Managing Multifocal Bronchioloalveolar Carcinoma/Lepidic Predominant Adenocarcinoma: Changing Rules for an Evolving Clinical Entity

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Abstract: Although the clinical entity of bronchioloalveolar carcinoma (BAC) has been reclassified into adenocarcinoma in situ, lepidic predominant adenocarcinoma, and mucinous adenocarcinoma, it continues to merit special consideration based on its distinct natural history and response to therapy. The clinical behavior of multifocal BAC is highly variable, as is its response to various treatments. This characteristic should encourage latitude for individualized judgment rather than reliance on dogma about how advanced non–small cell lung cancer (NSCLC) should be managed. Specifically, it is worth first questioning whether any of the visible disease is progressing at a clinically significant pace. If clear progression is unlikely to occur over several months or longer, an appropriate option is attentive clinical and radiographic follow-up with no intervention. If significant progression is demonstrated in an isolated area, it is very reasonable to consider local therapy—whether surgery or radiation—in this area alone. If progression is clearly apparent, then optimal systemic therapy should be used based on molecular findings. This is the same approach that is generally recommended for other forms of advanced NSCLC, with the presence or absence of a driver mutation used to guide the selection of an epidermal growth factor receptor inhibitor, an anaplastic lymphoma kinase inhibitor, or conventional platinum-based chemotherapy (with the potential addition of bevacizumab).

Introduction

Bronchioloalveolar carcinoma of the lung (BAC) has been redefined since 1960, when it was initially described.[1] The newest classification system for lung adenocarcinomas—developed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society[2]—no longer recognizes BAC as a distinct subtype of lung cancer. Instead, it categorizes unifocal noninvasive lung adenocarcinoma up to 3 cm in diameter as *adenocarcinoma in situ* (AIS); larger or multifocal, nonmucinous, noninvasive adenocarcinoma as *lepidic predominant adenocarcinoma* (LPA); and unifocal or multifocal, mucinous, noninvasive adenocarcinoma as *mucinous adenocarcinoma*.

Notably, the clinical syndrome that has historically defined BAC includes a spectrum of histologic findings. This spectrum ranges from purely noninvasive disease (as defined by AIS or LPA or a potentially noninvasive form of mucinous adenocarcinoma) to minimally invasive adenocarcinoma (MIA, with up to 5 mm of invasive adenocarcinoma) to predominantly invasive adenocarcinoma with BAC features (a noninvasive lepidic pattern combined with a variable amount of invasive disease >5 mm).[3]

The management of BAC has long been characterized by a discordance between the definitions enumerated by leading pathologists or staging committees and the clinicians who need to apply definitions from pathologists to clinical practice.[4] In this setting, the observed patterns of the extent of disease and the pace of progression guide recommendations more than the histologic definitions that are applied. Those with the most significant clinical experience recognize that differences in the clinical behavior and histologic appearance of BAC require it to be approached as a unique, clinically defined entity with a variable natural history that merits it being treated according to principles that may deviate from those of treating more common forms of lung cancer.

BAC can be remarkably indolent or tragically virulent, which makes it prone to either overtreatment or undertreatment. It has been subjected to significant misinformation, including claims about the futility of systemic therapy and about an extremely high probability of response to targeted therapies, both of which are oversimplified myths. An unfortunate challenge in reviewing the optimal management of multifocal BAC is the relative dearth of clinical data to guide treatment recommendations. This limitation is complicated by the heterogeneity of the patient population and the lack of large, multicenter trials. Small, single-institution trials are subject to selection bias that distorts conclusions.

Accordingly, the recommended approaches to BAC espoused here are based not on level 1 clinical evidence but on the judgment developed from extensive clinical experience in managing the care of a wide range of patients with extremely variable natural histories of BAC. These guidelines therefore do not presume to offer a clear path for all or even most patients with multifocal BAC, but rather to highlight the cases in which multifocal BAC merits an especially individualized approach and greater latitude for clinical judgment. In some cases, the treating physician will need to circumvent rules that are meant to apply to the more common subtypes of advanced non–small cell lung cancer (NSCLC). At the same time, physicians must learn from the broader principles that have been developed over the past several years for managing advanced NSCLC; specifically, the ability to use molecular markers to guide the most appropriate management of patients who require systemic therapy.

Perhaps more than any other clinically defined subset of lung cancer patients, the optimal treatment of multifocal BAC requires choosing among a broad range of options based on the specific clinical features of each patient's disease trajectory. There are 3 key questions to ask in the management of these patients. First, is the disease symptomatic, or progressing at a pace that is clinically significant enough to require treatment? Second, if so, are the symptoms caused by—or is that progression limited to—no more than a few lesions that may be addressed effectively with local therapy? Third, if there is more diffuse progression, what is the optimal systemic therapy? This article will review which principles of general NSCLC management may be rightfully questioned, and which ones continue to apply to the evolving clinical entity of multifocal BAC.

Evaluation of Patients With Multifocal BAC

The central issue in managing BAC as a functionally distinct clinical entity is that it demonstrates remarkable variability in clinical behavior. Specifically, what is technically considered multifocal BAC can describe anything from 2 or more subcentimeter ground-glass opacities that are growing at a barely perceptible pace over a few years in both of a patient's lungs, to wide and confluent areas of lobar infiltrates that cause a debilitating productive cough (bronchorrhea) and a rapid, inexorable progression to respiratory failure. Molecular features may include an activating mutation in the gene for the epidermal growth factor receptor (EGFR), a translocation in the gene for anaplastic lymphoma kinase (ALK), or no actionable target. Not surprisingly, the optimal treatment of these widely disparate presentations within the broad range of multifocal BAC may fall outside of standard recommendations that would apply for a more typical presentation of advanced NSCLC. As such, the general rules of managing advanced NSCLC may potentially represent overtreatment or, far less commonly, undertreatment.

