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REVIEW ARTICLE

Clinical Applications of Polymeric Micelle Carrier Systems in Chemotherapy and Image Diagnosis of Solid Tumors

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Polymeric micelles are assemblies of synthetic polymers and have been studied and developed as drug carriers for targeting solid tumors. Physicochemical characters and medical advantages of the polymeric micelle carrier systems are summarized, followed by an explanation of their recent application for contrast agent targeting. In the final section, future perspectives on the polymeric micelle carrier systems for tumor targeting are discussed, including a novel combination of contrast agent targeting and drug targeting that achieves tumor-specific image diagnosis and tumor-selective chemotherapy, respectively.

1. Polymeric Micelles as Nano-sized Drug Carriers[1–8]

In this review, I focused only on a brief explanation on fundamental aspects and on the present clinical situation of drug targeting with polymeric micelle carriers. The drug tumor targeting with polymeric micelle carriers has been attained first by Japanese researchers including the author of this review, and clinical trials of the polymeric micelle targeting had been started first in Japan. I do not describe recent developments of polymeric micelle carrier's research that must provide many references of non-Japanese groups. Therefore, a considerably large proportion of references in this review is written by Japanese groups. Please understand this situation, and if readers want to know recent developments of polymeric micelle drug carriers, please read other reviews.[1,2,4–8]

1.1. What is a polymeric micelle?

A polymeric micelle is a macromolecular assembly that forms from synthetic block copolymers or graft copolymers and that has a spherical inner core and an outer shell.[9] As shown in Figure 1, which features an AB-type block copolymer, a micellar structure forms in an aqueous medium if one segment of the block copolymer can provide interchain cohesive interactions sufficient for the micelle formation. Most drug carrier applications have been studied with AB- or ABA-type block copolymers because the close relationship between micelles' properties and the structure of polymers can be evaluated more easily with AB- or ABA-type block copolymers than with the other types of copolymers.

I describe two fundamental physicochemical characteristics of polymeric micelles in this section, and in the Passive drug targeting of solid tumors section, I describe the other beneficial drug-carrier characteristics (1.2). The first physico-chemical characteristic is the polymeric micelle's very small size as summarized in Table 1. Polymeric micelles are formed typically in a diameter range from 10 nm to 100 nm with a substantial narrow distribution. As described in Section 2, this size range is considered ideal for the attainment of stable, long-term circulation of the carrier system in the bloodstream. Alternatively, the small size of polymeric micelles is a big benefit in the sterilization processes in pharmaceutical productions. Polymeric micelles are easily (without micron-sized particle'sclogging) and inexpensively (without another separation process) sterilized by filtration using typical sterilization filters with 0.45-mm or 0.22-mm pores owing to a fact that polymeric micelles are essentially free of micro-sized particle's contamination. This is a good contrast to other typical pharmaceutical nano-sized carrier systems (e.g., nanoparticles, liposomes) which need a removal process of contaminated micron-sized particles.

The second physicochemical characteristic is high structural stability. It is known that polymeric micelles possess high structural stability provided by the entanglement of polymer chains in the inner core. This stability has two aspects: static and dynamic[10–13].

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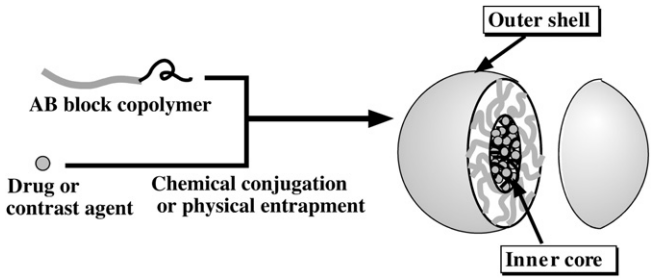

Figure 1 Design of a polymeric micelle carrier system.

Static stability is described by a critical micelle concentration (CMC). Generally, polymeric micelles show very low CMC values in a range from 1 μg/mL to 10 μg/mL. These values are much smaller than typical CMC values of micelles forming from low-molecular-weight surfactants. The second aspect, dynamic stability, is described by the low dissociation rates of micelles, and this aspect may be more important than the static one for *in vivo* drug delivery in physiological environments that are in nonequilibrium conditions. The high structural stability of polymeric micelles stated earlier is an important key to *in vivo* delivery in micellar forms and simultaneously eliminates the possible contribution of single polymer chains to drug delivery. Therefore, although they share the root word "micelle," polymeric micelles are very different from low-molecular-weight-surfactant micelles in their physicochemical properties. This difference is critical in the applications for drug carriers.

