Locoregional Cancer Treatment with Magnetic Drug Targeting

Christoph Alexiou, Wolfgang Arnold, Roswitha J. Klein, Fritz G. Parak, Peter Hulin, Christian Bergemann, Wolfgang Erhardt, Stefan Wagenpfeil, and Andreas S. Lübbe

Department of Otorhinolaryngology, Head and Neck Surgery [C. A., W. A., P. H.], Department of Experimental Oncology and Therapeutic Research [R. J. K., W. E.], and Institute for Medical Statistics and Epidemiology [S. W.], Klinikum rechts der Isar, Technical University of Munich, 81675 Munich; Physics-Department E 17, Technical University of Munich, 81675 Munich [F. G. P.]; Chemiecell, 10777 Berlin [C. B.]; and Cecilien-Klinik, 33175 Bad Lippspringe [A. S. L.], Germany

ABSTRACT

The specific delivery of chemotherapeutic agents to their desired targets with a minimum of systemic side effects is an important, ongoing challenge of chemotherapy. One approach, developed in the past to address this problem, is the i.v. injection of magnetic particles (ferrofluids [FFs]) bound to antitumor agents that are then concentrated in the desired area (e.g., the tumor) by an external magnetic field. In the present study, we treated squamous cell carcinoma in rabbits with FFs bound to mitoxantrone (FF-MTX) that was concentrated with a magnetic field. Experimental VX-2 squamous cell carcinoma was implanted in the median portion of the hind limb of New Zealand White rabbits (n = 26). When the tumor had reached a volume of ~3500 mm³, FF-MTX was injected intraarterially (i.a.; femoral artery) or i.v. (ear vein), whereas an external magnetic field was focused on the tumor region. FF-MTX i.a. application with the external magnetic field resulted in a significant (P < 0.05), complete, and permanent remission of the squamous cell carcinoma compared with the control group (no treatment) and the i.v. FF-MTX group, with no signs of toxicity. The intratumoral accumulation of FFs was visualized both histologically and by magnetic resonance imaging. Thus, our data show that i.a. introduction of FF-MTX is successful in treating experimental squamous cell carcinoma. This “magnetic drug targeting” offers a unique opportunity to treat malignant tumors loocregionally without systemic toxicity. Furthermore, it may be possible to use these magnetic nanoparticles as a “carrier system” for a variety of anticancer agents, e.g., radionuclides, cancer-specific antibodies, and genes.

INTRODUCTION

The difference between the success or failure of chemotherapy depends not only on the drug itself but also on how it is delivered to its target. Because of the relatively nonspecific action of chemotherapeutic agents, there is almost always some toxicity to normal tissue even under optimal conditions. Therefore, it is of great importance to be able to selectively target the antineoplastic agent to its tumor target as precisely as possible, to reduce the resulting systemic toxic side effects from generalized systemic distribution and to be able to use a much smaller dose, which would further lead to a reduction of toxicity. In the past, chemotherapy targeted by magnetic fields using magnetic albumin microspheres has shown encouraging results (1, 2). In 1996, Lübbe et al. (3) described in detail below, for experiments in which tumor-bearing experimental animals (nude mice and rats) were injected i.v. with a FF complex (magnetic drug) that was directed into the tumor using a magnetic field (permanent magnet; magnetic field strength, 0.5–0.8 Tesla). The FF complex was well tolerated by the animals, and tumor remission was achieved. As a second step, Lübbe et al. (4) also conducted the first Phase I clinical trial using this approach in patients with advanced, unsuccessfully treated cancers or sarcomas. This “magnetic drug targeting” approach was well tolerated.

Targeting and prolonged retention of the FF complex at the target site reduces its reticuloendothelial system (RES) clearance and facilitates extravascular uptake. To optimize intratumoral magnetic particle concentration, several features need to be considered: (a) the particles should be of a size that allows sufficient attraction by the magnetic field and their introduction into the tumor or into the vascular system surrounding the tumor; (b) the magnetic fields should be of sufficient strength to be able to attract the magnetic nanoparticles into the desired area; (c) the FF complex should deliver and release a sufficient amount of anticancer agent; and (d) the method of injection should have good access to the tumor vasculature and should avoid clearance by the reticuloendothelial system (“first pass effect”). The purpose of the present study was to compare different application methods (i.v., i.a.) of magnetic drug targeting for the treatment of experimental VX-2 squamous cell carcinoma. Because FFs are visible histologically and by imaging techniques such as MRI, we also wished to demonstrate the morphological intratumoral distribution of these magnetic nanoparticles in conjunction with an external magnetic field focused on the tumor region.

