Original Article

Celecoxib combined with hippocampus sparing intensity-modulated radiation therapy reduces the injury of cognitive function induced by radiotherapy in patients with nasopharyngeal carcinoma

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Abstract: Objective: In this study, we compared the effects of combination of celecoxib, intensity-modulated radiation therapy (IMRT) and hippocampal sparing, IMRT with hippocampal sparing and IMRT only on cognitive function, life quality and therapeutic effects in patients with nasopharyngeal carcinoma (NPC). Methods: From June 2015 to December 2016, 177 cases with NPC in our hospital were finally enrolled and randomly divided into three groups: IMRT only group (I group), hippocampal sparing IMRT (H group) and celecoxib combined with hippocampal sparing IMRT group (Ce group). Cognitive function and life quality were evaluated three months after treatment via Mini-Mental State Examination (MMSE) and Quality of life questionnaire (QLQ C30) respectively. Indicators for therapeutic effects including complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), adverse reactions, recurrence and metastasis of tumor and serum tumor marker carcinoembryonic antigen (CEA) level of patients were also compared. Results: Before the intervention, there was no difference in cognitive function score among all the patients (P=0.876). After the treatment, no significant difference was found for RR among groups (P=0.245), however, patients in the Ce group showed the highest cognitive function score (P<0.001); the differences in adverse reactions including dry mouth (P=0.026, Ce vs. H; P=0.000, Ce vs. I; P=0.000, H vs. I), oral mucositis (P=0.060, Ce vs. H; P=0.008, Ce vs. I; P=0.396, H vs. I), skin reaction (P=0.054, Ce vs. H; P=0.027, Ce vs. I; P=0.065, H vs. I), irradiation otitis media (P=0.097, Ce vs. H; P=0.009, Ce vs. I; P=0.051, H vs. I) had statistical significance, and their incidence rates in Ce group were lowest. Meanwhile, recurrence and metastasis were less in the Ce group although the differences were insignificant (P=0.302 and 0.638). The serum level of CEA was notably lower in Ce group (P=0.031, Ce vs. H; P=0.020, Ce vs. I; P=0.512, H vs. I). Life quality scores about cognitive function and role function of H group and Ce group were higher than that of I group while Ce group was the highest (Cognitive function: P=0.020, Ce vs. H; P=0.015, Ce vs. I and P=0.023, H vs. I; role function: P=0.039, Ce vs. H; P=0.011, Ce vs. I and P=0.031, H vs. I). Conclusion: Celecoxib combined with hippocampus sparing IMRT for the treatment of NPC patients could drastically alleviate cognitive dysfunction, improve life quality and reduce the occurrence of adverse events compared with hippocampal sparing IMRT and IMRT only.

Keywords: Cognitive function, intensity-modulated radiation therapy, hippocampus, nasopharyngeal carcinoma

Introduction

Originally, nasopharyngeal carcinoma (NPC), as a kind of head and neck cancer, was thought only common in southern China and rarely occurred in other areas of the world [1]. Recently, the evidence for occurrences of NPC in populations of geographic regions other than southern China had been reported, such as United Kingdom [2]. Non-keratinizing tumor, the typically pathological type, is sensitivity to radiotherapy [3]. However, the treatment did not always achieve the desired effect and was associated with substantial adverse reactions...
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Therefore, developing more effective and safer treatment strategies for NPC was still a hotspot in clinical research.

Intensity-modulated radiation therapy (IMRT) has been widely applied in the management of NPC [5]. However, the decline of cognitive functions and life quality had been observed in patients after whole brain radiation therapy, which is probably due to the injury of hippocampus, the major brain area involved with recognition and memory [6-8]. In order to better protect hippocampus, intensity-modulated radiation therapy (IMRT) with hippocampal sparing has been developed as it has more precise radiation and less injuries to normal brain tissue nearby [9, 10].

Cyclooxygenase-2 (Cox-2) could promote tumor angiogenesis, advance the invasion and metastasis of tumor cells and inhibit tumor cell apoptosis so as to participate in the progression of tumor [11]. Celecoxib as a selective Cox-2 inhibitor, which was firstly approved for treatment of adult arthritis, could inhibit Cox-2 activity, thereby restrain tumor cell proliferation and angiogenesis and promote tumor cell apoptosis to play a role in anti-tumor activity. Meanwhile, it could also fight against cancer through various other signal pathways [12, 13]. Basic research found that celecoxib could inhibit cancer cell proliferation [14]. The expression level of Cox-2 in NPC is as high as 78.8% that is closely associated with lymph node metastasis and poor prognosis [15]. Currently, both IMRT and celecoxib have been widely applied in various cancer therapies [16, 17], though there were several published studies focusing on the impact of these therapies for NPC on patients' health [18, 19], whether celecoxib combined with hippocampal sparing IMRT could preserve cognitive functions and improve life quality of NPC patients remained unclear.