1.2. Advantages of polymeric micelle as a drug carrier

As summarized in Table 1, the third advantage of the polymeric micelle carrier system as a drug carrier is its high water solubility even when it incorporates a large amount of hydrophobic drugs[14]. Accordingly, "large amount of drug loading" is listed as the forth advantage. Generally, in conventional synthetic polymer-drug conjugate systems and antibody-drug conjugate systems, a loss of the carrier's water solubility resulting from the conjugation of a hydrophobic drug creates a serious problem. Several research groups reported this problem of the polymer-drug conjugates in syntheses[15–17] and in their intravenous injections[18]. Polymeric micelles can incorporate a large number of hydrophobic drug molecules in the micelles' inner core, and simultaneously, the micelles can maintain their water solubility by inhibiting intermicellar aggregation of the hydrophobic cores with a hydrophilic outer shell layer that works as a barrier against intermicellar aggregation. This is a great advantage because many potent drugs that have been developed in recent years are very hydrophobic and are, therefore, water insoluble.

The beneficial characteristic of low toxicity may be described as the fifth advantage. Generally, polymeric surfactants are known to be less toxic than low-molecular-weight surfactants, such as sodium dodecyl sulfate. Furthermore, in theory, polymeric micelles are considered very safe in relation to chronic toxicity. Possessing a much larger size than that for critical filtration in the kidney, polymeric micelles can evade renal filtration, even if the molecular weight of the constituting block copolymer is lower than the critical molecular weight for renal filtration. On the other hand, all polymer chains can be dissociated (as single polymer chains) from the micelles over a long time period. This phenomenon results in the complete excretion of the block copolymers from the renal route if the polymer chains are designed with a lower molecular weight than the critical value for renal filtration. Such a result constitutes an advantage of polymeric micelles over the conventional (non−micelle forming) and nonbiodegradable polymeric drug carrier systems.

The sixth advantage is the fact that various chemical species can be incorporated into polymeric micelles. As explained previously, the most commonly examined chemical species are hydrophobic low-molecular-weight organic compound drugs. These drugs can be incorporated into the micelle inner core either by chemical conjugation to the inner-core-forming polymer block or by physical entrapment owing to hydrophobic interactions between the entrapped drug molecules and the hydrophobic inner-core-forming polymer block. Hydrophobic interactions also work as a driving force for micelle formation. On the other hand, polymeric micelles are formed through ionic interactions between charged polymer chains. For example, polymeric micelles form from poly(ethylene glycol) (PEG)-b-poly(lysine) block copolymers and poly(aspartic acid) (ASP) homopolymers where the poly(lysine) chain is positively charged and the poly(ASP) chain is negatively charged. If negatively charged polypeptides[19] or nucleic acid[20] are used in place of poly(ASP), these pharmacologically active macromolecules are incorporated into polymeric micelles for protein, gene, and small interfering RNA delivery purposes. Furthermore, metal ions or metal ions' chelates can be incorporated into polymeric micelles through coordination bonds or ionic interactions. A platinum chelate cisplatin, which is a widely used anticancer drug, was successfully incorporated into polymeric micelles forming from PEG-b-poly(ASP) through a ligand exchange reaction between a carboxylic acid residue of the poly(ASP) chain and a chloride ion of cisplatin. [21–23] Alternatively, gadolinium (Gd) ions, which can work as a magnetic resonance imaging (MRI) contrast agent, were incorporated into polymeric micelles by the use of a chelate-moiety-conjugated block copolymer. [24–26] As stated above, various pharmaceutical drugs, genes, and contrast agents can be incorporated into polymeric micelles with appropriate choices of block copolymer structures.

1.3. Disadvantages of polymeric micelle as a drug carrier

It is worthwhile to explain the disadvantages of the polymeric micelle systems and the advantages described above. The four disadvantages are summarized in Table 2. Two of them are polymeric micelle-specific ones, whereas the other two disadvantages are common for polymeric carriers including non-micelle-forming systems. The first disadvantage is a fact that relatively high levels of polymer chemistry are needed in the polymeric micelle studies. As illustrated in Figure 1, an AB type of block copolymer is one of the most favorable structures for polymeric micelle carriers. The architecture of the AB block copolymer is very simple, however, its synthesis is more difficult than that of random polymers, where different units are aligned on a polymer chain in a random manner.

