Nanoparticles offer ‘infinite’ possibilities for cancer treatment

After more than 3 decades of intense research, nanotechnology has moved out of the fiction realm and into the scientific domain. Preliminary data suggest nanotechnology — the engineering of devices so small that they are measured on a molecular scale — holds tremendous promise in cancer treatment, potentially allowing more effective therapies while reducing adverse effects.

Nanoscopic devices can range up to 100 nm. A single nanometer is about 1/90,000 the width of a human hair.

Nanoscopic medical devices are 10 to 10,000 times smaller than human cells. They are roughly the size of enzymes or receptors, according to the NCIC’s Alliance for Nanotechnology in Cancer website.

Nanoparticles — one of the most commonly used and researched nanotechnology devices — have demonstrated the ability to deliver high concentrations of drugs directly to cancer cells while bypassing healthy tissue.

“Anticancer drugs do not discriminate normal cells from cancer cells. … If you formulate [anticancer drugs] into nanoparticles, then you can change the biodistribution of the drug.”

— VINOD LABHASETWAR, PHD

Nanoparticles can “change the biodistribution of the drug.”

Vinod Labhasetwar, PhD, staff researcher in the department of biomedical engineering at Cleveland Clinic’s Lerner Research Institute, told HemOnc Today.

“They kill normal cells and cancer cells. If you formulate the nanoparticles, then you can change the biodistribution of the drug.”

“The technology could be especially effective in chemotherapy.

“You can dose lower amounts of the drug to a patient, have activity and still give the patient high quality of life.”

Mark E. Davis, PhD, a professor of chemical engineering at California Institute of Technology, who has studied nanoparticles in cancer for 15 years, said.

Sequester cuts research budgets ‘to the bone’

Cuts to health care funding resulting from the US government’s budget sequester may have a devastating effect on medical research and patient care, according to several clinicians.

The current cuts — which total approximately $85.4 billion during fiscal year 2013 — and provisions for similar cuts from 2014 to 2021 were enacted by the Budget Control Act of 2011.

They took effect on March 1.

On April 8, thousands of clinicians and researchers attended the Rally for Medical Research in Washington. The event, held in conjunction with the AACR Annual Meeting, was designed to encourage federal lawmakers to make funding for the NIH a priority.

Impact on institutions

The budget cuts are affecting research and patient care in two key ways. One is the reduction in grant funding, and the other is Medicare cuts that will affect patients who receive chemotherapy.

Candace Johnson, PhD, deputy director of Roswell Park Cancer Institute, told HemOnc Today.

Roswell Park, a free-standing NCI-designated center, will lose about $8 million the first year of sequestration, Johnson said.

About $6 million a’ that will be NIH budget cuts, and the other $2 million will be from Medicare.

Most of these institutions A SLACK Incorporated® publication
After encouraging early results, researchers aim to better control, design nanoparticle systems

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in an interview. "It is absolutely clear from clinical trials that nanoparticles carrying chemotherapeutic drugs are associated with much lower side effect profiles and greater safety than the drug itself."

Nanoparticles also appear to enhance the staying power of chemotherapy agents.

"That is one major issue with the anticancer drugs — they clear out from the tumor so you have to keep injecting," Lahbashewar said. "There is a risk of tumors developing drug resistance due to low-dose intermittent exposure. Using nanoparticles, you can charge this. You can keep the drug in the tumor for a longer time with sustained release nanoparticles. We have been working on such nanoparticles for treating breast and prostate cancers."

HemOnc Today spoke with several researchers about the potential role nanoparticles may play in several types of cancers, as well as the clinical challenges and safety concerns that must be overcome before the treatment becomes mainstream.

Existing therapies

The first clinical trials exploring the use of passively targeting nanocarriers in cancer treatment began in the mid-1980s, but the technology has only been introduced to biomedical settings within the past few years.

Nanotechnology-based drugs on the market include liposomal doxorubicin (Doxil, Jansen) and nanoparticle albumin-bound paclitaxel, or nab-paclitaxel (Abraxane, Celgene), which are nanoparticle formulations of standard chemotherapeutic agents.

"[Doxorubicin] is a very good drug and a very important drug to treat breast cancer," Lahbashewar said.

However, doxorubicin also was associated with significant side effects.

"Because of certain proteins present in the heart, the drug was accumulating there, and that was causing heart failure in some patients," Lahbashewar said.

Combining doxorubicin with a lipid-based nanoparticle changed the biodistribution of the drug. It no longer accumulated in the heart, preventing cardiotoxicity.

Nab-paclitaxel also eliminated toxicities, both from the chemotherapeutic agent and from Cremophor EL (polyoxyethylated castor oil, BASF Corp.), an organic solvent used in standard paclitaxel delivery.

"When you use albumin particulates to deliver paclitaxel, you don't need to use the solvent," said Piotr Grodzinski, PhD, director of the NCI Office of Cancer Nanotechnology Research. "Some of the side effects [of paclitaxel] are associated with the solvent itself."

