Local Administration of Monoclonal Antibody-Drug Conjugate: A New Strategy to Reduce the Local Recurrence of Colorectal Cancer

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ABSTRACT

This report investigates the application of monoclonal antibody A7 and its drug conjugate in locally controlling colorectal cancer. The experimental protocol consisted of local retention, lymphatic delivery, normal organ distribution, systemic toxicity, and tumoricidal effects. When 125I-labeled monoclonal antibody (Mab) A7 was injected into the pelvis and the thigh of Balb/c mice, a high local retention unrelated to antigen-antibody interaction was observed at the injected site for 24 h after injection. An analysis of local retention properties related to antigen-antibody interaction, conducted by intratumorally or peritumorally injecting 125I-Mab A7 into the tumor-bearing athymic nude mice, revealed a significantly higher tumor localization of Mab A7 in comparison to i.v. injection. 125I-Mab A7 accumulated to a great extent in the ipsilateral regional lymph node but not in the contralateral regional lymph node. Normal organ accumulation of Mab A7 was lower in the locally injected group than in the i.v. injected group. Intratumoral injection of Mab A7-neocarzinostatin (A7-NCS) led to the complete remission of established tumor in 5 of 6 antigen-positive xenograft-bearing mice but exhibited a complete remission in only 1 of 6 antigen-negative xenograft-bearing mice. A single local injection of A7-NCS inhibited tumor development in 12 of 16 and 5 of 15 antigen-positive tumor-bearing mice and antigen-negative tumor-bearing mice, respectively, whereas neither a systemic injection of A7-NCS and NCS nor a local injection of NCS had a notable inhibitory effect on tumor development. Systemic toxicity of NCS was markedly reduced when it was locally administered in the antibody-conjugated form. These findings indicate that local injection of immunoconjugate is a promising new field for controlling the local recurrence of colorectal cancer.

INTRODUCTION

Monoclonal antibody is now being used with a variety of cytotoxic agents ranging from well-known chemotherapeutic agents to newer agents. Several studies have demonstrated the potential clinical use of immunoconjugate; however, a number of problems with this approach to cancer therapy have recently been discussed and reviewed: minimizing the “foreignness” of the injected antibody (1, 2); reducing the circulating tumor antigen (3, 4) and human anti-mouse Ig antibody (5); increasing the amount of antibody that reaches the target tumor (3, 4, 6); and the problem of tumor antigen heterogeneity (7). In the clinical application of monoclonal antibody, therefore, there may be a limitation to therapeutic efficiency if monoclonal antibody is used in previously established ways. This information prompted us to try a new approach with monoclonal antibody-drug conjugate. Local administration is an encouraging new direction in the actual application of the conjugate in cancer chemotherapy.

During the last 30 years, despite the remarkable progress in surgical techniques, the average survival rate of patients undergoing radical surgery for advanced colorectal carcinoma has not improved. In spite of radical operations, a large number of patients have died of local recurrence without distant metastasis at rates of 19 to 42% (8–12). Preventing local recurrence is vital to colorectal cancer treatment, and consequently a new type of cancer therapy is required. For the most part, local recurrence of colorectal cancer is thought to result from a regrowth of remnant cancer cells surrounding the rectum (13–15). A new therapeutic mode of cancer chemotherapy, therefore, should be directed at eliminating residual cancer cells with target specificity and with fewer adverse side effects. Monoclonal antibody-drug conjugate may specifically target cancer cells and efficiently eliminate the cancer cells, especially with local administration.

In this study, we focused on the application of Mab3 A7 and A7-NCS, which selectively react to human colorectal cancer, for the local control of colorectal cancer. This is the first report describing the application of monoclonal antibody-drug conjugate in preventing the local recurrence of colorectal cancer.

MATERIALS AND METHODS

Monoclonal Antibody and Its Drug Conjugate. The murine monoclonal antibody A7, which is highly reactive to colorectal cancer (16), was prepared as described previously. One Mab A7 was conjugated to 2 mol of NCS through a disulfide bond by the N-succinimidyl-3-(2-pyridyldithio)propionate method (17). A7-NCS is known to retain antigen-binding activity identical to that of the parent Mab A7, shows strong cytoxicity in vitro to the antigen-positive cancer cell line SW1116, and yields a significant tumoricidal effect in vivo in tumor-bearing nude mice (18). A previous report (19) elucidated that A7-NCS was so stable that it showed a similar pharmacokinetic profile in vivo to parent Mab A7 when systemically administered. For biodistribution study, Mab A7 was labeled with 125I by the chloramine T method (20). Its specific activity was 5 μCi/μg.