Table 1 Advantages of polymeric micelles as drug carriers

1. Very small size (diameter = 10−100 nm)
2. High structural stability
3. Large amount of drug loading
4. High water solubility
5. Low toxicity
6. Incorporation of various chemical species

Table 2 Disadvantages of polymeric micelle drug carriers

1. Specific disadvantages of polymeric micelle carriers
   - A. Difficult polymer synthesis
   - B. Immature drug-incorporation technology
2. Common disadvantages of polymeric carriers
   - A. Slow extravasation
   - B. Possible chronic liver toxicity due to slow metabolic process

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Furthermore, researchers may encounter a problem in a synthesis of the block copolymer of a large industrial scale in a highly reproducible manner.

The second disadvantage, specifically, for the polymeric micelle systems is the immature technology for drug incorporation in a physical manner. Yokoyama et al reported that physical-incorporation efficiencies were dependent on various factors in drug-incorporation processes. Presently, there seem to be no universal incorporation method applicable to any polymer. Furthermore, in some methods the drug incorporation may be difficult on a large industrial scale, whereas the drug incorporation is easy and efficient on a small laboratory scale.

The third disadvantage (B-1 in Table 2) is much slower extravazation of polymeric carrier systems than that of low-molecular-weight drugs. This results from a difference in extravazation mechanisms between polymeric carrier systems and low-molecular-weight drugs. The polymeric systems translocate from the bloodstream to the interstitial space of organs and tissues through intra-cellular channels and inter-cellular junctions, whereas the drugs permeate directly through lipid bilayer cell membranes. Therefore, a long circulation character of the polymeric systems is an essential requirement for delivery of a therapeutic amount owing to compensation of the slow extravazation with a large Area Under the Curve value that results from the long circulation. The forth disadvantage is a risk of chronic liver toxicity. Drugs conjugated or incorporated in the polymeric carrier systems are metabolized in liver in a slower manner than free drug, since access of metabolic enzymes to drugs is inhibited because of the conjugation and incorporation. Therefore, toxic side effects of the conjugated and incorporated drug may be exhibited for a longer period than a case of free drug whose toxic effects can be lowered through metabolism in a short period.

2. Passive Drug Targeting to Solid Tumors

2.1. Methodology and significance of passive targeting to solid tumors

Drug targeting is defined as selective drug delivery to specific physiological sites—organs, tissues, or cells—where the drug's pharmacological activities are required. Different drug-targeting efforts could be thought of as reflecting one of two methods: active targeting and passive targeting[27,28]. Active targeting aims at an increase in the delivery of drugs to the target by using biologically specific interactions, such as antigen–antibody binding or by utilizing locally applied signals, such as heating and sonication. Carriers classified in this method include specific antibodies, transferrin, and thermoresponsive liposomes and polymeric micelles. On the other hand, passive targeting is defined as a method whereby the physical and chemical properties of carrier systems increase the target/nontarget ratio of a quantity of a delivered drug. Here, I discuss only passive drug targeting of solid tumors because the passive tumor-targeting method is important also for active tumor targeting. The reasons for this importance are twofold:

1. A greater part of a living body consists of nontarget sites. Even if a tumor occupies 1% of an entire body's weight (this would involve a very big tumor), the nontarget sites account for 99% of the body's weight (which is by no measure negligible, obviously). Drug carrier systems cannot access a target site once they are captured by nontarget sites. Therefore, the minimization of nonspecific capture at nontarget sites is important for active tumor targeting, and minimization is achieved in passive targeting.
2. Passive transfer phenomena precede biologically specific interactions for most active targeting systems (exceptions are cases of intravascular targets, such as vascular endothelial cells). Most tumor targets are located in extravascular space. To reach these targets through the bloodstream, the first step must be translocation through the vascular endothelium, followed by diffusion in the interstitial space. Even for active targeting systems based on cells' biologically specific receptors, such as tumor-specific antigens, the passive transendothelial step is both a necessary and an anterior one.