MATERIALS AND METHODS

MTX. The chemotherapeutic agent used in the experiments, MTX-HCl, (Novantron; Lederle, Wolfratshausen, Germany) is a synthetic anthracendion that inhibits DNA and RNA synthesis by intercalating in DNA molecules, which causes strand breaks. Actively dividing cells are the most sensitive, but MTX tends to be non-cell-cycle specific and also inhibits G2–M progression (5). MTX has been used systemically for breast carcinoma, non-Hodgkin’s lymphoma, and solid tumors (6–8) and has also been applied locoregionally (9–13). The body surface area and the dose of MTX (10 mg/m² of body surface area) used for the experiments were calculated according the instructions of Kirk and Bistner’s handbook of veterinary procedures and emergency treatment (14).

Magnetic Nanoparticles (FFs). The FFs used in the experiments were obtained from Chemiecell (Berlin, Germany; German patent application no. 19624426.9) and consisted of a colloidal dispersion formed by wet chemical methods from iron oxides and hydroxides to produce special multidomain nanoparticles (Table 1). The particles were surrounded by starch polymers for stabilization under various physiological conditions and to allow chemosorption binding. MTX has cationic characteristics and combines (amine groups of MTX-HCl with phosphate groups of the starch derivatives) at a pH of 7.4 (Fig. 1). The FF-MTX contained 6.5 mg of MTX per 10 ml. Because the drug bond is reversible (ionic binding), desorption of the bound drug was dependent on the physiological environment (pH, osmolality, temperature) and could be varied by changing the blood electrolyte concentration according to the specific need. In experiments, desorption of MTX took place within 60 min (Fig. 2), which ensured that the drug could act freely once localized to the tumor by the magnetic field. Pyrogenicity and sterility tests were performed by the Pharmacy Department of the Virchow Medical School (Humboldt-Universität, Berlin, Germany) according to good manufacturing practice guidelines. The characteristics of the FF-MTX are depicted in Table 1 (see also Figs. 1 and 2).

1 To whom requests for reprints should be addressed, at Department of Otorhinolaryngology, Head and Neck Surgery, Klinikum rechts der Isar, Technical University of Munich, 81675 Munich, Germany. Phone: 49-89-4140-2370; Fax: 49-89-4140-4853; E-mail: C.Alexiou@lrz.tu-muenchen.de.

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3 The abbreviations used are: FF, ferrofluid; i.a., intraarterially; MRI, magnetic resonance; MRL, MR imaging/image; MTX, mitoxantrone; MTX-FF, FF bound to MTX; MTX-HCl, MTX hydrochloride; MTC, magnetic-targeted carrier.
performed when the tumors had reached a volume of approximately 3500 mm³.

For application of the chemotherapy, the animals were anesthetized with an i.m. injection of ketamine (35 mg/kg body weight [Narketan 10; Chassot, Bern, Switzerland]) and xylazine (5 mg/kg body weight [Xylapan; Chassot, Bern, Switzerland]), the femoral artery was cannulized and an indwelling catheter [Venflon (0.8 mm); Ohmeda Co., Helsingburg, Sweden] was placed after separation of the femoral vein and the saphenous nerve ~2 cm distal to the inguinal furrow. The FF-MTX and the MTX alone were administered by perfuser over a period of 10 min. To prevent thrombosis, prophylaxis consisting of heparin sodium (heparin/natrium/25,000 IU Ratiopharm; Ratiopharm, Ulm, Germany) was given preoperatively, once immediately postoperatively, and twice daily for 5 days postoperatively (200 IU per kg of body weight, s.c.).