In this study, we compared the effect of combination of celecoxib and hippocampal sparing IMRT, hippocampal sparing IMRT and IMRT only on cognitive function, life quality and therapeutic effects in patients with NPC.

Materials and methods

General information

This is a retrospective study of patients with NPC treated in our hospital from June 2015 to December 2016. According to the computer generated random numbers method, all the enrolled patients were randomly divided into three groups: IMRT only group (I group), hippocampal sparing IMRT group (H group) and celecoxib combined with hippocampal sparing IMRT group (Ce group).

Inclusion criteria: (1) NPC patients diagnosed through pathology or cytology were naive for the treatment; (2) NPC patients without other malignant tumors, disturbance of consciousness, or mental illness; (3) NPC patients who understood the content of the questionnaire.

Exclusion criteria: Patients (1) with obvious symptoms of cognitive dysfunction before radiotherapy; (2) with distant metastasis before treatment; (3) with chemoradiation contraindication; (4) with long-term high blood pressure, coronary heart disease, diabetes, chronic obstructive pulmonary disease, epilepsy, cerebral vascular disease or a history of mental illness; (5) with a history of long-term use of sedatives, antidepressants or who had taken such drugs recently; (6) with drinking, smoking or having medication history for chronic disease for a long time; (7) could not complete the neuropsychological tests with any reason, such as obvious visual auditory dysfunction, language barrier and poor ability to understand, etc. (8) with abnormal intelligence could not cooperate with medical staff to complete relevant neuropsychological tests.

This study was approved by the Hospital Medical Ethics Committee, and informed consent was signed with the patients or their family members.

Therapeutic method

All patients received radical external therapy by using the professional radiotherapy equipment (ONCOR, SIEMENS AG, Germany) and 6 MV X-ray irradiation was used with beam number: nine; using full target IMRT, primary tumors and lymphatic drainage area were covered in an intensity modulation target zone. According to the scope determined by magnetic resonance (MR) or computed tomography, target region in H group was drawn on T1 MR image with IMRT workstation step by step using the method by Chera et al. [20]. Briefly, the temporal horn was...
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firstly identified and the hippocampus was inside the curve. Then, the curve was contoured caudally from the temporal horn to pons and pituitary gland. Thirdly, contour rostrally to the lateral ventricle and ambient cistern [21]. The preferences and main target dose were set as: GTVnx 7200 cGy/30F, GTVnd 6750 cGy/30F, PTVnx 6600 cGy/30F, PTV-1 6000 cGy/30F, PTV-2 5400 cGy/30F [20]. The dosage limit for bilateral hippocampi was $D_{40}\leq7.3$ Gy, $D_{mean}\leq10$ Gy and $D_{max}\leq17$ Gy.

Patients in I group received IMRT only, patients in H group received hippocampal sparing IMRT, however oral celecoxib capsules (Pfizer Pharmaceuticals LLC, USA), 200 mg/ time with two times per day for 42 days were used in Ce group since the first hippocampal sparing IMRT.

### Cognitive function evaluation

Mini-Mental State Examination (MMSE) was adopted to evaluate the cognitive functions of patients in each group before and after 3 months treatment [22]. Briefly, if the score $\geq$27, the patient had general cognitive function, conversely, if the score <27, the patient had cognitive dysfunction.

### Life quality assessment

Before and after 3 months treatment, quality of life was assessed via Quality of life questionnaire (QLQ C30) formulated by the European organization for research and treatment of cancer (EORTC), including five function scales and four symptom scales [23]. The life quality was positively related to the score of the function scale, while symptom scale was converse.

### Outcome measures

After treatment for three months, clinical therapeutic effect of three groups was evaluated and analyzed, and the standard was set according to Response Evaluation Criteria In Solid Tumors (RECIST) [24]: complete remission (CR), tumor disappear completely; partial remission (PR), the diameter of the largest tumor decreases $\geq$30%; stable disease (SD), maximum diameter of tumor lesion increases $\geq$20% but <30%; progressive disease (PD), the largest tumor diameter increases $\geq$30% or a new lesion is observed. Response rate (RR), $RR=(CR+PR)/$number of total patients $*$100%. Adverse reactions were recorded after treatment. During the 1-year follow-up period, the patients were reviewed every three months after treatment, meanwhile, recurrence and metastasis of tumor were observed. Serum level of tumor marker carcinoembryonic antigen (CEA) in patients before treatment and after three months treatment was also detected.
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Statistics analysis

Data was analyzed by using SPSS17.0 (IBM, Armonk, NY, USA). Measurement data was expressed as mean ± standard deviation, the general comparison among multiple groups should be done by ANOVA, and then followed by individual comparisons with post hoc test. Count data was expressed as ratio with chi-square test used to analyze the difference among the three groups as well as between the two independent samples. $P<0.05$ was considered statistically significant.