New formulations

Analysts at Infiniti Research, a global market intelligence firm, released a report in March that projects the nanotechnology drug delivery market in the United States will grow at a compound annual growth rate of 84.8% through 2016. The global market will grow at a compound annual growth rate of 74% in that same period, according to the report.

Preliminary research on nanoparticles that are still in development suggests they hold promise in several cancer types, including breast, prostate and bladder cancers, lymphoma and multiple myeloma.

"Nanoparticles carrying chemotherapeutic drugs are associated with much lower side effect profiles and greater safety than the drug itself."

— MARK E. DAVIS, PHD

Von Hoff and colleagues presented phase 1 data on BIND Therapeutics’ BIND-014, a PSMA-targeted nanoparticle containing docetaxel, at the AACR Annual Meeting in April.

BIND-014 was safe and well tolerated in 28 patients with advanced or metastatic solid tumors, the findings showed. The agent also demonstrated signs of antitumor activity, including one complete response and three partial responses. Five patients demonstrated stable disease that lasted at least four cycles (12 weeks).

"We have the ability to attach targeting ligands onto the surface of our nanoparticles. Our lead product targets PSMA, which is expressed on the surface of prostate cancer cells as well as the neo-vascularisation of most solid tumors," Gregory I. Berk, MD, chief medical officer of BIND Therapeutics, told HemOnc Today. "The BIND Accurin platform is quite modular, and we have the ability to load our particles with many different types of drugs, as well as the ability to change the targeting ligand. Furthermore, we engineer these Accurins to create the optimal circulation and release.
Do the benefits of nanotechnology outweigh potential safety concerns?

**POINT**

The safety of nanomedicines is exhaustively studied during regulatory approval. Nanomedicines, such as liposomal doxorubicin and taxol-containing albumin nanoparticles, have been in clinical use for many years and have been employed to treat hundreds of thousands of patients. There are currently about a dozen different nanoparticles types in clinical use in oncology, including truly novel agents — such as iron oxide nanoparticles for the thermal ablation of brain malignancies — that are currently approved in Europe but not in the United States. An entire new generation of "actively targeted" nanomedicines is in clinical trials, with the objective of adding localization specificity to the therapy. Many new nanomedicines are in preclinical development worldwide.

The fundamental concept behind nanomedicine is to attain an improved therapeutic index — that is, greater localization at the target lesion — with reduced off-target distribution and the resulting side effects. Thus, the whole concept behind the use of nanoparticles for therapy is to increase safety for a given therapeutic regimen. In addition, before entering clinical use, all nanotherapeutic agents must be tested for safety in phase I trials and reconducted during successive phases of clinical trials. It is true that, at times, the use of nanodrug industrious biodistributions that give rise to adverse side effects that are not found in conventional regimens; this is the case with the hand-and-foot syndrome in liposomal doxorubicin. However, effects of this type are exactly what clinical trials are designed to ascertain. Thus, the safety of nanomedicines for the patients is the very reason for their existence and is exhaustively studied during regulatory approval, as is the case for all other drugs.

Questions remain about the safety of health care workers, those who are near the patients and the environment. Although speculation on these adverse bystander effects is always possible and should actually be encouraged, it must be kept in mind that the chemotherapeutic agents themselves are very toxic substances (and that is why they are used), and they actually are much more toxic than the nanoparticles themselves. As is the case for all chemotherapeutic and biological cancer therapies, the management and disposition of nanomedicines is tightly controlled, thus reducing or eliminating the risk of adverse effects on health care workers, family members and the environment.

The situation for industrial nanoparticles is entirely different. There are hundreds of nanoparticle-containing commercial products currently in the marketplace, for which the toxicity profiles have not sufficiently been studied and to which no regulatory approval process was applied. Still, after 10 years of nanotechnology, no case has ever been reported of death or serious adverse health effect brought about by nanoparticles.

**COUNTER**

There is valid concern over nanoparticles’ long-term toxicity profile. After years of discussion, research and speculation, nanoparticles are beginning to make an impact in cancer therapy. Two recent studies, using entirely different approaches, have produced results that provide reasons for optimism. Results presented at the recent AACR Annual Meeting showed that a targeted polynucleotide nanoparticles formulation of docetaxel, BIND-014, has a favorable toxicity profile compared to that of docetaxel. This nanoparticulate therapy is being evaluated in several riled tumors. Earlier this year at the Gastrointestinal Cancer Symposium, data were presented showing that a protein-bound paclitaxel (Abraxane, Celgene) had clinical effectiveness against pancreatic cancer, which has been resistant to most chemotherapeutics. The term nanoparticle only refers to the size of the particle. Particles can be constructed using entirely different components. Some degrade easily and are readily excreted, whereas others do not degrade and remain in the body. The characteristics of the nanoparticle itself, as well as the characteristics of the pharmaceutical agents that the particle is carrying, will determine its toxicity.

