

CASE AND COMMENTARY

How Should Physicians Help Patients Understand Unknowns of Nanoparticle-Based Medicines?

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Abstract

When a patient wants to enroll in a clinical trial to gain early access to an apparently promising but unproven intervention, her physician should clarify differences between participating in research and receiving treatment to help her avoid therapeutic misconception, make a thoughtful decision, and consider relevant clinical and ethical details. These include a patient's disease and treatment experiences, needs, interests, values, the design and phase of the trial, and the nature of the intervention being studied. When an unproven intervention is a nanodrug, a physician's role is especially difficult, because though nanomedicine might offer real benefits, it can also pose unexpected or even unprecedented harms. Thus, a physician should help a patient explore possible outcomes while promoting realism, countering hype, and preserving hope.

Case

Dr R, an oncologist treating AM, a 42-year-old woman with multiple myeloma, is currently considering AM's different treatment options, since her cancer is now refractory to many conventional treatment regimens. Among the new options is a nanodrug currently in clinical trials.¹ AM has learned about the "miracles" of nanotechnology through various Facebook pages and groups and Twitter accounts she's followed, and she is eager to get access to the trial drug. Dr R is aware of a general lack of knowledge among health care professionals about long-term side effects of nanodrugs,² particularly those still being investigated, so she has been carefully trying to learn about the risks and benefits of this drug and is preparing how to convey information about this drug trial to AM. (Potential benefits of the use of nanoparticles in cancer drug delivery are these: improved drug bioavailability, decreased dosing frequency, and reduced toxicity from chemotherapy.³ Common risks include diarrhea, nausea, and vomiting.⁴ Less common but more severe side effects include neutropenia, lymphopenia, thrombocytopenia, neutropenic fever, and neutropenic sepsis.⁴)

Dr R has learned in a recent article that nanomaterials have key differences from traditional drugs in their biochemical, electromagnetic, and optical properties. As a result,

there are many unknowns regarding their activity within the human body. For example, nanomaterials are of similar size to organelles found within the cell and could potentially interfere with crucial cellular functions, leading to cell damage and death.⁵ In addition, nanoparticles might be rapidly cleared by the immune system because they are similar in size to pathogens that the immune system has evolved to fight.⁵ Upon contact with biological fluids (eg, blood, mucosal secretions), nanoparticles can become coated with immunoglobulins, albumin, fibrinogen, and complement cascade proteins that can change their surface charge and properties as well as facilitate their clearance by the immune system.⁵ There are limited data on interactions between nanomaterials and proteins (eg, blood proteins such as albumin, clotting factors, complement cascade proteins, antibodies) and on how various physiological conditions affect the clearance and fate of nanomaterials. For example, it has been shown that physiological stress can stimulate overexpression of acute-phase proteins that can increase complement activation and macrophage phagocytosis of pathogens.⁵ Dr R also learns that the long-term effects on human physiological pathways of nanoparticles' differences in size and surface-to-volume ratio from traditional drugs are not known. She wonders how to go about the process of helping her patient make an informed decision about participation in a clinical trial involving a nanodrug.

Commentary

As the patient's primary clinical oncologist, Dr R has undertaken the important task of helping her patient, AM, decide whether to seek enrollment in a nanodrug clinical trial. Because Dr R is not an investigator or otherwise engaged in the research that interests her patient, her role is necessarily general; she can learn more about the investigational drug, examine information about the trial on ClinicalTrials.gov, and, later, review the consent form with AM and offer help with her decision. Dr R and AM have probably considered many options together when seeking the best available next treatment for AM's multiple myeloma, so this kind of informed decision-making discussion—a precursor to informed consent—should be familiar to them both, with an important twist: Dr R needs to inform her patient about the clinical and ethical differences between participating in research and receiving treatment in order to avoid therapeutic misconception and help AM make the best decision for herself under the circumstances.^{6,7}

Nanomedicine's Appeal

AM is excited about the promise of nanodrugs and hopes they will be more effective—and less harmful—at lower doses than the same drugs would be if administered in conventional larger particle sizes that have different surface-to-volume ratios. This is what patients want, but it is also exactly what has not been proven about nanodrugs that are being tested in clinical trials. When hopes dominate decision making for patients who become research participants, therapeutic misconception might be interfering with understanding.

