Clinical and Immunologic Responses to Active Specific Cancer Vaccines in Human Colorectal Cancer

Dirk Nagorsen and Eckhard Thiel

Abstract

Colorectal cancer is a common malignant disease, which, despite some progress, still requires improved therapeutic options. Several clinical studies have used active specific immunotherapy (i.e., vaccination) in colorectal cancer. However, the literature still lacks a comprehensive meta-analysis of this approach in advanced colorectal cancer. We did a systematic review with a meta-analysis of clinical studies to evaluate the objective clinical and immunologic response to active specific immunotherapy in patients with colorectal cancer. We conducted a search of Medline and the Web of Science, manually reviewed the literature, and consulted with experts. Criteria for including studies were colorectal cancer patients, active specific immunotherapy to induce a response directed against cancer or cancer antigens, an evaluable tumor burden (i.e., advanced or metastatic colorectal cancer), and precise classification of the patient, disease, and response. Response rates were assessed according to WHO criteria. Primary end points were the objective clinical response rate and the rate of immunologic responses. The secondary end point was the distribution of immune and clinical responses in relation to the route of vaccination and the type of vaccine. Thirty-two phase I/II studies reporting on 527 patients with advanced or metastatic colorectal cancer met all inclusion criteria. Pooled analysis showed an overall response rate (complete response + partial response) of 0.9% for advanced/metastatic colorectal cancer patients who underwent active specific immunization with a broad variety of substances (e.g., autologous tumor cells, peptide vaccine, dendritic cells, idiotypic antibody, and virus-based vaccine). Humoral immune responses were reported in 59%, and cellular ones were reported in 44% of the cases. Mixed or minor responses and disease stabilization are described in 1.9% and 8.3% of colorectal cancer patients, respectively. Pooled results of clinical trials reveal a very weak clinical response rate of <1% for active specific immunization procedures currently available for advanced colorectal cancer. Immune response induction is described in approximately half the patients.

Significant advances in treating metastatic colorectal cancer were achieved by introducing new chemotherapeutic agents and monoclonal antibodies, and yet most patients die of their disease (1, 2). Improved treatment is urgently needed. Since the discovery of tumor-associated antigens during the early 1990s, rapid progress has been made in identifying antigens and describing immune interactions in cancer patients (3, 4). Immunotherapeutic approaches have entered the clinical phase. Active specific immunotherapy is defined as treatment strategy aiming at the in vivo induction of a tumor-directed immune response and must be distinguished from passive immunotherapy (antibody, adoptive T-cell transfer) and nonspecific immunotherapy (including cytokines or immunostimulants). Most experience with active specific immunotherapy has been gained in melanoma patients (5). However, colorectal cancer is also a promising and challenging target disease for active specific immunotherapy for three reasons: (a) It is a common disease that requires new therapeutic options. (b) Several tumor-associated antigens have been described in colorectal cancer [at least 24 tumor antigens have been identified for colorectal cancer (6)]. (c) Like other tumors, colorectal cancer shows spontaneous T-cell responses to tumor antigens in patients without prior immunotherapy, suggesting immunogenicity of this cancer (7, 8). After a period of unspecific immunotherapy mainly with Bacillus Calmette-Guerin during the 1970s and early 1980s (9), more sophisticated approaches were used, including tumor antigen–derived peptides, dendritic cells pulsed with peptides, anti-idiotypic antibodies, viruses encoding antigen sequences and costimulatory molecules, and autologous tumor cell vaccines (10).

The immunotherapy of cancer is now being assessed. A controversy recently flared up over the clinical efficacy of active specific immunotherapy of cancer. Although some researchers are discouraged by the objective response rate of 2.6%, mainly...
among melanoma patients (11), others regard positive preclinical data as an incentive to further exploit the potential of active specific cancer vaccines (12). We are contributing to this ongoing discussion by adding more data on colorectal cancer. Although encouraging results have been reported for colorectal carcinoma patients with minimal residual disease (10), there has not yet been any comprehensive analysis covering only colorectal cancer patients with a measurable tumor burden. However, conclusions regarding the objective clinical response rates can only be drawn based on such an analysis.