Local Injection of 125I-Mab A7. Ten μl of saline solution containing 125I-Mab A7 (2.0 × 10⁶ cpm) were locally injected into the pelvises of Balb/c mice (8 weeks, 20–25 g) via the anal mucosa. The mice were sacrificed 1, 6, 12, and 24 h after injection, and the blood and pelvis containing the injected site were excised and weighed. The radioactivity of the excised tissue was measured in a gamma counter. In a separate experiment, 125I-Mab A7 (2.0 × 10⁶ cpm) was injected into the thigh of mice, and the mice were sacrificed 1, 6, 12, and 24 h after injection. The blood and the thigh tissue containing the injected site were removed, and the radioactivity was measured in a gamma counter.

Peritumoral Injection of 125I-Mab A7. A solution containing human colon cancer cell line SW1116 (5 × 10⁶ cells) was injected into the posterior thigh of athymic nude mice (Balb/c, nu/nu). The mice developed a palpable tumor on their thigh 14 days after inoculation, which ranged from 0.2 to 0.4 g in weight. 125I-Mab A7 and nonspecific IgG

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The abbreviations used are: Mab, monoclonal antibody; NCS, neocarzinostatin; i.t., intratumorally.

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(5 × 10⁶ cpm) were administered locally to the thigh muscle at the distal portion of the tumor. The mice were sacrificed 6, 12, 18, and 24 h after injection. The tumor were resected and weighed, and the radioactivity was measured in a gamma counter. For comparison, ¹²⁵I-Mab A7 was injected i.v. into the athymic nude mice. The following procedure was the same as described above.

Intratumoral Injection of ¹²⁵I-Mab A7. Human colon cancer cell line SW1116 and human epidermoid cancer cell line KB were used as antigen-positive cells and antigen-negative cells, respectively. Each cell line (5 × 10⁶ cells) was injected into the thighs of athymic nude mice. After the development of palpable tumors, the mice were given 10 μl of saline i.t. containing ¹²⁵I-Mab A7 (1 × 10⁶ cpm). The mice were sacrificed 1, 6, 12, 24, 48, and 72 h after injection, and the tumors and blood were measured and weighed. The radioactivities of the tumor and blood were measured in a gamma counter. The antibody retention in tumor and blood was compared with that of the SW1116 xenograft-bearing mice and the KB xenograft-bearing mice.

Lymph Node Accumulation. Ten μl of saline solution containing ¹²⁵I-Mab A7 (1 × 10⁶ cpm) were injected into the pelvis of Balb/c mice, and the mice were sacrificed 12 and 24 h after injection. Blood, liver, spleen, kidney, and lung were removed and weighed, and the radioactivities were measured in a gamma counter.

Normal Organ Distribution. Ten μl of saline solution containing ¹²⁵I-Mab A7 (2 × 10⁶ cpm) were injected into the peritoneum of Balb/c mice via the anal mucosa. The mice were sacrificed 2 h after injection. The ipsilateral and contralateral popliteal, paraaortic, and pericolic lymph nodes were removed, and the radioactivity was measured in a gamma counter.

In an another experiment, 10 μl of saline solution containing ¹²⁵I-Mab A7 (1.0 × 10⁶ cpm) were injected s.c. into the right foot pad of Balb/c mice. Mice were sacrificed at various times after the injection. The ipsilateral and contralateral popliteal lymph nodes were removed and weighed, and the radioactivity was measured in a gamma counter.

Local Injection of A7-NCS into Mice Bearing Cancer Cells but No Palpable Tumor. Initially, a solution containing SW1116 cells (5 × 10⁶ cells) was injected into the thighs of athymic nude mice. Three days after the injection, single local 50-μl injections of a solution of A7-NCS equivalent to 5 units of NCS and 37 μg of Mab A7 was examined by injecting ¹²⁵I-Mab A7 into the foot pads or the pelvises of mice. In the pelvic injections, a significantly higher accumulation of ¹²⁵I-Mab A7 was observed in the paraaortic and pericolic lymph nodes, compared to the popliteal nodes. In the foot pad injections, the ipsilateral popliteal and the paraaortic lymph nodes exhibited a larger accumulation of ¹²⁵I-Mab A7 compared to the contralateral popliteal and the pericolic lymph node (Table 1).