The passive targeting of polymeric micelles on solid tumors can be achieved owing to the enhanced permeability and retention effect (EPR effect). Maeda and Matsumura presented this passive drug-targeting strategy in 1986.[29–31] Vascular permeability of tumor tissues is enhanced by the actions of secreted factors, such as kinin and vascular permeability factor. As a result of this increased vascular permeability, macromolecules selectively increase their transport from blood vessels to tumor tissues. Furthermore, the lymphatic drainage system does not operate effectively in tumor tissues. Therefore, macromolecules are selectively retained for a prolonged time in the tumor interstitium. The EPR effect was first proven for a natural peptide, albumin, as shown in Figure 2. Evans blue-stained albumin was observed to accumulate at an S-180 tumor transplanted on skin in a much higher concentration than that which characterizes normal skin. The high concentrations at the tumor were maintained for a long period (upto 6 days) after intravenous injection. It is worth mentioning that a relatively long period is required (48 hours in Figure 2) for albumin to reach a peak concentration because macromolecular albumin has a much lower transvascular rate than is the case with low-molecular-weight drugs that reach the peak concentrations at tumors in a range between several minutes and several tens of minutes. After the discovery of the EPR effect for albumin, it was revealed that the EPR effect can also be applied to synthetic polymers and nano-sized carrier systems, such as liposomes and polymeric micelles. In the EPR effect, specific targeting moieties, such as antibodies are not necessary. However, the carrier systems must fulfill the following two requirements to avoid nonspecific capture at non-tumor sites:

1. The drug carrier systems must possess an appropriate size or molecular weight. The diameter of carriers must be smaller

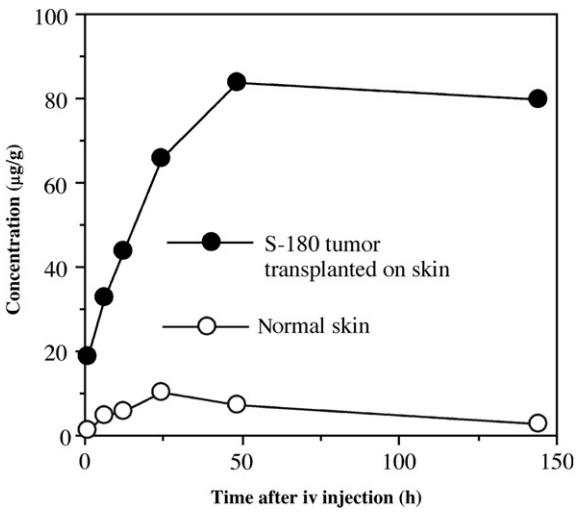

Figure 2 Enhanced permeability and retention effect shown with Evans blue-albumin. iv = intravenous.

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than approximately 200 nm if the reticuloendothelial system's uptake is to be evaded.[32] Additionally, molecular weights greater than a critical value (approximately 40,000) are favorable for evading renal filtration.

2. The drug carrier systems must not exhibit strong interactions or uptake with or by normal organs (especially the reticuloendothelial systems). These strong interactions and uptakes are typically seen for cationic[33] and hydrophobic carriers.[34] Therefore, the carrier systems must possess hydrophilic surfaces, and their surface charge must be neutral or weakly negative. Furthermore, the carrier systems must possess no other chemical structures that would be biologically recognizable to normal tissues.

Concerning the two aforementioned requirements, polymeric micelles are very advantageous because polymeric micelles are formed in a diameter ranging from 10 nm to 100 nm. The size requirement for the EPR effect is inherently fulfilled for polymeric micelle drug carrier systems. Additionally, the second requirement can be easily fulfilled through a choice of hydrophilic and neutrally or weakly negatively charged polymers for the outer shell–forming block. With this choice, polymeric micelles can circulate in the bloodstream for a long time period by evading nonspecific capture, resulting in successful attainment of the EPR effect. Because most anticancer drugs are hydrophobic [and because a considerable number of anticancer drugs are positively charged molecules, such as doxorubicin (DOX)], inhibition of strong nonspecific interactions resulting from drug molecules is a critical matter for the attainment of the EPR effect. For efficient EPR-effect-attainment, polymeric micelle carrier systems have a great advantage in their phase-separated structure, in which the drug-incorporating inner core is structurally separated from the outer shell that plays an essential role in interactions with the nontarget normal organs.