Materials and Methods

We conducted a search of the Medline database from January 1985 to January 2006, using the following keywords: “colorectal” OR “colon” OR “rectal” AND “cancer” OR “carcinoma” AND “immunization(s)” OR “vaccination(s)” OR “vaccine(s).” We also searched the Web of Science, manually reviewed the literature, and consulted with experts. Criteria for including studies were treatment of at least three colorectal cancer patients, active specific immunotherapy to induce an immune response directed against cancer or cancer antigens, a measurable tumor burden (i.e., advanced or metastatic colorectal cancer), precise classification of patients and their disease, no concurrent chemotherapy, publication date of 1985 or later, English language, and publication in a regular scientific article (exclusion of abstracts).

All articles included were intensively analyzed for the type of vaccine, the route of vaccination, the adjuvants given, the number of evaluable colorectal cancer patients, the toxicity, the humoral and cellular immune responses, the so-called “soft” response criteria [e.g., tumor marker decrease, mixed or minor response (MR), and stable disease (SD)], and the objective clinical responses. Published clinical response rates had to meet the WHO criteria: 50% decrease in the sum of the products of perpendicular diameters of all lesions and no increase in any lesion. MRs as well as disease stabilizations were accepted as given in the respective publication.

To calculate objective clinical response rates, the number of objective clinical responses [i.e., complete response (CR) and partial response (PR) according to the WHO criteria, if given] was divided by the total number of patients evaluable for CR and PR. For rates of MR and SD, the number of recorded MR and SD was divided by the total number of patients evaluable for CR and PR. The assessment of immunologic responses included only studies analyzing cellular and/or humoral immune responses. The numbers of patients with humoral and cellular responses were separately divided by the number of patients evaluated. We have introduced a new term to analyze patient subsets: the clinical benefit rate (CBR). The CBR represents the sum of CR, PR, MR, and SD rates. Thus, for subset analysis, the CBR was calculated as the sum of CR, PR, MR, and SD based on the various vaccine formulations (e.g., autologous tumor and dendritic cells) and routes of vaccination (e.g., s.c. and i.v.).

Results

One hundred eight publications on immunization in colorectal cancer, mostly clinical trials, were analyzed in detail. Thirty-two of these studies met all inclusion criteria. Other studies were excluded mainly because of adjuvant vaccination after tumor resection (i.e., no measurable tumor burden), insufficient clinical data on the disease and response, and concurrent chemotherapy. More than 90% of the studies disclosed no striking differences among the various vaccination regimens. The vaccine formulation and the route of vaccination. Detailed results are given in Tables 2 and 3. In brief, we found a CBR of 46% for autologous tumor cell vaccine, 17% for dendritic cell–based vaccines, and 13% for peptide-only vaccines (Table 2). The CBR ranged between 10% and 14% regardless of the route of vaccination (Table 3).

Toxicity was mild in the vast majority of studies and manifested mainly as local redness, pain, and swelling at the injection site; half the studies report transient flu-like symptoms in some patients. Elevated liver enzymes were found in six studies, and single cases of anemia were found in five. Further side effects include rare cases of adenopathy, nausea, diarrhea, rashes, fatigue, malaise, and transfusion-like reactions. All other symptoms were described only in single cases and/or are most probably due to the advanced malignant disease.

The immunologic response was analyzed in 22 studies (69%), 59% being evaluable for the cellular immune response and 31% for the humoral one. Immunization led to a positive humoral immune responses in 59% (121 of 204) of the patients tested and to positive cellular immune responses in 44% (106 of 242). We did a post hoc analysis to exploratorily calculate the immunologic responses in subsets according to the vaccine formula used and the route of vaccination. Detailed results are given in Tables 2 and 3. This preliminary analysis disclosed no striking differences among the various vaccination strategies.

