstrated allergic reaction. We considered it could be an allergic reaction to Chinese medical herbs, and could be prevented by slowing down the infusion speed and prescribing premedication containing dexamethasone.

Discussion

Recurrence and metastasis is the main cause of death in colorectal cancer (Le Voyer et al., 2003; Sobrero et al., 2007). Chemotherapy plays an important role in comprehensive treatment for colorectal cancer (Sougilakos et al., 2006). Currently, FOLFOX4 regimen is one of the best treatments for advanced colorectal cancer patients (Haydon, 2003; Saltz et al., 2008). But, chemotherapy often brings about serious side effects. Therefore, how to reduce side effects of chemotherapy, in the meantime increase efficacy and improve quality of life have aroused more and more attention.

At present, objective of chemotherapy is not only to extend survival of patients, but also to improve quality of life. Thus, the Food and Drug Administration of the USA proposes that the evaluation of new drugs should involve survival time and quality of life. It is a distinguishing feature of traditional Chinese medicine to contribute in this area.

Aidi Injection is developed and manufactured by Guizhou E&H Pharmaceutical Co., Ltd in China. Studies (Rong et al., 2000; Fang, 1993) have shown that the main active ingredient of Mylabri is cantharidin, which has characteristics of anti-cancer without causing myelosuppression, and it can promote hematopoietic stem cells to accomplish differentiation into myelomonocytic in order to increase the leukocyte. Astragalus Polysaccharide is another important component which can improve the phagocytic function of reticuloendothelial system, and enhance anti-cancer activity of T cells, NK cells, LAK cells and IL-2 cells (Ma, 2007). Ginsenosides and Ginseng Polysaccharide can increase immunity and leukocyte. Acanthopanax Polysaccharide has the similar immunological enhancement as Ginseng and Astragalus (Liu et al., 2001; Lu, 2009). Our study shows that the differences of short-term efficacy in two groups were not statistically significant, but the clinical benefit rate, and Karnofsky score improvement of experimental group were significantly higher than that of control group. Aidi Injection combined with FOLFOX4 regimen, which used for treatment of advanced colorectal cancer, can reduce side effects causing by chemotherapy, and improve quality of life. In summary, Aidi Injection deserves to be further investigated by randomized controled clinical trials.

Acknowledgements

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References


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