Magnetic Field. An electromagnet with a magnetic flux density of a maximum of 1.7 Tesla was used to produce an inhomogeneous magnetic field. The magnetic flux density was focused onto the region of the tumor with a specially adapted pole shoe that was placed in contact with the surface of the tumor. On the tip of the pole shoe, the gradient (Fig. 3, yellow arrows) has its maximum. Fig. 3 demonstrates the dependence of the magnetic flux density on the distance to the pole shoe. A magnetic flux density of 1.7 Tesla was estimated in the region of the tumor surface and at 10 mm below the tip of the pole shoe, 1.0 Tesla (Fig. 3). The magnetic field was focused on the tumor during FF infusion and for 60 min in total (Fig. 3). Experimental Protocols. The 26 animals were divided into six groups, depending on the type of treatment, as shown in Table 2. Group 1 received an i.a. infusion of FF-MTX with the magnetic field at a dose equivalent to 20 and 50% of the systemic dose MTX (group 1a and group 1b, respectively). Group 2 received an i.a. infusion of MTX alone without the magnetic field at doses equivalent to 20, 50, 75, and 100% of the systemic dose. Group 3 received an i.a. infusion of FF alone with the magnetic field at equivalent doses compared

Animals. The experimental animals were female New Zealand White rabbits (2000–2500 g body weight, 12–15 weeks old; Charles River, Sulzfeld, Germany) that were housed individually in a room with an artificial 12/12 h light/dark cycle (exposed to light from 0700 to 1900 h). The rabbits were fed hard rabbit chow pellets (Altromin, Lage, Germany), carrots, dry bread, and tap water.

Surgical Intervention. Fragments of viable VX-2 tissue, 1 mm in size, were taken from the tumor periphery in donor animals. These fragments were placed in a special medium [RPMI 1640, 2.0 g/liter NaHCO₃, and L-glutamin (Seromed); Biochrom, Berlin, Germany] and were immediately implanted under sterile conditions into the hind limb of anesthetized recipient rabbits (n = 26) in the supply area of the femoral artery. The experiments were

<table>
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<th>Group</th>
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<th>Dose</th>
<th>Application</th>
<th>External magnetic field</th>
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<tr>
<td>1a</td>
<td>FF-MTX</td>
<td>20%</td>
<td>i.a.</td>
<td>Yes</td>
</tr>
<tr>
<td>1b</td>
<td>FF-MTX</td>
<td>50%</td>
<td>i.a.</td>
<td>Yes</td>
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<td>2</td>
<td>MTX</td>
<td>20%, 50%, 75%, and 100%</td>
<td>i.a.</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>FFs</td>
<td>equivalent amounts compared with groups 1a and 1b</td>
<td>i.a.</td>
<td>Yes</td>
</tr>
<tr>
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<td>FF-MTX</td>
<td>20%</td>
<td>i.v.</td>
<td>Yes</td>
</tr>
<tr>
<td>4b</td>
<td>FF-MTX</td>
<td>50%</td>
<td>i.v.</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>FF-MTX</td>
<td>20% and 50%</td>
<td>i.a.</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Control</td>
<td>Control</td>
<td>Control group</td>
<td>Control group</td>
</tr>
</tbody>
</table>

a. n, number of the tumor bearing animals.
b. Percentage of the regular systemic mitoxantrone dose (10 mg/m²).
c. i.a. was in femoral artery; i.v. was in ear vein.
d. Focused on the tumor.
e. MTX, chemotherapy (MTX) alone.
f. FFs, FFs alone.
RESULTS

Tumor Volume. In the control group without treatment (Group 6, △, Figs. 4–10) the tumor volume increased to 14.723 mm\(^3\) (median value) at 12 days, and palpable metastases appeared after 30 days. The animals of group 1a (Fig. 4, ●), treated i.a. with 20% FF-MTX, had a 50% reduction in volume after 3–12 days (mean, 6 days) and complete tumor remission between the 15th and 36th day (mean, 26 days) after treatment. This reduction in tumor volume was significant by the 6th day (\(P = 0.047; P < \alpha\)) and highly significant by the 15th day (\(P < 0.001; P < \alpha\)). The animals of group 1b (50% FF-MTX; Fig. 5, □) had a decrease in tumor volume similar to that of group 1a (Fig. 5, ●), with a 50% decrease in volume after 3–6 days (mean, 4.2 days) and complete tumor remission after 12–57 days (mean, 21.8 days). The decrease in tumor volume was highly significant by the 6th day (\(P = 0.001; P < \alpha\); Figs. 4 and 5).