RESULTS

Local Retention Property Unrelated to Antigen-Antibody Interaction. The local retention property of Mab A7 unrelated to antigen-antibody interaction was examined by the local injection of ¹²⁵I-Mab A7 into the thigh and the pelvises of mice (Fig. 1). The local retention property was evaluated by noting both the percentage of the injected amount remaining at the injection site and the tissue:blood ratio. In the pelvic injections, high and low localization of ¹²⁵I-Mab A7 was observed in the antigen-positive and -negative target tumors, respectively (Fig. 2B). Low and high localization was observed in the blood of antigen-positive and -negative tumor-bearing mice, respectively (Fig. 2A). ¹²⁵I-Mab A7 accumulation in the tumor was greater in the peritumoral injection than in the i.v. injection. Peritumoral injection of ¹²⁵I-labeled nonspecific IgG showed a lower accumulation in the tumor than that of ¹²⁵I-Mab A7 (Fig. 3).

Lymph Node Accumulation. Lymph node accumulation of Mab A7 was examined by injecting ¹²⁵I-Mab A7 into the foot pads or the pelvises of mice. In the pelvic injections, a significantly higher accumulation of ¹²⁵I-Mab A7 was observed in the paraaortic and pericolic lymph nodes, compared to the popliteal nodes. In the foot pad injections, the ipsilateral popliteal and the paraaortic lymph nodes exhibited a larger accumulation of ¹²⁵I-Mab A7 compared to the contralateral popliteal and the pericolic lymph node (Table 1).

Toxicity. Systemic toxicity of A7-NCS to the Balb/c mouse, when given locally or i.v., was investigated and compared with that of free NCS and saline solution. Various amounts of A7-NCS or NCS, ranging from 10 to 300 units of NCS, were administered locally or i.v. to 8 mice in each group. The posterior thigh and the tail vein were selected as the local injection and i.v. injection sites, respectively. The mice were monitored for systemic toxicity, which was defined as the number of deaths 7 and 14 days after treatment.
LOCAL INJECTION OF MONOCLONAL ANTIBODY-DRUG CONJUGATE

The accumulation of antibody in lymph nodes with time was measured by following the radioactivity of the popliteal lymph node after the injection of $^{125}$I-Mab A7 into the foot pads. The ipsilateral popliteal lymph node exhibited a significantly higher accumulation of Mab A7 than the contralateral popliteal lymph node for 24 h after antibody injection. The accumulation reached a similar level 48 h after injection (Fig. 4).

Normal Organ Distribution. To elucidate the difference in normal organ distribution between local injection and systemic injection, $^{125}$I-Mab A7 was injected locally into the pelvis and injected i.v. into different groups of mice, and the resulting radioactivity was compared. Data were expressed as a percentage inhibition dose/g 12 and 24 h after injection. The radioactivity in all organs examined was lower in the pelvic injection group than in the i.v. injection group (Fig. 5).

Tumoricidal Effect in Intratumoral Injection. The tumoricidal effect of A7-NCS in intratumoral injection was examined using the SW1116 and KB xenograft-bearing athymic nude mice. The criteria for a positive response to therapy was designated as a reduction of tumor size, while that of a cure was designated as a complete remission with a flat and fibrotic scar. In the SW1116 xenograft-bearing mice, an intratumoral injection of either A7-NCS or NCS inhibited tumor growth, whereas the tumor progressively proliferated with the intratumoral injection of saline. The intratumoral injection of A7-NCS caused a cure for SW1116 tumor, with a flat and fibrotic scar in 5 of 6 mice, while only one cure was observed in the intratumoral injection of NCS. In the KB tumor-bearing mice, intratumoral injection of either A7-NCS or NCS led to an inhibitory effect on tumor growth, although the total disappearance of the tumor was observed in only one mouse given A7-NCS i.t. (Table 2).

Inhibitory Effect of Locally Injected A7-NCS on Tumor Development. To confirm that the local injection of A7-NCS can prevent tumor development, athymic nude mice bearing...
SW1116 or KB cells but no palpable tumor were used in this study. The therapeutic effect of each preparation was evaluated by noting the ratio of mice which developed a palpable tumor after the initiation of therapeutic treatment. In the mice treated locally with saline, palpable SW1116 tumor developed in 17 of 18, 18 of 18, and 18 of 18 mice 7, 14, and 21 days after the treatment, respectively, whereas in the mice treated locally with A7-NCS palpable SW1116 tumors were observed in only 0 of 16, 4 of 16, and 4 of 16 mice 7, 14, and 21 days after the treatment, respectively. In the mice treated simultaneously with a local injection of A7-NCS and 100-fold the amount of free Mab A7, palpable SW1116 tumors were observed in 8 of 15, 8 of 15, and 11 of 15 mice 7, 14, and 21 days after the treatment, respectively. With intratumoral injections of NCS, tumors were observed 10 of 16, 4 of 16, and 4 of 16 mice 7, 14, and 21 days after the treatment, respectively (Table 3).