Despite the broad variety of antigens described, carinoembryonic antigen was used in 15 studies included in the present review. We, therefore, did a post hoc analysis to characterize the subset of carcinoembryonic antigen–based vaccination studies. One PR, one MR, and 18 SD were reported in a total population of 214 patients (CBR = 9.3%). After immunization,
carcinoembryonic antigen induced a humoral immune response in 48% of the patients and a cellular one in 37%.

Discussion

Numerous studies have been done on vaccination in colorectal cancer patients. Thirty-two studies met all inclusion criteria and were selected for the present meta-analysis. We found an objective response rate of 0.9% for 527 colorectal cancer patients treated with active specific immunotherapy in 32 different studies. These data are in accordance with those reported by Rosenberg et al. (11), who found that vaccinated patients had an objective response rate of 2.6% in their own study (96% melanoma patients) and 3.8% in other investigations, including three studies dealing specifically with colorectal cancer patients. Apart from this objective response rate, a CBR (CR, PR, MR, and SD) of 11.2% was obtained in our study by applying so-called soft response criteria like SD or MR. Although objective clinical responses are undeniably the preferred end points of clinical vaccination studies (11), we cannot completely abandon soft response criteria, because we would risk ignoring small benefits that could add up to a clinically relevant result.

In stark contrast to the exiguous objective clinical response rate of <1%, about half the colorectal cancer patients responded immunologically to the vaccines. However, these immunologic data were collected by diverse methods and must therefore be carefully interpreted. Nevertheless, they give a good indication of the degree to which immune responses can be induced. Despite the use of new and more sophisticated methods, particularly to analyze cellular immune responses (14), the

