Re: Medroxyprogesterone Acetate and Metastases: Of Mice and (Wo)Men

I read with interest the article by Palmieri et al. (1), which demonstrated a novel use for the compound medroxyprogesterone acetate. This compound led to reduced metastatic outgrowth of breast cancer cells, apparently via induction of expression of the metastasis suppressor gene Nm23-H1. Because metastases are responsible for most breast cancer deaths, I applaud this work, which may lead to novel approaches to prevent metastatic progression. However, I was concerned by the statement in the accompanying editorial by Jordan (2) that “[t]he received wisdom for breast cancer is that metastatic spread has often occurred by the time of diagnosis of the primary tumor.” This is indeed true, but it is important to avoid confusing “metastatic spread” with the development of clinically relevant, lethal metastases (“metastatic outgrowth”). Metastasis is a process, and the fact that early steps in the process (i.e., metastatic seeding) may have already occurred before diagnosis does not mean that the outgrowth of these cells is inevitable. It is not necessary to, as Jordan suggests, “prevent the initial colonization of organs with metastatic cells” (2), because this is not the only therapeutic window for preventing the formation of lethal metastases. The strategy proposed by Palmieri et al. would not need to be used in a “chemoprevention” setting, as suggested by Jordan (2)—it could also, as proposed by Palmieri et al. (1), have great utility in preventing progression of cells already seeded to distant organs.

As my colleagues and I noted in a review article (3), “The metastatic growth phase fortunately is a clinically broad target, and any treatment that limits growth of metastases prior to their causing irreversible harm to the patient has the potential to be clinically useful. A variety of therapeutic approaches to target this phase are under active development, including inhibition of angiogenesis or signal transduction pathways needed to support the growth of metastatic cells.” Outgrowth of metastases is responsible for much of cancer mortality and morbidity, and this phase of the metastatic process is therefore an important clinical target for therapeutic development (4–6). For example, my group recently demonstrated the utility of targeting metastatic outgrowth in a murine model of postsurgical dietary intervention (7). In that study, outgrowth of metastatic tumor cells that had been seeded before surgery was inhibited by a dietary intervention that was initiated after surgical resection of the primary tumor.

The elegance of the study by Palmieri et al. (1) is that it shows that growth suppression of cells seeded in metastatic sites can be achieved by reactivating metastasis suppressor gene function. This study demonstrates that it is not too late to treat metastases at the time of cancer diagnosis. A clinical therapeutic window exists, so long as metastatic cells have not grown to the point of causing irreversible damage to the patient. Inhibition of outgrowth of cells that have started the metastatic process by being seeded to distant organs is therefore an important goal for antimetastatic therapy development.

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REFERENCES

(3) Chambers AF, MacDonald IC, Schmidt EE, Morris VL, Groom AC. Clinical targets for anti-metastatic therapy. Expert Opin Ther Targets 2004;8:527–36.

RESPONSE

Chambers raises an interesting argument [based on her recent publications noted in (1)] about treating patients after metastatic spread. In fact, the comments illustrate that the implementation of clinical treatment strategies, translational research, and the conduct of cancer cell biology can each be separate worlds divided by the same language.

No one is disputing the interesting results obtained by Palmieri et al. (2) in vivo. It is important that new ideas be explored in the search for treatments for estrogen receptor (ER)–negative micrometastatic breast cancer. My criticism was with the use of the words “metastatic colonization,” which Palmieri et al. stated to be the end point of the assay in vivo.

Webster’s dictionary provides several definitions of the word “colonization.” I like “the act of establishing colonies,” or perhaps one could select “becoming established in a habitat” or, alternatively, “migration to and settling in.” All define colonization as the first stages of spread and survival of a foreign group in a new area. The subsequent stage is micrometastatic growth, which can result in the death of a patient.

An optimal assay for Palmieri et al. (2) to demonstrate inhibition of “metastatic colonization” would be to prevent colony formation completely in the mouse lung by treating the mice with medroxyprogesterone acetate (MPA) at the same time as the breast cancer cells are injected. The cells might not establish colonies, and the resulting strategy of chemoprevention would be an effective application of an increase in the Nm23-H1 tumor suppressor gene with MPA. However, the authors did not use this approach, and as a result the assay was not optimal. Cells were injected into mice, and 4 weeks later, after the authors had checked that colonies had formed in the lungs, the mice were treated with...
MPA. At this point, the act of establishing colonies was complete and the MPA was used to activate a target to stop the growth of the micrometastases.

This idea and the treatment strategy are described as adjuvant therapy by the clinical and translational research communities. Chamber quotes (1) from her recent review the statement that a variety of therapeutic approaches to targeting the micrometastatic growth phase are currently under active development. The clinical breast cancer community has been actively engaged in implementing this strategy for the past 30 years (3), with some success, but it is not referred to as targeting metastatic colonization. It is adjuvant therapy. To their credit, Palmieri et al. (2) plan to test MPA as adjuvant therapy in select ER-negative patients after colonization is complete.

The issues over the timing of treatment demonstrate how the jargon used in the laboratory can be Lost in Translation for the clinical community. Nevertheless, perhaps both communities can agree that the early adjuvant testing of MPA, with its many side effects, should be followed, in the decades ahead, by chemoprevention with a selective glucocorticoid modulator designed to prevent colonization with micrometastases.

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REFERENCES


NOTES

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