2.2. An example of polymeric micelle's passive tumor targeting

Here, I introduce the first successful example of tumor targeting with a polymeric micelle carrier. Yokoyama, Okano, and Kataoka et al succeeded in getting an anticancer drug, doxorubicin (DOX) (=adriamycin), with a polymeric micelle system, to passively target solid tumors[35–45] was chemically conjugated to ASP residues of PEG-poly(ASP) block copolymers (PEG-poly(Asp)) by amide bond formation. The PEG segment was hydrophilic, whereas the DOX-conjugated poly(ASP) chain was hydrophobic. Therefore, the obtained drug-block copolymer conjugate (PEG-poly(Asp(DOX))) formed micellar structures owing to its amphiphilic character. In the second step, DOX was incorporated into the inner core by physical entrapment using hydrophobic interactions with the chemically conjugated DOX molecules. As a result, polymeric micelles containing both the chemically conjugated and the physically entrapped DOX in the inner core were obtained with the PEG outer shell. It was revealed that only physically entrapped DOX exerted anticancer activity, and that the chemically conjugated DOX did not show any cytotoxic activity.

The physically entrapped DOX circulated in the bloodstream for a long time and was delivered to the solid tumor site at much higher concentrations than that of free DOX as shown in Figure 3.[39] Furthermore, the observed time profile with a peak concentration at 24 hours post–intravenous injection and postinjection retention of these high concentrations for longer time periods were highly consistent with passive delivery by the EPR effect[29] as shown in Figure 2 for albumin. On the other hand, accumulation of the physically entrapped DOX in the polymeric micelles in normal organs and tissues was the same as or lower than the accumulation of free DOX. As a result of the aforementioned biodistributions, high

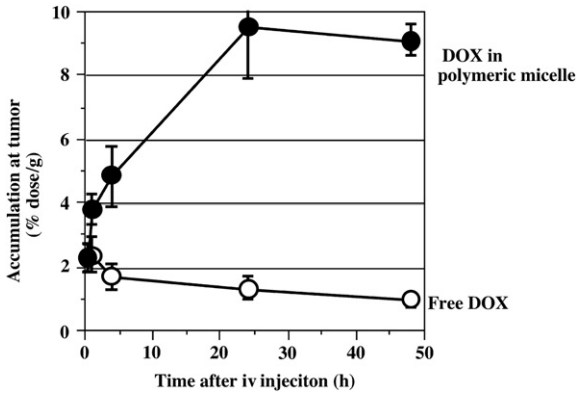

Figure 3 Passive targeting of a DOX-containing polymeric micelle. DOX = doxorubicin; iv = intravenous.

ratios of tumor to normal organs or of tumor to normal tissues were successfully obtained, as summarized in Table 3. In accordance with this highly selective delivery to solid tumor sites, dramatic enhancement of antitumor activity was observed.[39] Complete tumor eradication against murine colon adenocarcinoma 26 (C26) was achieved at two doses of DOX-incorporated polymeric micelles, whereas partial inhibition of tumor growth was obtained only at one maximum tolerated dose for free DOX. All these results clearly demonstrate the successful passive targeting of a solid tumor by an anticancer drug with the polymeric micelle carrier system.

I would like to make two additional comments on this DOX-incorporated polymeric micelle. First, concerning selectivity, a considerably high tumor to heart ratio was obtained in measurements with radiolabel on the physically entrapped DOX, as summarized in Table 2. From clinical viewpoints, this is very important because cardiotoxicity is a critical toxicity of DOX. Therefore, this high ratio suggests that the system has high clinical potential although the cardiotoxicity was not evaluated in this *in vivo* study. However, this ratio value does not suggest a specific limit to the targeting selectivity in the EPR effect–based passive targeting because no detectable amount was found in the heart when biodistribution was measured with radiolabeled chemically conjugated DOX. This fact indicates a route of delivery to the heart of the physically entrapped DOX; the physically entrapped DOX was released from the polymeric micelle in the bloodstream, and the released DOX accumulated at the heart. Therefore, a higher tumor to heart selective ratio can be obtained through further optimization of the DOX drug-release rate.

The second point concerns accumulation behavior at the liver. The report by Yokoyama et al[39] identifies an interesting pharmacokinetic behavior of the micellar DOX. Within 1 hour after intravenous injection, an accumulated amount of the micellar DOX in the liver was smaller than that of free DOX. This inequality indicates that the targeting strategy based on the EPR effect was effective in this targeting system even for the liver, which is known to possess pores large enough for micelles' extravasation in the liver's vasculature. In contrast, at 4 hours and later, after intravenous injection,

Table 3 Tumor-targeting selectivity of DOX-incorporated polymeric micelle (24 hours after intravenous injection)

	Accumulated amount at tumor (% dose/g tumor)	Ratio of accumulated amounts	
		Tumor:heart	Tumor:muscle
DOX-incorporated polymeric micelle	9.6	5.8	11.5
Free DOX	1.1	1.3	1.2

DOX = doxorubicin.