In group 2 (i.a. MTX alone, no magnetic field), lower dosages (20 and 50% of the systemic dose) did not result in tumor remission (Fig. 6, ●), and enlarged, palpable inguinal lymph nodes were found after 48 days. At higher doses (75 and 100%), complete remission of tumor occurred at the 36th (75%) and 33rd day (100%; Fig. 6, □). The two group-3 animals (i.a. FF alone with the magnetic field, amount of FFs alone equivalent to groups 1a and 1b) demonstrated a progressive increase in tumor volume (Fig. 7, △) with palpable, enlarged inguinal lymph nodes (metastases) after 45 days.

Statistical Analysis. The tumor volume was calculated using the formula for an elliptical mass (\(1/6 \pi a^2 b\), where \(a\) = width on the horizontal axis and \(b\) = length on the vertical axis). We considered change of volumes as percentages of tumor volumes (100%) found at day 0 (day of treatment). Statistical analysis for relative tumor volumes was performed using the one group comparison (with a conservatively fixed value of 100% for the control group) and a Welch t test for two independent samples. For blood parameters (absolute values), we applied the t test for two independent samples. The resulting two-sided Ps were considered significant if \(p \leq 0.05\). The result was considered highly significant at \(P = 0.01\) or 0.05 and highly significant if \(p < 0.01\). The Ps were calculated using the Statistical Package for Social Sciences (SPSS) version 9.0 and Microsoft EXCEL version 97.

MAGNETIC DRUG TARGETING

Fig. 4. Group 1a: effect of i.a. application of FF-MTX [20% of the regular systemic dose (●)] on relative tumor volume after magnetic drug targeting compared with control group [group 6 (△), control (no treatment)]. Symbols, the median tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).

Fig. 5. Group 1b: effect of i.a. application of FF-MTX (50% of the regular systemic dose, □) on relative tumor volume after magnetic drug targeting compared with control group [group 6 (△), control (no treatment)]. Symbols, the median tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).

Fig. 6. Group 2: effect of i.a. application of MTX—20 and 50% (●) and 75 and 100% (□) of the regular systemic dose—on relative tumor volume compared with control group [group 6 (△), control (no treatment)]. Symbols, the median tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).
The six animals of group 4 (i.v. injection via the ear vein of 20% and 50% FF-MTX with magnetic field) showed a slight tumor remis-
sion, but the reduction of volume was not statistically significant in
comparison to the control group (P: group 4a 0.48–0.70, group 4b 0.26–0.96 (P. a); Fig. 8, E; Fig. 9, h).

The two animals of group 5 (i.a. FF-MTX 20 and 50%, without a
magnetic field) showed a discontinuation of tumor growth and no
evidence of metastases, but no remission of the tumor was seen (Fig.
10, FF-MTX; 20%, r; FF-MTX 50%, f). At the time of treatment,
<5% of the animals showed a small necrotic fraction in the area of the
tumor area (Fig. 10).

Local and Systemic Effects. Similar to the description in the
literature (18), the general condition of the control group animals
(limited to two animals for ethical reasons) worsened during the
observation period, and the animals developed pneumonia, which
explains the increase of leukocytes as seen in Fig. 11.

All of the animals in the groups treated with FF and a magnetic
field developed a slight gray discoloration of the skin covering the
tumor. In addition, scattered, dark injected vessels were seen in the
tumor region. The gray discoloration, caused by the strong magnetic
field strength which attracted the FFs throughout the whole tumor to
this layer (not shown as a figure), was completely reversible and
lasted for approximately 48 h.

None of the animals of group 1 had any evident side effects such as
alopecia, ulcers, or muscular atrophy; and their general condition
(weight, food intake, excrement, urine, activity, fur condition) re-
mained normal during the whole 3-month observation period com-
pared with the physiological data of healthy animals (breeder’s state-
ment by Charles River, Sulzfeld, Germany). No significant changes in
serum iron or leukocyte values were seen in this group (Fig. 11a).

The urine of one animal in group 2 (50% MTX) showed blue-green
discoloration, and this animal developed mild alopecia in the region of
the digits after 48 days. Both animals with low-dose MTX (20 and
50%) had a decrease in leukocyte values, but this was not statistically
significant (P = 0.29). Both of the group-2 animals with high-dose
(75 and 100%) MTX had temporary blue-green urine discoloration, as
well as a unilateral alopecia (palmar region of the digits to the knee
joint) of the limb in which the tumor was implanted developing after
33 days. This hairless area developed cutaneous inflammation and
ulceration, followed by mild alopecia of the ipsilateral fore limbs and
head. The musculature of the treated limb became atrophic, and the

Fig. 7. Group 3: effect of i.a. application of FFs with magnetic field (▲). ▲, control (no treatment). Symbols, the median relative tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).