Nanomedicine research presents a complicated picture, however. Employing nanoparticles in health care appears to be a new approach, but, in fact, nanoparticles have been used in treatment and clinical research for some time. Nanoparticles are currently used in many settings, from over-the-counter products like sunscreen to virus-transgene combinations that are studied for their potential to treat genetic diseases. Their very small particle size causes nanodrugs to work differently from agents with larger-than-nano particle sizes; this difference could introduce new and potentially unknown risks of harm. At present, information about potential benefits and risks of harm from nanodrugs is limited because nanoparticles vary considerably in both composition and size.⁸ Moreover, there is no agreed-upon standard for determining which particle sizes should be given the “nano” label.⁸

However, the term *nanomedicine* carries a certain mystique, potentially reinforcing a public perception that nanomedicines, even when unproven, hold special promise. Having learned about nanomedicines through social media, AM seems to subscribe to this view; she hopes that the investigational nanodrug will be her miracle. Social media and public information can be wonderful tools for patients and patient advocates, but misinformation and exaggeration, even when based on genuine scientific excitement about a new biotechnology,^{7,9} could inflate expectations and potentially cause harm.

Nonetheless, when a patient like AM faces a life-limiting illness for which there are no further approved therapies, it is expectable and understandable that she might seek other potential means of prolonging her life. This search may be especially familiar to patients with multiple myeloma, whose survival time has lengthened in recent years as a result of earlier diagnosis and an expanding armamentarium of new treatments and research opportunities.¹⁰ However, patients like AM still face many side effects, setbacks, and recurrences¹¹ and thus can sometimes put themselves at considerable risk when pursuing new approved treatments or enrolling in clinical trials. Thus, as much as AM and Dr R both hope that AM can benefit, Dr R will need to explain that therapeutic benefit to patient-subjects is not the primary goal of clinical trials.^{6,7}

Supporting Patients’ Decision Making About Nanomedicine Research

It is essential for Dr R to emphasize that research is intended and designed to obtain knowledge to benefit future patients; she should discuss in general terms what that goal could mean for patients who are research participants. In this conversation, Dr R should lay out the framework of how an investigational medication should be considered within the overall clinical care plan for AM. A compassionate but clear discussion about research participation will enable Dr R to balance 3 factors: care for her patient within the context of their long-standing therapeutic relationship, maintenance of realistic hope, and an honest approach to AM’s prognosis. While this approach is always necessary when a clinician is considering referring a patient to learn about a clinical trial, Dr R has already determined that her patient’s situation might be more complex because of the

potentially unique characteristics of the investigational nanodrug and AM's excitement about its potential benefit for her.

Because Dr R is not one of the researchers, her discussion with AM about the goals of the research study, what to expect from the research consent process, and what she might experience as a study participant will be based on what she learns about the design of the study. Information about study design includes whether the research is at an early or more advanced stage, which is usually signaled by whether the primary goal of the study is (1) to find a safe and tolerable dose, (2) to determine whether the drug appears to work in a small number of participants, or (3) to compare it to approved and well-characterized treatments. Dr R will also need to learn about the investigational nanodrug itself—about how extensively it has been tested so far and what has been learned about it. If, as is likely, the nanodrug is being tested as an addition to standard therapies, AM's experience in the trial will be quite different from the experience of being in an [early trial](#) in which the drug is being given to humans for the first time and participants who enroll first receive smaller doses than participants who enroll later in order to test safety and find a maximum tolerated dose. If the drug has been determined safe in an early trial and is now being studied at the safe dose but AM does not meet the trial's inclusion criteria, she might even decide to seek access to the drug without enrolling in research by using the new federal "right to try" law,¹² which has its own promise and perils. In that case, Dr R would need to explore her own views about this form of expanded access, determine how to counsel AR, and decide whether to assist with her access request.¹³

