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IMMUNOTHERAPY FOR COLORECTAL CANCER

Validity of combination active specific immunotherapy for colorectal cancer: a meta-analysis of 2993 patients

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Abstract

Background aims. The aim of this study was to investigate whether active specific immunotherapy (ASI) is able to demonstrate therapeutic efficacy against colorectal cancer. *Methods.* We conducted a systematic review of published papers from MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, the Wanfang Database, the China Science and Technology Periodical Database and China Journal Net. Published data were extracted independently by two authors who used predefined database templates. The effects of ASI were compared with those of surgery alone, and a pooled analysis was performed with the use of the data from random- or fixed-effect models. *Results.* Twelve trials matched our inclusion criteria ($n = 2993$, including 1842 control subjects). The overall analysis showed a significant survival benefit [1-, 2-, 3-, 4-, 5-, 6- and 7-year overall survival (OS), $P < 0.05$; 10-year OS, $P < 0.001$] in favor of ASI immunotherapy combined with surgery, but there was not an improvement in the 8- or 9-year OS ($P > 0.05$). The disease-free survival (DFS) rate was improved after the combination of ASI immunotherapy (2-, 3-, 5- and 10-year DFS, $P < 0.05$), but no significant improvement was noted for the 1-, 4-, 6-, 7-, 8- or 9-year DFS ($P > 0.05$). In addition, the disease-specific survival (DSS) was improved at some time points after the combination of ASI immunotherapy and surgery (2-, 3-, 4-, 5- and 6-year DSS, $P < 0.05$, but not the 1-, 7-, 8- or 9-year DSS, $P > 0.05$). An improved 2-, 3-, 4-, 5- and 6-year recurrence-free interval (RFI) ($P < 0.05$) was also observed in patients who received ASI therapy, but this was not observed for the 1-year RFI ($P > 0.05$). Furthermore, an analysis of the recurrence-free survival (RFS) showed that it was significantly increased in the ASI plus surgery group (1-, 2-, 3-, 4-, 5- and 6-year RFS, $P < 0.001$). The funnel plots showed that the analyses were relatively reliable and the publication bias was small. *Conclusions.* The combination of ASI immunotherapy and surgery was superior in prolonging the overall survival time and enhancing the recurrence-free survival rate compared with surgery alone.

Key Words: *active specific immunotherapy, bacillus Calmette-Guérin, colorectal cancer, meta-analysis, Newcastle disease virus*

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies in the industrialized world and is the second most common cancer [1,2]. The 5-year survival rate of patients with CRC after surgery alone varies between 60% and 90% for stage I and II (Dukes A and B), 25% and 60% for stage III (Dukes C) and <5% for stage IV (Dukes D) disease [1,3]. The recurrence rate for stages II–III CRC varies from 20% to 60% as the result of the presence of micro-metastasis at the time of surgery [4]. Adjuvant treatment with 5-fluorouracil/leucovorin is now considered the standard therapy for stage III colon carcinoma and results in an absolute survival benefit of approximately 10% [5,6]. Combining chemotherapy and immunotherapy may improve the prognosis for stage III patients, especially considering that active specific immunotherapy and chemotherapy have shown synergistic effects in preclinical tumor models [7].

Active specific immunotherapy (ASI), which uses vaccines with autologous tumor cells and an

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immunomodulating adjuvant such as bacillus Calmette-Guérin (BCG) or Newcastle disease virus (NDV) for their potent immunostimulatory properties that affect both the innate as the adaptive immune system, elicits a long-term anti-tumor immune response and is more effective than other approaches in a minimal residual disease setting [8]. It has been demonstrated that BCG has a T_H1-stimulatory effect, primarily inducing cell-mediated immunity, which results in alterations in the cytokine response patterns in such a way that the T_H2 immunological response promoting humoral immunity is inhibited [9]. NDV infection of tumor cells leads to an improved tumor cell/T-cell interaction and an increased T-cell co-stimulatory activity, consequently increasing the cytotoxic potential of T cells [10]. In pre-clinical models, ASI and chemotherapy were shown to have a synergistic anti-tumor effect. This modality of therapy, developed in the L10 guinea pig model by Hanna and Peters [11,12], was translated into a clinical phase I/II trial in colon carcinoma patients in the early 1980s. Promising results with regard to improving the time to recurrence were obtained with this adjuvant therapy and led to a comprehensive multicenter randomized phase III trial that showed good clinical benefits [13].

Apart from the capacity to directly destroy micrometastases, ASI has been demonstrated to disrupt the characteristically compact structure of metastatic foci, enabling chemotherapy to reach deeper into the cancer tissue. One retrospective study was performed to investigate whether the beneficial effects of ASI given as adjuvant treatment correlated with the presence of micro-satellite instable (MSI), which is considered to be an important biological determinant of colon cancer. The results indicated that patients with MSI tumors did well, irrespective of the treatment arm and tumor stage [14,15]. Currently, BCG-based immunotherapy is established for bladder cancer and is under evaluation for the treatment of prostate, renal, pancreatic and hepatocellular carcinomas, as well as glioma [16,17].

Several studies have demonstrated that the magnitude of delayed-type hypersensitivity reactions (DTH) after autologous tumor cell vaccinations correlates strongly with the recurrence and survival rate of the cancer [18]. The presence of a DTH response to tumor cells within 48 h after the vaccination regimen is used as a measure of immunogenicity and reflects the adequacy of the vaccination and the general immune status of the patient. Thus far, DTH has been the only suitable parameter for evaluating anti-tumor immunity and is the best early predictor of the clinical efficacy of vaccination therapies. In one study, the DTH was demonstrated to correlate well with *in vitro* lymphocyte-proliferative responses to mitomycin C–treated autologous tumor cells. Thus, in our study, we collected the DTH data for the included studies, but the DTH reaction was positive after the immunotherapy and negative before therapy in all of the included studies.

The aim of our present study was to investigate whether ASI immunotherapy including BCG and NDV has beneficial effects when given as treatment for CRC. Moreover, the clinical outcomes were extracted in terms of the overall survival (OS), recurrence-free interval (RFI), recurrence-free survival (RFS), disease-free survival (DFS) and disease-specific survival (DSS). Among these outcomes, the term "RFI" is used herein to refer to the time (in years) to the first CRC recurrence after censoring patients with second primary cancer as a first event or death without evidence of recurrence. The RFS was defined as the time from surgery to the first local, regional or distant tumor recurrence, with second primary cancers, contralateral events and deaths without evidence of disease treated as censored events.

Methods

Search strategy and selection criteria

Trials were identified by an electronic search of the PubMed database (1976 onward), Embase (1966 onward), the Cochrane Central Registry of Controlled Trials (no date restriction), the Wanfang Database (no date restriction), the China Science and Technology Periodical Database (no date restriction), China Journal Net (no date restriction), reference lists of published trials and relevant review articles. The search strategy included the following medical subject headings: "colon cancer," "autologous tumor cell," "bacillus Calmette-Guérin," "Newcastle disease virus," "immunotherapy," "active specific immunotherapy," "colon cancer," "colorectal carcinoma" and free text searches. No language limits were applied. The initial search was performed in November 2013 and updated searches were conducted in January 2015. We also performed manual searches of reference lists, conference proceedings of the American Society of Clinical Oncology Annual Meetings and the European Cancer Conference. We also searched the http://www.ClinicalTrials.gov website for information on prospective and ongoing trials. We excluded abstracts that were never subsequently published as full papers and studies on animals and cell lines.

Data extraction and quality assessment

Data extraction was independently conducted by two reviewers through the use of a standardized approach. Disagreement was adjudicated by a third reviewer after