In the KB cell-inoculated mice, palpable tumors were observed in 10 of 15, 13 of 15, and 16 of 16 mice 21 days after the treatment for i.t. A7-NCS, i.t. NCS, and i.t. saline groups, respectively (Table 4).

Toxicity. Systemic toxicity of A7-NCS in local administration was evaluated by following the number of mice deaths after the injection of A7-NCS. The death rates for the local administration of A7-NCS were 5 of 8 and 0 of 8 mice for 300 and 200 units equivalent to NCS, respectively, whereas those for i.v. administration of A7-NCS were 8 of 8 and 0 of 8 mice for 200 and 50 units equivalent to NCS, respectively. When NCS alone was administered i.v. to the mice, the death rates were 8 of 8 and 0 of 8 at 50 units NCS and 10 units NCS, respectively, while the death rates for the local injection of NCS were 8 of 8 and 0 of 8 mice for 100 and 25 units of NCS, respectively (Table 5).

DISCUSSION

To reduce the remnant cancer cells surrounding the rectum and subsequently improve the prognosis of rectal cancer patients, some adjuvant chemotherapies are required in addition to radical surgery (21-23). An anticancer agent will be able to contribute to the reduction of the local recurrence of rectal cancer if the agent is present at a sufficiently long time at local sites at a sufficient dose and passes sufficiently into the lymphatic vessels. Local administration of an anticancer agent conjugated with a macromolecule the size of IgG (M, 150,000) may be appropriate for accomplishing these objectives.

In most cases, conventional anticancer drugs used clinically appeared to be rapidly absorbed from the interstitial space through the capillaries, resulting in low drug concentration at the target organ (24). Recently, some authors (25-27) have reported that the conjugation with macromolecules can alter the pharmacokinetic behavior of the drug and can cause the drug to be retained at the target area for a long time. Monoclonal antibody is a good candidate for pharmacokinetic alteration of the drug. Disappearance of antibody from the injected site was slow in the tumor-free mice, and the amount of antibody remaining at the injected site was much higher than that for the systemic injection (Fig. 1). The high retention of locally injected Mab, observed in this study, results from the fact that the antibody molecules of the size of IgG are prevented from passing into the blood capillaries by the tight vascular endothelium and by the presence of a continuous basement membrane (28).

Antigen-specific monoclonal antibody can presumably retain a drug on the cancer cell surface by antigen-antibody interaction, inhibit the absorption of the drugs from the interstitial

Table 2 Therapeutic effect by intratumoral injection

<table>
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<tr>
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<th>SW1116</th>
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<tr>
<td>Saline i.t.</td>
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Table 3 Tumor development rates: antigen-positive

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<th>21 days</th>
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<td>4/16</td>
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<td>8/15</td>
<td>11/15</td>
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<td>A7-NCS i.v.</td>
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<td>14/18</td>
<td>16/18</td>
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<tr>
<td>NCS i.t.</td>
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<td>10/16</td>
<td>12/16</td>
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<td>18/18</td>
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Table 4 Tumor development rates: antigen-negative

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<td>7/15</td>
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<td>8/15</td>
<td>11/15</td>
<td>13/15</td>
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<td>Saline i.t.</td>
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Table 5 Systemic toxicity

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<th>300 units</th>
<th>200 units</th>
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<th>50 units</th>
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<tr>
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<td>6/8</td>
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<td>NCS i.t.</td>
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<td>NCS i.v.</td>
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space into the blood, and maintain a high concentration of the drug at the target area. In this study, the antigen-specific local retention property of Mab A7 was examined by injecting 125I-Mab A7 peritumorally or i.t. into the tumor-bearing mice and following the radioactivity of the tumor. The result showed that Mab A7 localized at the target tumor through antigen-antibody interaction to a greater extent after the peritumoral and the intratumoral injections than after the systemic injection (Figs. 2 and 3). The amount of antibody reaching the target tumor via these forms of administration was several to several dozen times greater than the amount reaching the target tumor via systemic administration. There have been several reports describing the limitation of monoclonal antibody as a carrier of anticancer agents because of the low doses of antibody which reach the target tumor in systemic administration (29-33). In contrast, the local injection of Mab, as shown in this study, significantly increases the amount of monoclonal antibody which reaches the target tumor. The tumor localization index for peritumoral injection was not as high as previously predicted. This finding may indicate that, even if administered to an area adjacent to the tumor, monoclonal antibodies encounter some physiological barriers before reaching the target tumor, as in the case of systemic administration. The tumor localization of Mab in peritumoral injection is mainly attributed to antibody binding and retention at the tumor surface, but not to the accumulation via the blood supply. However, a notably high tumor localization of Mab in peritumoral injection may be observed when Mab is administered to a small tumor burden, particularly when cancer cells are scattered.