Results

Patients’ characteristics

Twenty three cases in the 200 patients diagnosed with NPC were ruled out, containing 6 death cases, 6 cerebral infarction cases and 11 ineligible cases. Then 177 enrolled patients were randomly divided into three groups according to the treatments: I group, H group, Ce group. There was no significant differences in age ($P=0.871$), gender ($P=0.736$), tumor stage ($P=0.513$), World Health Organization classification of tumors ($P=0.902$) or education degree ($P=0.990$) among patients in the three groups (Table 1).

Post-treatment cognitive function score

After intervention, cognitive function score in Ce group (27.32±3.01) was slightly lower than that before the treatment (28.11±3.21) without significant difference ($P=0.876$). Additionally, compared with I group, patients in the other two group had the higher MMSE scores after the treatment while the Ce group was highest ($P=0.000$, Ce vs. H; $P=0.000$, Ce vs. I and $P=0.035$, H vs. I, Table 2).

Curative effect

There were 36 patients with CR, 22 patients with PR, two patients with SD and one patients with PD in Ce group of which the rate of RR (95.1%) was higher than that of I group (87.3%) and H group (86.9%), however, the difference was not statistically significant ($P=0.245$, Table 3).

Side effects

There was no significant difference in the incidences of limitation of opening mouth, hematologic toxicity, skin reaction, irradiation otitis media, inappetence, nausea and vomiting (Table 4).

Table 4. Comparison of incidence rate of the recurrence and metastasis in three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrence</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nasopharynx</td>
<td>Neck</td>
</tr>
<tr>
<td>I group (n=55)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>H group (n=61)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ce group (n=61)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>1.13</td>
<td>1.40</td>
</tr>
<tr>
<td>$P$</td>
<td>0.568</td>
<td>0.496</td>
</tr>
</tbody>
</table>

Note: At the same time, compared with I group, $^aP<0.05$; at the same time, compared with H group, $^bP<0.05$.

Table 5. Comparison of incidence rate of the recurrence and metastasis in three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CEA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>I group (n=55)</td>
<td>13.45±2.01</td>
</tr>
<tr>
<td>H group (n=61)</td>
<td>12.98±1.98</td>
</tr>
<tr>
<td>Ce group (n=61)</td>
<td>13.01±2.34</td>
</tr>
<tr>
<td>ANOVA</td>
<td>1.34</td>
</tr>
<tr>
<td>$P$</td>
<td>0.881</td>
</tr>
</tbody>
</table>

Note: In the same group, compared with CEA before treatment, $^aP<0.05$; At the same time, compared with I group, $^bP<0.05$; At the same time, compared with H group, $^cP<0.05$.

Table 6. Comparison of CEA in three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CEA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Ce group (n=61)</td>
<td>13.01±2.34</td>
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<tr>
<td>ANOVA</td>
<td>1.34</td>
</tr>
<tr>
<td>$P$</td>
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</tr>
</tbody>
</table>
logic toxicity, inappetence, nausea and vomiting of three groups (all P>0.05). However, the differences in dry mouth (P=0.026, Ce vs. H; P=0.000, Ce vs. I and P=0.000, H vs. I), oral mucositis (P=0.060, Ce vs. H; P=0.008, Ce vs. I and P=0.396, H vs. I), skin reaction (P=0.654, Ce vs. H; P=0.027, Ce vs. I and P=0.065, H vs. I), irradiation otitis media (P=0.097, Ce vs. H; P=0.009, Ce vs. I and P=0.051, H vs. I) of three groups had statistical significance, and Ce group had the lowest incidence rate (Table 4).

Incidence of the recurrence and metastasis

Although Ce group seemed to have the lowest incidences of the recurrence and metastasis, the differences among three groups had no statistical significance (P=0.302 and 0.638, Table 5).

Serum level of CEA

The concentration of CEA in serum after treatment was apparently lower than that before treatment for all groups (all P<0.05), while its level in Ce group after the treatment was evidently lower than that in other two groups (P=0.031, Ce vs. H; P=0.020, Ce vs. I and P=0.512, H vs. I, Table 6).

Post-treatment life quality

Except for the cognitive function and role functions, there was no significant differences in post-treatment life quality scores among three groups after treatment (all P>0.05). Especially, after the treatment, life quality scores of cognitive function and role function in H group and Ce group were higher than those in I group, while Ce group was the highest (Cognitive function: P=0.020, Ce vs. H; P=0.015, Ce vs. I and P=0.023, H vs. I; role function: P=0.039, Ce vs. H; P=0.011, Ce vs. I and P=0.031, H vs. I, Table 7).