Table 1. Vaccine trials in patients with advanced colorectal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine</th>
<th>Adjuvants</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhattachary-Chatterjee et al. (21)</td>
<td>Antibody anti-Id 3H1</td>
<td>Aluminum hydroxide</td>
<td>i.c.</td>
</tr>
<tr>
<td>Conny et al. (22)</td>
<td>Vaccinia virus expressing CEA</td>
<td>None</td>
<td>i.d. vs s.c.</td>
</tr>
<tr>
<td>Conny et al. (23)</td>
<td>CEA/HepB-Plasmid</td>
<td>HbsAG</td>
<td>i.m.</td>
</tr>
<tr>
<td>Denton et al. (24)</td>
<td>Antibody105AD7</td>
<td>Aluminum hydroxide</td>
<td>i.m.</td>
</tr>
<tr>
<td>Fong et al. (25)</td>
<td>DC + CEA peptide</td>
<td>None</td>
<td>i.v.</td>
</tr>
<tr>
<td>Foon et al. (26)</td>
<td>Antibody anti-Id CEA</td>
<td>Aluminum hydroxide</td>
<td>i.d.</td>
</tr>
<tr>
<td>Goydos et al. (27)</td>
<td>Synthetic MUC-1 peptide</td>
<td>BCG</td>
<td>i.d.</td>
</tr>
<tr>
<td>Horig et al. (28)</td>
<td>ALVAC expressing CEA and B7.1</td>
<td>ALVAC, B7.1</td>
<td>i.m.</td>
</tr>
<tr>
<td>Itoh et al. (29)</td>
<td>DC + CEA peptide</td>
<td>IFN-α, TNF-α</td>
<td>i.v.</td>
</tr>
<tr>
<td>Liang et al. (13)</td>
<td>Auto-tumor + NDV</td>
<td>NDV</td>
<td>i.d.</td>
</tr>
<tr>
<td>Liu et al. (30)</td>
<td>DC + CEA peptide</td>
<td>None</td>
<td>Intranodal (inguinal lymph node)</td>
</tr>
<tr>
<td>Marshall et al. (31)</td>
<td>Vaccinia/avipox virus expressing CEA</td>
<td>GM-CSF, IL-2</td>
<td>s.c.</td>
</tr>
<tr>
<td>Marshall et al. (32)</td>
<td>Vaccinia/avipox virus expressing CEA + TRICOM</td>
<td>TRICOM, some GM-CSF</td>
<td>i.d./s.c.</td>
</tr>
<tr>
<td>Matsuda et al. (33)</td>
<td>DC + CEA peptide</td>
<td>None</td>
<td>s.c.</td>
</tr>
<tr>
<td>McAneny et al. (34)</td>
<td>Vaccinia virus expressing CEA</td>
<td>None</td>
<td>i.d.</td>
</tr>
<tr>
<td>Miyagi et al. (35)</td>
<td>SART3-peptides</td>
<td>Incomplete Freund's adjuvant</td>
<td>s.c.</td>
</tr>
<tr>
<td>Morse et al. (36)</td>
<td>DC + CEA peptide</td>
<td>1pt. IL-2</td>
<td>i.v./some i.d. + i.v.</td>
</tr>
<tr>
<td>Morse et al. (37)</td>
<td>DC CEA mRNA transfected</td>
<td>Few IL-2</td>
<td>i.v. + i.d.</td>
</tr>
<tr>
<td>Morse et al. (38)</td>
<td>DC infected with fowlpox expressing CEA + TRICOM</td>
<td>TRICOM</td>
<td>i.d. and s.c.</td>
</tr>
<tr>
<td>Moulton et al. (39)</td>
<td>β-HCG-peptide conjugated to dipherthia-toxin</td>
<td>Diphertheria toxin</td>
<td>i.m.</td>
</tr>
<tr>
<td>Moviglia (40)</td>
<td>Tumor B-cell lymphocyte hybridoma</td>
<td>B cells</td>
<td>i.m.</td>
</tr>
<tr>
<td>Neidhart et al. (41)</td>
<td>EpCAM protein with MPL</td>
<td>MPL liposomes/GM-CSF</td>
<td>s.c.</td>
</tr>
<tr>
<td>Rains et al. (42)</td>
<td>DC + tumor RNA</td>
<td>KLH</td>
<td>i.v.</td>
</tr>
<tr>
<td>Sadanaga et al. (43)</td>
<td>DC + MAGE 3 peptide</td>
<td>None</td>
<td>i.v.</td>
</tr>
<tr>
<td>Samonigg et al. (44)</td>
<td>Antibody SCV106 mimicking 17-1A</td>
<td>Aluminum hydroxide</td>
<td>s.c.</td>
</tr>
<tr>
<td>Sato et al. (45)</td>
<td>Multi-peptide (SART, Ick, CyB)</td>
<td>Montanide isa-51</td>
<td>s.c.</td>
</tr>
<tr>
<td>Sobol et al. (46)</td>
<td>Autologous tumor + retrovir vector-IL-2 in autologous fibroblasts</td>
<td>Fibroblasts producing IL-2</td>
<td>s.c.</td>
</tr>
<tr>
<td>Tsuruma et al. (47)</td>
<td>Survivin peptide</td>
<td>None</td>
<td>s.c.</td>
</tr>
<tr>
<td>Ueda et al. (48)</td>
<td>DC + CEA peptide</td>
<td>None</td>
<td>s.c./i.d.</td>
</tr>
<tr>
<td>von Mehren et al. (49)</td>
<td>ALVAC expressing CEA and B7.1</td>
<td>B7.1</td>
<td>i.d.</td>
</tr>
<tr>
<td>Wiseman et al. (50)</td>
<td>Autologous tumor</td>
<td>None</td>
<td>intralymphatic</td>
</tr>
<tr>
<td>Woodlock et al. (51)</td>
<td>Allogeneic tumor cells + IL-1a</td>
<td>DETOX, in some IL-1a</td>
<td>i.d.</td>
</tr>
</tbody>
</table>

Total

Abbreviations: ND, not done; NI, not identifiable; NR, not reported; CEA, carcinoembryonic antigen; IC-FC, intracellular cytokine flow cytometry; DC, dendritic cells; NDV, Newcastle disease virus; ELISPOT, enzyme-linked immunosorbent spot; IL, interleukin; β-HCG, β-human chorionic gonadotropin.
immunologic response rates are comparable with those achieved 10 years ago (see Table 1).