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this situation was reversed. The micellar DOX exhibited larger accumulation amounts in the liver than free DOX. This inequality resulted from rapid clearance of free DOX in the liver through the liver's metabolic activity for drugs, whereas the micellar DOX concentration in the liver did not undergo a significant drop, probably because the physically entrapped DOX in the micelle core was greatly protected from the metabolic activity. Consequently, the concentration of the micellar DOX was several-fold larger than that of the free DOX. However, toxic side effects of the DOX polymeric micelle system in the liver was on the same level of the free DOX as observed in alanine aminotransferase- and aspartate transaminase-level measurements. This means that the liver toxicity was not enhanced in the DOX polymeric micelle. Therefore, chronic liver toxicity merits careful examination not only for the polymeric micelle systems but also for all nano-sized drug carrier systems, such as PEG-coated liposomes, particularly for drugs for which liver toxicity is a major adverse effect.

3. Contrast Agent Targeting[24–26,40–47]

As described in the Passive drug targeting of solid tumors section, drug molecules were successfully targeted at solid tumors by the use of polymeric micelle carriers. It is a natural way to expand this tumor-targeting application of contrast agents. If contrast agents are targeted at solid tumors, clearer tumor images can be obtained with contrast agent carrier systems[24–26,41,42,44,45,47] than conventional image diagnosis of tumors. The targeted contrast agents not only provide high contrast in tumor images but also can lower the size limit of small tumor detection. In the present diagnoses of tumors, it is not easy to detect tumors whose size is less than 1 cm in diameter in the image diagnosis, and therefore, the ability to detect tumors smaller than 1 cm in diameter is considered a big success of imaging diagnosis. On the other hand, the minimum size attributable to tumors expressing the EPR effect is considered to be approximately 2–3 mm in diameter for the following two reasons.[31]

First, the enhanced permeability of tumor vasculatures is considered to be one physiological phenomenon of angiogenesis.[48–50] Two, tumors are expected to start exhibiting angiogenesis at approximately 2–3 mm in diameter because tumors encounter a serious problem in oxygen supply from the normal blood vessels beyond this tumor size.[51–53] Angiogenesis is a phenomenon involving sufficient oxygen supply to tumor cells from newly formed blood vessels in the tumor tissue. This minimum size should be dependent on tumor type and species. Although there are no solid data concerning the minimum tumor size for the EPR effect's expression, many articles have reported EPR effect–based tumor targeting for tumors of approximately 5–6 mm in diameter. [34,35,54,55] In targeting chemotherapy, efficacy against large tumors is meaningful. In contrast, in the targeting contrast agent case, successful targeting of smaller tumors is more highly appreciated because the success leads to the detection of small tumors—a type of detection that is of much value but is often scarce in present cancer medicine. As stated earlier, contrast agents exhibiting EPR effect–based tumor targeting may greatly contribute in reducing the minimum size of tumor detection in clinic.

In addition to the aforementioned clinical significance of the EPR effect–based tumor-targeting contrast agents, a clinical merit results from a combination of image diagnosis and chemotherapy by the use of a single carrier system. The concept of this combination medicine is illustrated in Figure 4. In human clinical cases, tumor characteristics (e.g., growth rate, metastatic activity, angiogenesis, tumor blood vessel density, vascular permeability) vary among each patient to a much greater degree than in animal tumor models, which tend toward uniformity regarding these

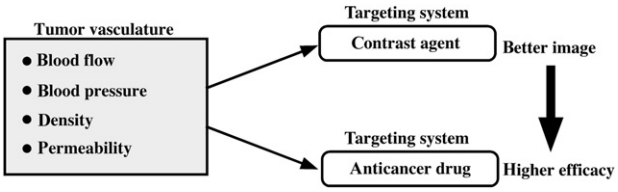

Figure 4 Combination of image diagnosis and chemotherapy against a tumor by means of a single carrier system.

characteristics. For EPR-based targeting of solid tumors, the following four characteristics are considered important: degree of blood flow, blood pressure, density, and permeability (for nano-sized carriers) of tumor vasculature. If one patient's tumor exhibits favorable aspects in these characteristics (high blood flow, high blood pressure, high density, and high permeability), this tumor is expected to provide a clear image in an image diagnosis if an EPR effect–based contrast agent is used for visualization of the tumor. Accordingly, considerable antitumor activity is also expected against this well-visualized tumor when targeted chemotherapy is performed on this patient with the same carrier system incorporating anticancer drugs. Therefore, this combined medical system can provide a greater response rate for the patients whose tumors are clearly visualized in the imaging diagnosis with the nano-sized contrast agent system. As described in the Section 1.2, polymeric micelle carrier systems possess a great advantage in terms of ability to incorporate various kinds of chemical species, contrast agents, and anticancer drugs. Therefore, polymeric micelles are favorable as a carrier for combined diagnosis and therapy systems.