Fig. 8. Group 4a: effect of i.v. application of FF-MTX 20% with magnetic field (●). ●, control (no treatment). Symbols, the median relative tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).

Fig. 9. Group 4b: effect of i.v. application of FF-MTX 50% with magnetic field (□). □, control (no treatment). Symbols, the median relative tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).

Fig. 10. Group 5: effect of i.a. application of FF-MTX 20% (●) and 50% (■) without magnetic field. ▲, control (no treatment). Symbols, the median relative tumor volume; bars, the maximum and minimum values; metastases, onset of metastases; treatment, the day of treatment (singular treatment).
circumference was noticeably smaller (by 3 cm) at the end of the 3-month observation period. There was no marked difference in the severity of the side effects between the two animals, except for the fact that the animal with the higher MTX dose (100%) developed the changes several days sooner. Group-2 animals with 50, 75, and 100% of the regular systemic MTX dose.

The MRI was made 6 h after treatment. The tumor is situated at the medial portion of the hind limb (dotted circle), and the concentration of FF is seen by extinction of signal. Fig. 16a (i.a. FF-MTX) shows definite extinction of signal and Fig. 16b (i.v. FF-MTX) only a very discrete signal extinction. The area marked j is at the head of the femur and appears to be hypodense.

**DISCUSSION**

Chemotherapy is a balancing act between efficacy and toxicity and a number of strategies have been developed that aim to resolve this dilemma. Regional chemotherapy via a regional artery administers a more concentrated dose of the active agent directly into the tumor (19). The advantage of this approach is limited, however, by drain-off via the venous blood, which limits exposure time and reduces the overall efficacy. Magnetic drug targeting is a means of holding the chemotherapeutic agent at the desired site of activity, thus increasing efficacy and diminishing systemic toxicity. In the present study, the authors found that this approach led to complete tumor remission with reduced doses of 20 and 50% FF-MTX (Figs. 4 and 5). The application was well tolerated by the animals, and no signs of toxicity were detected. On the contrary, i.a. infusion of the same doses, 20 and 50%, of MTX alone (group 2, Fig. 6) resulted in no reduction of tumor volume, and the animals developed metastases and suffered from chemotherapeutic side effects. Only when the dose of MTX alone was increased to 75% and 100%, was a tumor remission seen, but this resulted in severe side effects (alopecia, ulcers, and leukopenia as seen in Fig. 11b). i.v. infusion of the FF-MTX complex was also ineffective inasmuch as only a slight tumor remission that was not statistically significant resulted (Figs. 8 and 9). The same was true of i.a. infused FF-MTX without an external magnetic field, because the tumor remained at the same size, without remission (Fig. 10). Thus, the combination of i.a. infusion with a magnetic field was safe, effective, and well tolerated by the animals and was very effective in treating the tumor even though the dose of chemotherapeutic agent was markedly reduced.

At present, i.a. delivery of chemotherapeutic agents is approved and well accepted for treatment of liver metastases (20) and has occasionally been used for other tumor types also (e.g., inoperable head and neck tumors); but it has often necessitated complicated, time-consuming operative procedures, including general anesthesia (21). Experimentally, Swistel et al. (18) described encouraging results using i.a. chemotherapy for VX-2 squamous cell carcinoma.
Adriamycin in four of six animals, whereas i.v. infusion of Adriamycin caused severe toxicity and resulted in complete remission in only two cases.

A potential complication that could arise with the use of FF compounds is the fact that, with larger particles, embolization could occur, preventing a sufficient concentration of the chemotherapeutic agent from reaching the tumor. On the other hand, if the particles are too small, the external magnetic field might not provide sufficient attraction so that the particles are drawn into the tumor. The particles used in the study were FF compounds.
in the present study had a size of 100 nm. No embolization was seen in the main vascular system of the tumor, and the particles were attracted throughout the entire tumor including its surface (Fig. 12). An additional helpful factor is that microvascular permeability in neoplastic tissues is increased (8-fold compared with normal tissue) as is diffusion (33-fold; Ref. 22). Our histological findings showing distribution of FF particles throughout the tumor strongly support the concept that high-molecular-weight substances such as chemotherapeutic agents or monoclonal antibodies can be effectively targeted to tumor tissue. In addition, the fact that the FF alone with a magnetic field failed to cause tumor remission (Fig. 7) indicates that the therapeutic effect resulted from the action of the chemotherapeutic agent itself, rather than intratumoral embolization by the particles.