A post hoc analysis was done to search for a trend toward a higher clinical benefit or better immunologic response, depending on the vaccine formula or vaccination route. We found a CBR of 46% in patients treated with autologous tumor followed by 17% and 13% for dendritic cell–based and peptide-only vaccines, respectively. These explorative data

Table 1. Vaccine trials in patients with advanced colorectal cancer (Cont’d)

<table>
<thead>
<tr>
<th>Colorectal cancer patients</th>
<th>CR + PR</th>
<th>MR</th>
<th>SD</th>
<th>Humoral immune response</th>
<th>Cellular immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type of response</td>
<td>n / total</td>
<td>Type of response</td>
<td>n / total</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td>Anti-anti-idiotypic</td>
<td>ND</td>
</tr>
<tr>
<td>20</td>
<td>17/23</td>
<td></td>
<td></td>
<td>Lymphoproliferation</td>
<td>0/20</td>
</tr>
<tr>
<td>17</td>
<td>0/17</td>
<td></td>
<td></td>
<td>Lymphoproliferation</td>
<td>9/13</td>
</tr>
<tr>
<td>13</td>
<td>0/4</td>
<td></td>
<td></td>
<td>Proliferation/tetramer</td>
<td>7/12</td>
</tr>
<tr>
<td>23</td>
<td>17/22</td>
<td></td>
<td></td>
<td>Lympoproliferation</td>
<td>10/23</td>
</tr>
<tr>
<td>30</td>
<td>7/22</td>
<td></td>
<td></td>
<td>ELISPOT</td>
<td>3/11</td>
</tr>
<tr>
<td>13</td>
<td>2/12</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/11</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>ELISPOT</td>
<td>7/10</td>
</tr>
<tr>
<td>13</td>
<td>0/25</td>
<td></td>
<td></td>
<td>CTLp</td>
<td>7/10</td>
</tr>
<tr>
<td>10</td>
<td>0/35</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>11</td>
<td>0/25</td>
<td></td>
<td></td>
<td>ELISPOT</td>
<td>7/10</td>
</tr>
<tr>
<td>35</td>
<td>0/10</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>17</td>
<td>0/7</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>12</td>
<td>0/12</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>11</td>
<td>0/7</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>11</td>
<td>0/7</td>
<td></td>
<td></td>
<td>LD</td>
<td>7/10</td>
</tr>
<tr>
<td>77</td>
<td>56/77</td>
<td></td>
<td></td>
<td>Anti-β-HCG antibody</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>0/2</td>
<td></td>
<td></td>
<td>Anti-β-HCG antibody</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>8/11</td>
<td></td>
<td></td>
<td>Anti-β-HCG antibody</td>
<td>ND</td>
</tr>
<tr>
<td>15</td>
<td>0/2</td>
<td></td>
<td></td>
<td>Anti-β-HCG antibody</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>0/3</td>
<td></td>
<td></td>
<td>Anti-β-HCG antibody</td>
<td>ND</td>
</tr>
<tr>
<td>21</td>
<td>17/21</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>7/12</td>
</tr>
<tr>
<td>10</td>
<td>0/11</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>4/8</td>
</tr>
<tr>
<td>10</td>
<td>0/3</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>2/6</td>
</tr>
<tr>
<td>17</td>
<td>0/1</td>
<td></td>
<td></td>
<td>Tetramer/ELISPOT</td>
<td>1/17</td>
</tr>
<tr>
<td>11</td>
<td>0/3</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>2/7</td>
</tr>
<tr>
<td>28</td>
<td>0/6</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>2/7</td>
</tr>
<tr>
<td>3</td>
<td>0/1</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>2/7</td>
</tr>
<tr>
<td>22</td>
<td>0/1</td>
<td></td>
<td></td>
<td>Chromium release</td>
<td>2/7</td>
</tr>
</tbody>
</table>