To obtain the combined (dual) targeting system described earlier, Shiraishi and Yokoyama et al[24–26] reported a polymeric micelle MRI contrast agent. Using a poly(ethylene glycol)-b-poly(L-lysine) block copolymer derivative[25], they prepared a polymeric micelle binding Gd ions that enhance MRI contrasts by shortening the T_1 relaxation times of protons of water. This polymeric micelle was found to be targeted to a murine tumor C26, and the tumor was successfully visualized with the targeted MRI contrast agent. It is worth mentioning that biodistribution of the MRI contrast agent was the same as that of an anticancer drug-targeting system. As shown in Figure 5, distributions of the Gd-ion-containing polymeric micelle in a C26 murine solid tumor, the heart, and muscle were the same as with those of a DOX-containing polymeric micelle. This fact indicates the feasibility of the combined tumor medicine of MRI image diagnosis and chemotherapy by the use of the polymeric micelle carrier system that carries an MRI contrast agent and an anticancer drug.

4. Future Perspectives

Currently (January 2011), Japanese, US, and British teams are examining clinical trials for five polymeric micelle anticancer drug-targeting systems, as summarized in Table 4 [Additional two polymeric micelle formulations (No. 6 and 7) whose purpose is other than targeting have also been listed].[56–72] Chemical structures of the inner-core-forming polymer blocks vary depending on the incorporated drug, whereas the PEG chain is used for the outer shell in all cases. Tumor targeting is the primary objective of these carrier systems. However, these systems possess another objective: the system exhibits a function to solubilize a water-insoluble drug. Matsumura et al reported that NK-105-incorporating paclitaxel exhibited highly tumor-selective delivery in murine tumor models.[60,62,63] In clinical stages, NK-105 can

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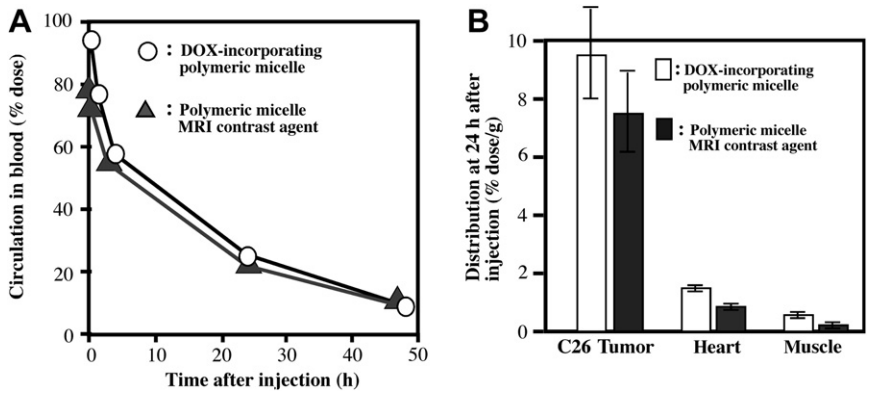

Figure 5 Comparisons of the biodistribution of two polymeric micelles. (A) Blood and (B) tumor, heart, and muscle. DOX = doxorubicin; MRI = magnetic resonance imaging.

exhibit two solubilization-related advantages over the conventional paclitaxel formulation Taxol (Bristol-Myers Squibb, Priceton, NJ, USA). The first advantage attributable to NK-105 is its relatively low toxic side effects, which reflects the fact that the block copolymer is much less toxic than Cremophor EL used in Taxol. The second advantage attributable to NK-105 is that it does not need the premedication that Taxol requires for reducing its own side effects.