Dr R can help prepare AM for the research consent process by discussing what AM has learned about and expects from nanomedications and what she herself has learned, stressing points of agreement and identifying points of divergence. She can help AM formulate general questions about the study and the investigational medication as well as about the risks of harm, potential benefits, and other implications of enrolling in the study. In the process of reviewing these themes, Dr R should directly address the concept of therapeutic misconception with AM. She must discuss with AM how hope for medical progress creates a temptation for investigators and clinicians to overstate the potential benefits and minimize the risks of harm associated with investigational medications, including nanodrugs. Heightened expectations about emerging biotechnologies are common, are strengthened by overoptimistic discussion in both traditional and social media, and can give rise to unrealistic hope by leading patients to view receiving unproven interventions in research as their best treatment options; this is the therapeutic misconception. Investigational nanodrugs might be particularly attractive for cancer patients like AM, whose previous treatment experience is often characterized by progress at the cost of significant side effects. Yet the possibility that investigational nanodrugs might be more effective and have fewer side effects at lower doses than approved drugs with larger particle sizes is precisely the reason to study these unproven

agents and to learn whether their potential is real. It is not a reason to seek treatment using them until more is known, especially because very small molecules can have paradoxical and unusual effects.^{9,14}

Therefore, Dr R must help AM understand that her hope can mistakenly encourage her to view clinical research as just like medical treatment. She should directly acknowledge AM's probable view that research participation could seem like her best option simply because all approved treatments have failed her.^{15,16} And she must remind her that novel interventions like nanomedicines need to be studied precisely because their potential benefits and risks of harm are uncertain and unknown. She must do so in a compassionate, balanced way, clearly explaining why the primary goal of research is not treatment, so that AM can make a decision based on her own goals and values and on reasonable expectations about study participation. This conversation is one aspect of working with AM to develop an ongoing clinical care plan for her as she potentially faces the end of her life.

Scenario Planning

One method that Dr R could use to help illustrate the role of clinical research to AM while providing concrete examples of her options for standard medical care is scenario planning.¹⁷ Using this method would help Dr R explain best-case and worst-case scenarios for her condition in general and for the protocol currently under consideration in particular so that together they can address in open, honest conversation what it could be like to be enrolled in a clinical trial involving nanomedicine at this stage of AM's disease. Scenario planning can also begin to illuminate the "if this, then that" situations that often unfold at the end stage of a disease and at the end of a person's life. For example, a best-case scenario that envisions AM's trial participation might address successful life prolongation while also considering the need to manage side effects and to face uncertainty about both the long-term effects of the investigational nanodrug and the potential for future disease recurrence. A worst-case scenario that envisions AM's trial participation might involve discussing a potential care plan addressing goals of care at the end of life in a supportive manner that would help to maintain AM's hope for improvement of her illness while ensuring that she knows she will not be abandoned if the investigational agent does not produce the miracle for which she hopes. Using scenario planning, Dr R can help AM re-examine her expectations about participation in the research study, prepare for the research decision-making process, and gain insight into the experience of being in a nanomedicine trial. She can also discuss AM's ongoing clinical care while she is enrolled in the trial and introduce the prospect of planning for potential progression of her disease regardless of whether she enrolls in the trial.

If and when more information about the trial is available—for example, if AM meets with a study team member and brings the consent form to Dr R so that they can discuss the trial in more detail—Dr R can use scenario planning to more clearly illustrate for AM

what it might be like to participate in the research based on the characteristics of the study and of the nanodrug. If the new drug is being studied as an addition to standard therapies, Dr R can review those therapies and discuss AM's previous (or probable) experiences with them. Dr R could explain many aspects of the trial in lay terms to help clarify what participation might entail on a daily or weekly basis, including details of administering the investigational agent, lab draw or assessment schedules, and any additional testing that AM might need to undergo as part of the protocol. They could then talk together about how participation might affect AM's daily life and health, ideally enabling a frank discussion about how AM would like to spend her remaining time.

Advice for Clinicians

Dr R's primary duty is to care for AM, and while AM might desire to participate in a research study, Dr R should remain mindful of the bigger picture of AM's care. It is not her role to encourage or discourage AM's participation in research. Instead, as a physician with a therapeutic relationship with AM, Dr R is uniquely equipped to combine AM's previous experiences during her illness journey with her own knowledge of AM's disease progression and her newly acquired knowledge of the study design and characteristics of this particular nanoagent. Dr R should support AM in decision making by (1) promoting reasonable expectations about study participation as she hopes for the best outcome that the study and the investigational agent can offer; (2) helping AM to think about her priorities and goals of care moving forward and to consider how participation in a nanomedicine study might affect those goals; and (3) caring for and about her, regardless of whether she enrolls in research, as she lives with—and faces dying with—her disease.

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Editor's Note

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