Current clinically approved nanotherapeutics (liposomes) are most of the nanoparticles under clinical investigation, such as BIND-014 and Abraxane, are biodegradable and comprised of materials that have been deemed safe by the FDA. Thus, the delivery of chemotherapeutics by these nanoparticles has not caused any increase in concern over their toxicity. In fact, the delivery of chemotherapeutics by these nanoparticles has generally shown reduced toxicity in clinical trials.

Although current data support the supposition that nanoparticle delivery does not alter the cancer’s mechanism of action, it is possible that a particular nanoparticle and chemotherapy combination can have new effects on cells and, in turn, new toxicities. It is important to note that a number of nonbiodegradable nanoparticles are being evaluated as potential cancer treatments. These are generally comprised of metals such as gold and hafnium. Although these metal nanoparticles are considered inert, no long-term toxicity data exist for these therapeutics. Based on the non-biodegradable nature, there is valid concern over their long-term (over decades) toxicity profile.

There is risk in any new therapeutic approach. The toxicity risks from nanoparticles need to be carefully and fully assessed by preclinical and clinical studies, but they are not now inherently more dangerous than the standard agents that are being delivered.

Mauro Ferrari, PhD, is president and CEO of The Methodist Hospital Research Institute, director of the Institute for Academic Medicine at The Methodist Hospital, executive vice president of The Methodist Hospital System, senior associate dean and professor of medicine at Weill Cornell Medical College in New York, and president of the Alliance for Nanohalth in Houston. He can be reached at The Methodist Hospital Research Institute, 6670 Bertner St, MS 82-216, Houston, TX 77030 email: mferrari@thmh.org.

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One of the greatest challenges associated with that disease is how it develops drug resistance to doxorubicin, said Basar Bilgicer, PhD, an assistant professor of chemical and biomolecular engineering and chemistry and biochemistry at the University of Notre Dame.

"The drugs that you initially start the treatment with may appear to be working well and treating the disease," Bilgicer said in an interview. "However, after a while they lose their efficacy. The drug resistance develops due to the adhesion of the multiple myeloma cells to the bone stromal cells in the bone marrow. This adhesion activates a mechanism that develops drug resistance."

Bilgicer and colleagues targeted one of the receptors responsible for drug resistance, very late antigen-4 (VLA-4).

"By doing so, we prevented these receptors from interacting with their microenvironment and targeted the particles more directly and more efficiently to the tumor," Bilgicer said.

In addition, they promoted particle uptake, allowing more precise delivery of doxorubicin.

"You will be directing the drug only to the site of the tumor," he said.

"They built in a controlled release mechanism, so the tumor gets the full amount of drug; there is no leaking or migrating to other parts of the body."

"The drug is not released until it is taken up by the tumor itself," Bilgicer said. "The change in pH activates the release of the drug only after it is taken up by the tumor cells."

Bilgicer and colleagues hope to make this nanoparticle available for human use soon.

"Our aim is to actually figure out the best formulation as soon as we can, so we can do the transition from bench to bedside as quickly as possible," he said.

Barriers to use

Despite the promise demonstrated by these studies, there are barriers to the widespread use of nanotechnology in cancer.

As researchers try to create nanotechnology with more function, the complexity increases, Davis said. The increased complexity makes manufacturing more challenging and raises questions about how to regulate the technology.

The FDA already announced it would have no special rules for nanotechnology.

"The FDA feels you can use the procedures that are currently in place for other cancer drugs," Davis said. "If you make a nanoparticle for cancer, it will follow the same route."

Another significant question is clearance.

"Everyone wants to know that nothing of this stays in the body and they’re eliminating it," Labhasetwar said. Safety also is a concern.

"You have to be very careful here. It depends on which nanoparticles you’re talking about," Davis said. "I live in Los Angeles. We breathe nanoparticles every day from truck exhaust. There are health issues associated with those."

"But when you talk about trying to create nanoparticle medicine, that’s a well-designed nanoparticle that is going to be tested a lot in animals before it’s tested a lot in humans," he added.

"That’s an entirely different issue than an environmental exposure that you have through an inherent nanoparticle. You have to delineate whether these nanoparticles are being injected into the patient or are being breathed through the environment."

From promise to practice

The benefits of nanoparticles may extend beyond tumor treatment. Research shows they also can aid in cancer diagnosis.

"We can see these nanoparticles being used as contrast agents in imaging to determine the location of the tumor, as well as the tumor behavior after therapy to see if the tumor is shrinking," Grodzinski said.

Although considerable research must be undertaken and completed before nanotechnology becomes mainstream in oncology, there is reason for optimism, Davis said.

"The field is so new that, over the next several years, it’s going to be very interesting to see how it all plays out," Davis said. "So far, it’s encouraging. What we are seeing from a number of these studies, and from moving things into the clinic, is the opportunity to make highly effective therapies with a high quality of life for patients. It is only going to improve. These are sophisticated systems and, as people learn more about how to control them and design their properties, things can only get better."

Grodzinski agreed.

"The number of possibilities is infinite," Grodzinski said. "We need to mature this technology, select which ones are most promising and move them to the clinical environment — by Colleen Owens


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