The electromagnet used for this study produced a magnetic flux density of a maximum of 1.7 Tesla, which decreased depending on the distance to the pole shoe (Fig. 3). The magnetic gradient can be seen as a collection of vectors that point in the direction of increasing values as shown in Fig. 3 (yellow arrows). The arrow sizes correspond to the strength of the magnetic gradient. Both factors (direction and magnitude) reflect the inhomogeneous character of the magnetic field, which is of key importance for magnetic drug targeting. In previous studies, it was suggested that a magnetic field strength of 8000 Gauss (0.8 Tesla) is sufficient to exceed linear blood flow in the intratumoral vasculature and allow 100% localization of magnetic carrier containing 20% magnetite (23). In contrast, Goodwin et al. (24) applied MTCs i.a. in a swine model, focusing a magnetic field of only 250-1000 Gauss (0.025–0.1 Tesla; permanent neodymium magnet) to the desired compartments in the liver and lungs. The depth of this MTC targeting was 8–12 cm and the particle size was 0.5–5 μm. With this model, MTCs with a predefined activity had a concentration of 67% in the liver and 50% in the lung localized by the magnet.

The magnetic field strength with a maximum of 1.7 Tesla used in the present investigation was the strongest ever applied for magnetic drug targeting. We achieved a high concentration of FFs within the tumor after i.a. infusion of FFs, which was seen by histological (Figs. 12–15) and MRI (Fig. 16a) methods. The VX-2 squamous cell carcinoma in the present study was superficially exposed and had no migratory motion, as was the case with the liver and lung targets (breathing fluctuations) in the swine model of Goodwin et al. (24). In addition these organs lie deeply in the body cavity (8–12 cm from the body surface), greatly complicating focusing of the magnetic flux density onto the tumor area. Two approaches to overcome this problem are possible: (a) the use of larger particles, as previously suggested by Lübke and Bergemann (25); or (b) the use of a stronger magnetic field. The particles (FF-MTX) used in the present study were 100 nm in size (hydrodynamic diameter) and have shown good...
MAGNETIC DRUG TARGETING

therapeutic results in smaller animals (mouse, rat) as well (3, 4). The strong magnetic field was very efficacious in combination with these particles, but additional experiments (which we have already begun) should be performed using marked FFs to clarify the optimal magnetic field strength and particle size. For example, to more effectively treat deep body cavities (i.e., pancreatic cancer and so forth) rotating magnetic fields could be used to focus the particles to the region of interest. It is also important that the tumor has a sufficient blood supply so that the particles access the particular area.

A remarkable feature of using ionically bound pharmaceuticals is that the anticaner agents are able to desorb from the carrier (FF) after a defined time span and the low-molecular-weight substances (e.g., the molecular weight of MTX 517) can then pass through the vascular wall or interstitium into the tumor cells. This is important because once the FF-MTX complex has been directed to the tumor by the magnetic field, the drug must dissociate to act freely within the tumor. As shown in Fig. 2, MTX desorbs from the FF after 30 min (half-life), and, therefore, 50% of the drug is free to act on the tumor after 30 min.

Dextran-coated iron oxides have been shown to produce signal loss by MRI and have been used as a contrast medium for the detection of metastatic lymph nodes (negative contrast; Ref. 26). We found total enrichment and sensitive detection of disseminated tumor cells in patients with head-neck SCC. J. Pathol., 154: 133–139, 1990.

Magnetic microspheres loaded with the 90Y-emitting radioisotope 90Y have also been successfully used as a form of radiouclide therapy. In one study, this compound was maneuvered within the body of a mouse to a s.c. lymphoma, resulting in eradication of the tumor (30). Magnetic fluids have also been used for the so-called “magnetic fluid hyperthermia” that has been used to control the local growth of murine mammary carcinoma (31). Additional modification of the magnetic particles so that they could bind monoclonal antibodies, lectins, peptides, hormones or genes could make delivery of these compounds more efficient and also highly specific. Therefore, magnetic particles could make important contributions to molecular and cell biology (e.g., in vitro transfection with genes), which would result in advances in both basic science and clinical practice (32).

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