527 5 (0.9%) 10 (1.9%) 44 (8.3%) 121/204 (59%) 106/242 (44%)

Table 2. Influence of vaccine, post hoc explorative analysis

<table>
<thead>
<tr>
<th>Rate CR, PR, MR, and SD</th>
<th>Humoral response</th>
<th>Cellular response</th>
</tr>
</thead>
<tbody>
<tr>
<td>46% (21/46)</td>
<td>(0/4)</td>
<td>(2/6)</td>
</tr>
<tr>
<td>17% (12/70)</td>
<td>ND</td>
<td>53% (20/38)</td>
</tr>
<tr>
<td>13% (9/69)</td>
<td>29% (7/24)</td>
<td>33% (19/58)</td>
</tr>
<tr>
<td>3% (3/80)</td>
<td>69% (46/67)</td>
<td>53% (19/36)</td>
</tr>
<tr>
<td>3% (4/135)</td>
<td>(4/4)</td>
<td>37% (20/54)</td>
</tr>
<tr>
<td>8% (10/127)</td>
<td>61% (64/105)</td>
<td>52% (26/50)</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.
must also be interpreted with great caution because the studies lack well-defined criteria for MR and SD and have small numbers of patients in the subgroups. Further subset analyses did not reveal substantial differences among various vaccines or vaccination routes.

A number of questions are now of topical interest in this connection. Is it a good sign that researchers are able to induce immune responses in a substantial number of patients? Is it a bad sign that this can be done without a clinical response? Are we on the right track using active specific immunotherapy in cancer? Is an immune response rate of about 50% without hard signs of clinical response reason enough to continue this type of immunotherapy?

We think it is worthwhile to continue investigating active specific immunotherapy for several reasons, one being its low toxicity rate. Moreover, it can help us to understand processes in the interaction between the tumor and the immune system that could also be useful for other immunotherapeutic approaches, one example being adoptive transfer of in vitro expanded T cells, which has been successfully tested in melanoma patients [50% response rate, (15, 16)]. There is yet another reason for continuing investigations: despite the nearly complete lack of a clinical response in patients with advanced colorectal cancer, a few studies have shown that adjuvant active specific immunotherapy may be beneficial in subgroups of patients after colorectal cancer resection (10, 13, 17, 18). However, we should not expect too much clinical effectiveness from vaccination in patients with a high tumor burden.

As previously postulated (19), it might be better to analyze immune responses not only systemically in peripheral blood but also at the tumor site. We may expect the discovery or clinical introduction of new malignancy-associated antigens with a stronger influence on tumor proliferation, like Wilms tumor gene 1 (WT1) (20). Most studies, thus far, have used single epitopes or antigens. Our explorative analyses showing the highest CBR among patients vaccinated with autologous tumor suggest that higher success rates may be achieved by multiepitopic and more individualized vaccines.

Furthermore, we must gain a better understanding of T cell functions, such as T-cell avidity for tumor cells, T-cell homing to the tumor site, durability of the T-cell response, and activation of more than one effector mechanism. Although patients with advanced colorectal cancer have thus far derived no substantial clinical benefit from vaccination, we do not know enough to abandon our efforts in this direction. We agree with those who find it premature to give up on active cancer vaccines, although much work remains (12).

References

24. Denton GW, Durant LG, Hardcastle JD, Austin EB, Sewell HF, Robins RA. Clinical outcome of colorectal


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