We must wait for the final results of clinical trials to answer the question "Are the polymeric micelle systems effective and approved in cancer chemotherapy?" While waiting for the answer, we can take comfort in the fact that Phase I clinical studies have already yielded important information concerning toxic side effects.[56–60] Even for targeted drugs, serious side effects arise because doses are escalated until dose-limiting toxicities become observable. The important obtained information has revealed the toxicity profiles of the polymeric micelle drugs, which turned out to be the same as those of the corresponding free drugs. Most of the toxic side effects of the polymeric micelle drugs appear to result from the carriers' release of the drug in the bloodstream. The absence of uncommon and unexpected types of toxicities is a greatly meaningful fact that can contribute to the safety of clinical use. We have not obtained enough clinical results to draw a general conclusion that synthetic block copolymers can be safely used in clinical stages. However, basic-study researchers and clinicians must develop their studies while keeping in mind this potential clinical advantage of the drug carrier.

Here, I would like to describe future perspectives on polymeric micelle research and developments in cancer treatment. First, various combinations of anticancer drugs and cancers should and will be examined. In the anticancer drug—incorporated polymeric micelle systems listed in Table 4, choices of anticancer drugs have been made according to the general usefulness and effectiveness of the drugs in cancer chemotherapy. In the future, polymeric micelle anticancer drugs can be studied with regard to the different reasons for the anticancer drugs' general usefulness. One example is the use of retinoids. Retinoids, such as *cis*-retinoic acid, express their anticancer activity through differentiation of cancer cells, not through cytotoxic actions that are common in most currently available anticancer drugs. We successfully incorporated *cis*-retinoic acid and other retinoids into polymeric micelle carriers.[70–74] If we compared these *in vivo* anticancer activities with those of the polymeric micelles containing common cytotoxic anticancer drugs, we would see that the retinoid-incorporated polymeric micelles would exhibit lower levels of activity than the cytotoxic ones. However, I believe, owing to the unique action mechanism of the retinoids, retinoid-incorporated polymeric micelles may exhibit great therapeutic effects against specific cancers. Alternatively, polymeric micelle systems may be used in an injection route other than the intravenous route. One example is convection-enhanced delivery to brain tumors. This is a direct injection to brain solid tumors with a special injection needle and a very slow rate of injection, such as 5 μL/min. In a special corresponding application, polymeric micelle carriers were used for inhibition of rapid elimination from the injection site through the bloodstream.[74,75] If small-molecular-weight anticancer drugs are injected by the convection-enhanced delivery, they are very rapidly eliminated from the injection site owing to their high translocation rates through vascular endothelia. Accordingly, effective anticancer activity cannot be obtained. This is a novel application approach to polymeric micelle systems.

My second perspective concerns the combination of anticancer drug targeting and contrast agent targeting as described in the previous section. Visualization of small tumors with the EPR effect—based targeting contrast agents is one example of molecular targeting because the hyperpermeability of tumor vasculature is a physiological event induced by angiogenesis-related molecules, such as the vascular permeability factor and kinin. Molecular imaging is one hot and rapidly developing field in the 21st century. Therefore, clinical developments in drug-targeting therapy can be accelerated if drug targeting is combined with molecular imaging.

The third perspective concerns a combined use of a drug that boosts the EPR effect. The hyperpermeability of tumor vasculature essential for the EPR effect is induced by natural factors originating in tumor cells. Recently, artificial induction and escalation of the hyperpermeability have been examined for enhancement of EPR effect—based tumor targeting. Transforming growth factor-β inhibitors,[76,77] nitroglycerin,[78] and a combretastatin derivative[79] have been examined for tumor-targeting enhancements of macromolecular drugs or polymeric micelles. In particular, nitroglycerin is an approved drug for angina pectoris, and the combretastatin derivative known as cderiv is an anti-cancer drug under clinical trial (the combretastatin derivative known as cderiv); therefore, their clinical applications are feasible. All these studies are in a basic stage with animal experiments. I believe that once

Table 4 Polymeric micelle anticancer drug-targeting systems in clinical trials

No.	Trade name	Purpose	Incorporated drug	Progress	References*
1	NK-911	Targeting	Doxorubicin	Phase II	46
2	NK-105	Targeting	Paclitaxel	Phase II	47, 49, 50
3	NK-012	Targeting	SN-38	Phase II	52
4	NC-6004	Targeting	Cisplatin	Phase I	21, 48
5	NC-4016	Targeting	DACH-platin	Phase I	51
6	Genexol-PM	Solubilization	Paclitaxel	Approved	63, 64
7	SP-1049C	Anti-MDR effect	Doxorubicin	Phase II	65, 66

* Review references 56—58 cover No. 1—5 systems.

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authorities approve a polymeric micelle anticancer drug product, its applications will likely undergo dramatic expansion owing to the use of these hyperpermeablity-inducing agents.

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