In human gastrointestinal cancer, lymphatic flow plays an important role in the spread of cancer and determines the prognosis of the cancer patient to a considerable degree. This information has prompted many surgeons to prevent and eliminate lymphatic metastasis of cancer cell in gastrointestinal cancer therapy by additional adjuvant chemotherapy (24, 28, 34–37). In this study, we investigated the lymphatic delivery of Mab A7 in tumor-free mice, with the aim of eliminating lymph node metastasis by using the monoclonal antibody-drug conjugate. The result showed that large amounts of locally injected Mab A7 reached regional lymph node in both injections (Table 1; Fig. 4). Lymphatic delivery of monoclonal antibody has been investigated extensively by Weinstein et al. (38-40). They described the superiority of the lymphatic delivery of monoclonal antibody in local injections over that via systemic injection. Human lymphatic flow differs from murine, since the human lymphatic flow is more complex, especially in the pelvis. However, our present study indicates the possibility that the locally injected Mab A7 may readily pass through lymphatic vessels and reaches the regional lymph node in humans to a high degree. This high lymphatic delivery of antibody can be explained by the fact that lymph vessels have no continuous basement membranes and no endothelial lining that contains clefts between cells.

The tumoricidal effect of locally injected A7-NCS was evaluated using the mice bearing palpable tumors and mice bearing cancer cells but no palpable tumors. A single local injection of A7-NCS prior to palpable tumor formation exhibited a prominent inhibitory effect on tumor development, whereas the systemic injection of A7-NCS and the local injection of NCS did not show a markedly inhibitory effect. Simultaneous local injection of A7-NCS and large amounts of free Mab A7 showed a higher ratio of tumor development than the local injection of A7-NCS alone (Table 3). In addition, a single local injection of A7-NCS did not lead to a notable inhibitory effect on tumor development in the antigen-negative tumor-bearing mice (Table 4). These findings suggest that a local injection of A7-NCS can contribute significantly in inhibiting a tumor growth initiated by scattered cancer cells with antigen specificity. This animal model is comparable to a clinical setting in which a primary tumor has been surgically resected but a residual small tumor or scattered cancer cells are present. An alternative to local injection of the conjugate, the intratumoral injection of A7-NCS has led to a complete remission of the established tumor, with a flat and fibrotic scar, depending on the antigen expression (Table 2). This therapeutic effect of direct injection of A7-NCS results from the high dose of the conjugate taken up by the target tumor. The few complete tumor remissions in the antigen-negative xenograft indicate that the tumoricidal effect of a direct injection of the conjugate depends on the antigen-antibody interaction.

An advantage to the use of monoclonal antibody as a drug carrier may be a reduced systemic toxicity of the anticancer agent. Our study showed that the systemic toxicity of A7-NCS was lower for local administration than when A7-NCS or NCS was systemically administered (Table 5). Thus, anticancer agent-NCS is the least toxic to the host in local administration when conjugated with antibody. This result suggests that the low toxicity of the local administration of A7-NCS is attributed to low normal organ accumulation, since macromolecules the size of IgG cannot readily penetrate into vital organs such as the liver, kidneys, lungs, etc. There have been several reports indicating that the toxicity of an anticancer agent is reduced when the agent is conjugated to a modifier (41, 42). A problem with the local administration of an anticancer agent is local inflammation at the injected site, which occasionally leads to tissue necrosis. This problem will, however, be overcome by adjusting the concentration of the injected anticancer agent. Another problem in the administration of murine antibody to the host is the development of an anti-murine immune response which leads to an allergic reaction and a reduced therapeutic efficacy (43-45). Although not examined in this study, the reduced therapeutic efficacy due to an anti-murine antibody may be reduced in local administration, since the locally injected antibody can access the target tissue without entering the blood, where most of the anti-murine antibody is contained.

In conclusion, the monoclonal antibody A7, when injected locally, showed a high local retention, regardless of antigen-antibody interaction, and high lymphatic delivery. In contrast to systemic injection, the local administration of A7-NCS yielded a significant tumor reduction and was effective in preventing tumor development with low toxicity. These findings suggest that the conjugate in local administration can efficiently reduce colorectal cancer mass, often with a complete remission and possibly prevent local recurrence of rectal cancer. Since there are as yet no clinical data on the application of monoclonal antibody in preventing local recurrence of rectal cancer, the feasibility of such an approach in humans can be inferred only from the animal study as described in this report.

REFERENCES

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