Discussion

NPC is a kind of malignancy with low five-year survival rate. Currently, there are only few therapeutic options for patients with NPC. IMRT, which belongs to the precise radiotherapy technology with the advantage of improving the target dose, could reduce the exposure dose to the surrounding normal tissues and organs, so as to enhance local control of tumor, prolong the survival time of patients, reduce the complications and improve the patient’s life quality. Celecoxib, as the nonsteroidal anti-inflammatory drug, is a selective Cox-2 inhibitor that could inhibit tumor cell proliferation and angiogenesis, promote tumor cell apoptosis, reduce immune escape, and control tumor cell invasion, thus to play a positive role in anti-tumor activity. So, in this study, we try to explore the therapeutic efficacy of the combination of celecoxib and hippocampal sparing IMRT to treat NPC.

Cognitive function refers to the ability for human to process thoughts [25, 26]. Aging and disease and some other factors may affect cognitive function over time, resulting in problems like memory loss and trouble speaking or writing the right words [27]. In this study, a total of 177 patients were successfully treated and the analysis result of cognitive function score and life quality score showed that celecoxib combined hippocampal sparing IMRT could significantly preserve cognitive function. The mechanisms might be that: on the one hand, celecoxib

<table>
<thead>
<tr>
<th>Projects of life quality score</th>
<th>Before treatment</th>
<th>P</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I group (n=55)</td>
<td>H group (n=61)</td>
<td>Ce group (n=61)</td>
<td>P</td>
</tr>
<tr>
<td>Social function</td>
<td>55.23±10.56</td>
<td>56.09±8.39</td>
<td>54.32±9.09</td>
<td>0.344</td>
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<tr>
<td>Body function</td>
<td>53.41±11.02</td>
<td>53.89±9.89</td>
<td>54.12±10.91</td>
<td>0.211</td>
</tr>
<tr>
<td>Emotional function</td>
<td>47.51±7.80</td>
<td>47.89±9.71</td>
<td>47.73±8.97</td>
<td>0.431</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>64.37±9.18</td>
<td>65.01±8.79</td>
<td>65.45±10.02</td>
<td>0.122</td>
</tr>
<tr>
<td>Role functions</td>
<td>59.45±10.32</td>
<td>58.76±9.98</td>
<td>59.22±8.98</td>
<td>0.310</td>
</tr>
<tr>
<td>Cancerous fatigue</td>
<td>56.88±7.01</td>
<td>57.34±6.54</td>
<td>57.11±7.77</td>
<td>0.142</td>
</tr>
<tr>
<td>Cancerous pain</td>
<td>61.09±10.23</td>
<td>62.32±9.56</td>
<td>61.77±8.95</td>
<td>0.512</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>46.71±14.56</td>
<td>45.82±13.55</td>
<td>57.00±14.13</td>
<td>0.098</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>55.67±13.33</td>
<td>56.14±14.03</td>
<td>56.22±13.98</td>
<td>0.120</td>
</tr>
</tbody>
</table>

Note: In the same group, compared with project before treatment, *P*<0.05; At the same time, compared with I group, **P**<0.05; At the same time, compared with H group, ***P***<0.05.
could decrease the expression of Cox-2 to regulate NO pathways in the brain to form oxygen free radicals which are associated with the inflammation and brain damage [28]; on the other hand, as glutamate is involved in nerve cell degeneration and apoptosis through NMDA receptors, celecoxib could inhibit glutamate release, thus reduce the neurotoxic effect of radiation brain injury [29, 30].

And the RR in Ce group was 95.5%, which is in accordance with the research report of Mohammadianpanah [31], suggesting that the combination therapy of hippocampal sparing IMRT and celecoxib (cox-2 inhibitor) has good curative effect on local NPC. What’s more, celecoxib as a chemotherapy drug did not increase the related adverse reactions which most caused by cranial radiation. Meanwhile, its application could not only reduce the incidences of dry mouth, oral mucositis, skin reaction and irradiation otitis media, but also improve post-treatment life quality which is in according with our findings. In this study, all patients could tolerate the complete treatment, indicating the safety and good application prospect of this kind of combination treatment for NPC.

The low serum level of CEA in Ce group might increase the long-term survival more effectively than the therapy without celecoxib, which needs more evidences to confirm since the duration of follow-up is too short in this study. Meantime, the sample size is relatively small which might lead to the deviation of results in our research. Therefore, the prospective experiment with adequate samples and longer follow-up time will be conducted in the future, so as to promote the wide use of celecoxib combined with hippocampal sparing IMRT to treat NPC patients in clinic.

In conclusion, celecoxib combined with hippocampal sparing IMRT for the treatment of NPC patients could significantly improve their cognitive dysfunction, therapeutic effect, the quality of life and reduce adverse after radiotherapy, therefore, this combination therapy is worthy of consideration in clinical application.

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Disclosure of conflict of interest

None.

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