using other cell lines such as a monophasic epithelioid mesothelioma cell line.

Chu and colleagues are to be congratulated on their excellent basic research leading to translational research. Their results highlight the promise of their strategy as an optimal treatment option for multimodality therapy in patients with malignant pleural mesothelioma.

References

1. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. *J Thorac Oncol*. 2012;7:1631-9.
2. Krug LM, Pass HI, Rusch VW, Kindler HL, Sugarbaker DJ, Rosenzweig KE, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol*. 2009;27:3007-13.
3. Opitz I, Lauk O, Meerang M, Jetter A, Aeschlimann B, Seifert B, et al. Intracavitary cisplatin-fibrin chemotherapy after surgery for malignant pleural mesothelioma: a phase I trial. *J Thorac Cardiovasc Surg*. 2020;159:330-40.e4.
4. Chu NQ, Liu R, Colby A, Forcrand C, Padera RF, Grinstaff MW, et al. Paclitaxel-loaded expansile nanoparticles improve following cytoreductive surgery in pleural mesothelioma xenografts. *J Thorac Cardiovasc Surg*. 2020;160:e159-68.
5. Liu R, Colby AH, Gilmore D, Schulz M, Zeng J, Padera RF, et al. Nanoparticle tumor localization, disruption of autophagosomal trafficking, and prolong drug delivery improve survival in peritoneal mesothelioma. *Biomaterials*. 2016;102:175-86.
6. Lei H, Hofferberth SC, Liu R, Colby A, Tevis KM, Catalano P, et al. Paclitaxel-loaded expansile nanoparticles enhance chemotherapeutic drug delivery in mesothelioma 3-dimensional multicellular spheroids. *J Thorac Cardiovasc Surg*. 2015;149:1417-24.

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Commentary: One nano-step for murinekind, one giant leap for mesothelioma

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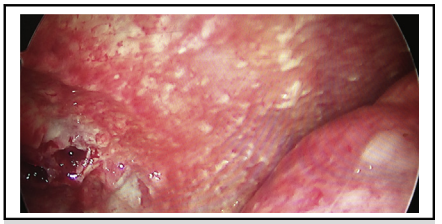

Mesothelioma in need of therapy.

CENTRAL MESSAGE

We review a well-executed study evaluating the increased efficacy and improved survival of nanoparticle-targeted drug delivery in a murine mesothelioma model.

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm, in part due to the latent period between onset and presentation, allowing for insidious progression of tumor burden. As treatments have become increasingly aggressive, one would hope that the survival rates for this notoriously lethal variant would improve. Unfortunately, due to limitations of conventional systemic administration of drugs, and their toxic off-target effects, that has not necessarily been the case. The fear of unwanted effects, without significant hope for improved survival, has contributed to a discrepancy in compliance with national mesothelioma treatment guidelines. A retrospective study from the National Cancer Database identified that 31.1% of patients with mesothelioma did not receive any treatment.[1] Although the outlined treatment plans are associated with overall survival improvement, these treatments could be improved by implementing a treatment plan that limits the toxicities and potentially improves the oncologic response.

The current landscape of treatment in MPM involves a multimodal approach that includes surgical debulking followed by adjuvant chemotherapy (with or without radiation) for additional disease control. Despite these measures, there is still significant morbidity/mortality from recurrence. What can be done to change this? Chu and colleagues propose a strong answer to that question as they continue to evaluate their innovative work on the

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antitumor efficacy of paclitaxel-loaded expansile nanoparticles (PTX-eNPs) in xenograft models of malignant mesothelioma. Previously, this group found markedly increased antitumor results when applying similar methodology to intraperitoneal mesothelioma malignancy.[2] With this knowledge, they sought to fill a greater need—having identified that intrathoracic tumor spread makes up a larger percentage of cases, in particular those with the most unfavorable prognostics. Their study demonstrated that PTX-eNP drug delivery in the thoracic cavity is feasible, safe, and superior to conventional systemic chemotherapy in murine models of both limited and advanced-stage MPM.[3] The PTX-eNPs work to effectively target the tumors, allowing the drugs to accumulate predominantly where needed and less in off-target areas. In fact, this group has previously demonstrated that these expansile nanoparticles result in prolonged drug delivery with nearly a 1000-fold increase in release of drug locally when compared with conventional systemic methods.[4] In the work highlighted here, the authors demonstrate the sustained presence of nanoparticles in vivo. Considering the majority of patients with MPM present with advanced-stage disease, it is of importance to highlight that PTX-eNPs showed the ability to work in conjunction and enhance the efficacy of cytoreductive surgery.

Chu and colleagues have identified a novel drug-delivery solution that transcends severity of disease. They distinguished their study from others by selecting a cell line (MSTO-211H) that allowed for noninvasive and uninterrupted assessment of disease advancement and treatment response. This cell line also represents an aggressive variant of biphasic human mesothelioma, not frequently considered a good candidate for surgery. The possible implications that the results of this study could have for a subset of patients that aren't usually offered curative treatment is intriguing. Another thought-provoking element to these results is the fact that they were obtained using paclitaxel, which is not used in practice as a first-line treatment for MPM, suggesting that delivery is truly the issue here. Looking forward, it will be key to further understand the mechanism of these effects at an even deeper level. The endocytosis of the particle with prolonged intratumoral entrapment seems to make a clear difference for this malignancy. It will be exciting to compare the results of this study with those obtained once nanoparticle constructs capable of delivering current first-line therapeutics are developed, in hopes that survival rates continue to improve on the way to the giant leap for mesothelioma treatment that is so desperately needed.

References

1. Espinoza-Mercado F, Borgella JD, Berz D, Alban RF, Sarkissian A, Imai HTA, et al. Disparities in compliance with national guidelines for the treatment of malignant pleural mesothelioma. *Ann Thorac Surg*. 2019;108:889-96.
2. Schulz MD, Zubris KA, Wade JE, Padera RF, Xu X, Grinstaff MW, et al. Paclitaxel-loaded expansile nanoparticles in a multimodal treatment model of malignant mesothelioma. *Ann Thorac Surg*. 2011;92:2007-14.
3. Chu NQ, Liu R, Colby A, Forcrand C, Padera RF, Grinstaff MW, et al. Paclitaxel-loaded expansile nanoparticles improve survival following cytoreductive surgery in pleural mesothelioma xenografts. *J Thorac Cardiovasc Surg*. 2020;160:e159-68.
4. Tewari D, Java JJ, Salani R, Armstrong DK, Markman M, Herzog T, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*. 2015;33:1460-6.