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Combination of Arginine Depletion and Chemotherapy in Thoracic Malignancies

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See accompanying article on page 1778

Thoracic malignancies, especially lung cancer and malignant pleural mesothelioma (MPM), account for a huge disease burden with devastating mortality worldwide. The unprecedented advances in the development of anticancer therapies in the past few years reflect the importance of precision medicine. For advanced non–small-cell lung cancer (NSCLC), the current standard of care is to determine the presence of actionable targets, such as epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement, that allow logical use of specific targeted therapies.1-4 Recent data also support the upfront use of immunono-logic agents (pembrolizumab, an anti–programmed death 1 or PD1 antibody) among the subgroup of patients with advanced NSCLC that strongly expresses PD-L1.5 In contrast, death 1 or PD1 antibody among the subgroup of patients with advanced non–small-cell lung cancer (NSCLC), the current standard of care is to determine the presence of actionable targets, such as epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement, that allow logical use of specific targeted therapies.1-4 Recent data also support the upfront use of immuno-oncologic agents (pembrolizumab, an anti–programmed death 1 or PD1 antibody) among the subgroup of patients with advanced NSCLC that strongly expresses PD-L1.5 In contrast, the current standard therapeutic options for advanced MPM are limited, with pemetrexed platinum doublet as the standard of care, whereas emerging data support the potential role of bevacizumab6 and immuno-oncologic agents7 in recent years. An urgent need still exists for novel and personalized cancer therapeutics in both advanced lung cancer and MPM.

In the article that accompanies this editorial, Beddowes et al8 report a phase I trial of pegylated arginine deiminase (ADI-PEG 20), cisplatin, and pemetrexed in nine patients with advanced NSCLC or MPM who are deficient in argininosuccinate synthetase 1 (ASS1). Because ASS1 is the key enzyme involved in the urea cycle for biosynthesis of arginine, tumors deficient in ASS1 are predictably susceptible to therapeutic arginine depletion (ie, arginine auxotrophic) with agents like ADI-PEG 20. Apart from determining the recommended dose of ADI-PEG 20 for future study, this small phase I study also provides a glimpse of the clinical activity of this combination, especially in MPM. The approach in selecting tumors on the basis of ASS1 expression by immuno histochemistry (IHC) is biologically sound. However, because IHC expression of ASS1 is a continuum rather than a dichotomized biomarker, the exact cutoff values need to be clinically determined. Beddowes et al8 defined ASS1 deficiency by 0 or 1+ IHC staining in >50% tumor cells, which is based on preclinical studies.9,10 The same definition of ASS1 deficiency has also been adopted in the Arginine Deiminase and Mesothelioma (ADAM) study, which reported favorable progression-free survival with ADI-PEG 20 monotherapy compared with best supportive care in ASS1-deficient MPM.11 Nonetheless, the appropriate and clinically relevant cutoff that defines ASS1 deficiency requires a robust clinical investigation that preferably involves separate training and validation cohorts, which is lacking at the moment. The biologic response to arginine depletion also may vary between tumors, and whether the same cutoff can be used in different tumor types remains to be determined.

The main limitation that precludes sustained response to ADI-PEG 20 is the development of a neutralizing antibody. In the ADAM study with monotherapy of ADI-PEG 20 in MPM, approximately two thirds of patients developed an anti–ADI-PEG 20 antibody, which resulted in a rebound increase in plasma arginine level by the third month of treatment.11 Similarly, a previous phase I study of the combination of ADI-PEG 20 and docetaxel in various advanced solid tumors also detected autoantibodies to ADI-PEG 20 as early as 6 weeks after treatment, which resulted in a gradual return to baseline levels of plasma arginine.12 On the other hand, no neutralizing antibody production against ADI-PEG 20 was observed in early clinical trials in melanoma13 and hepatocellular carcinoma.14 Of note, Beddowes et al8 show that the combination of ADI-PEG 20, cisplatin, and pemetrexed can rapidly deplete plasma arginine levels and sustain these levels throughout the 18 weeks of treatment, although no data during ADI-PEG 20 monotherapy beyond the combination phase are reported. This finding is corroborated by the detection of a neutralizing antibody against ADI-PEG 20 by 8 to 10 weeks at low titers until 18 weeks of treatment. The exact explanation for the low level of antidrug antibody with this combination, in contrast to monotherapy with ADI-PEG 20 in the ADAM study,11 needs to be further elucidated but could be related to the use of corticosteroid premedication, chemotherapy-specific effects, or simply chance as a result of the small sample size.9 Future development of arginine depletion therapy with ADI-PEG 20 will hinge on the effective ways to prevent the production of neutralizing antidrug antibody.

Although one should avoid overemphasis of the clinical efficacy observed in a small-scale phase I study, Beddowes et al8 report a notable objective response rate of 78% with the combination therapy, which is unusual for biphasic and sarcomatoid MPM, and these encouraging results warrant confirmation in future large-scale randomized controlled trials. Compared with data from the ADAM study, the best response attained with ADI-PEG 20 monotherapy at 4 months was only disease stabilization despite a predominance of nonsarcomatoid histology of MPM,11 which could be partly due to the rapid emergence of antidrug
antibody that led to unsustained depletion of plasma arginine in the majority of subjects. Because continuation maintenance therapy with pemetrexed is an established standard of care in advanced nonsquamous NSCLC, future clinical trials also should explore the role of a maintenance doublet with ADI-PEG 20 and pemetrexed for patients who respond to triplet induction therapy.

In the ADAM study, some concerns exist about the safety of ADI-PEG 20 treatment, which was associated with grade 3 anaphylaxis in four patients (9%) and with serum sickness in two.\(^6\) However, in the study by Beddowes et al,\(^8\) the combination of ADI-PEG 20, cisplatin, and pemetrexed was well tolerated. In the only patient who experienced an infusion-related adverse effect, the hypersensitivity reaction was ascribed to cisplatin rather than to ADI-PEG 20. If this reaction is confirmed in future large-scale clinical trials, corticosteroid premedication similar to the usual premedication in four patients (9%) and with serum sickness in two.\(^1\) A persensitivity reaction was ascribed to cisplatin rather than to ADI-PEG 20. If this reaction is confirmed in future large-scale clinical trials, corticosteroid premedication similar to the usual premedication for pemetrexed should be considered for ADI-PEG 20 therapy.

Following in the footsteps of L-asparaginase in the treatment of acute lymphoblastic leukemia, arginine depletion therapy has now emerged as a novel therapeutic for biomarker-selected thoracic malignancies. Future development of ADI-PEG 20 as an arginine depletor with or without systemic chemotherapy will add to the growing armamentarium in the fight against advanced lung cancer and MPM.

REFERENCES


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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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