Notable as well is the possibility that the disease may demonstrate a different pace and behavior across distinct areas of disease within a single patient, with one or more foci of disease demonstrating a markedly more aggressive natural history than other areas. Although the medical literature does not include clinical trials to shape optimal therapy here, it is appropriate to pursue management of the different areas of disease independently, as I discuss below.

Question 1: Is Disease Progressing at a Threatening Pace?

As mentioned earlier, the first key question regarding the management of multifocal BAC is whether the disease is symptomatic or progressing at a pace that is clinically significant enough to require treatment. The reclassification

of BAC—as AIS to describe nonmucinous, noninvasive adenocarcinoma in a solitary lesion up to 3 cm, and LPA to describe a multifocal process—implies a relevant clinical behavior. An in situ, precancerous lesion will typically have an indolent natural history and an extremely favorable prognosis after resection of solitary lesions. In contrast, LPA refers to disease that is life threatening in many cases yet displays extreme indolence in other cases, with a doubling time that can sometimes be measured in years.[5-7]

At the time of initial diagnosis of multifocal BAC, clues typically are present that suggest whether any or many lesions are progressing at a clinically significant pace that will lead to symptoms or threaten survival in the next several months or years. The concept of clinically significant progression is subjective and eludes any formal definition, but clinically experienced oncologists have several tools available to help predict whether a patient's cancer is likely to threaten quality or quantity of life. The diagnosis of multifocal BAC is most commonly made after trials of antibiotics, corticosteroids, or other interventions, often with repeat imaging that provides an estimated doubling time for the lesion(s). Positron emission tomography scans, well known for their potential to provide false-negative results for BAC by overlooking the presence of lesions with a low growth index, can corroborate a high probability of an indolent progression trajectory if a patient has what appears to be slow-growing disease with a low level of metabolic uptake in observed lesions.

Although patients with symptomatic disease and those whose cancer has progressed visibly over several months merit timely treatment, a subset of patients with multifocal BAC—including some with a significant tumor burden of visible disease—can have such an indolent pace of disease that they do well for years with no intervention. Certainly, some patients and physicians may be anxious about leaving documented disease untreated. One risk of postponing treatment is that the tumor cells might develop a mutation that changes the fundamental behavior of the cancer and leads to a much more aggressive disease pattern. Nevertheless, the limited array of effective treatment options for patients over time, the potential adverse effects of treatment, and the recognition that deferring treatment does not preclude treatment in the future, all make the strategy of attentive clinical and radiographic follow-up without intervention a very reasonable and arguably optimal approach for some patients. The patients who may benefit from this approach are those in whom we can anticipate a long time before disease develops that likely will limit their survival and/or quality of life. This thoughtful approach addresses the reality that the treatment can be worse than the disease for certain patients with indolent, and especially asymptomatic, disease.

Question 2: Is Disease Progression Limited?

If the disease is symptomatic or progressing rapidly, the second key question is whether the progressing disease is unifocal or limited, and amenable to local therapy. The unique behavior of some cases of multifocal BAC enables consideration of local therapy for unifocal or limited progression, even in the setting of established disease. If 1 or several lesions are progressing at a rate at which they are likely to significantly outpace more diffuse progression, it is reasonable to discount the background minimally or nonprogressing foci and pursue local therapy. This situation can be thought of as *precocious progression*, much like the well-described clinical situation of the patient with *precocious metastasis* of NSCLC to the brain or an adrenal gland.[8,9] By "getting out the lead runner" (throwing out the runner who has advanced farthest on base, to use a baseball analogy) with local therapy, the pace of the disease process may be reset to that of the indolent cancer in the background. Outcomes with such an approach can be very favorable. A recently published single-center case series[10] demonstrated that among 39 patients with multifocal BAC and a single dominant nodule, only 9 (23%) demonstrated appreciable radiographic progression of a remaining, unresected nodule over a mean follow-up of greater than 30 months.

Patients with preexisting multifocal disease have a higher risk of metachronous or diffuse progression compared with those who have no additional lesions beyond a solitary focus of actively progressing NSCLC. This fact makes local therapy that minimizes morbidity and loss of functional lung parenchyma particularly appealing. In this situation, the opportunity to treat such lesions definitively with stereotactic ablative radiation therapy—also known as stereotactic body radiation therapy—has emerged as an attractive option. With the value of local therapy still poorly established but having a compelling rationale, such an approach transcends the boundaries of current standard of care but confers little risk.

The natural history of multifocal BAC often follows the natural history of serial, metachronous lesions. In an era in which minimally invasive video-assisted thoracic surgery or stereotactic ablative radiation therapy is increasingly readily available, some patients may present with metachronous lesions that are amenable to serial resection or radiosurgical ablation. Such a strategy may be extremely appropriate for patients in whom the interval between appearances of new or progressing lesions is measured in years, and treatments are limited to areas of demonstrated progression and not just identifiable, stable nodules. With such local therapies readily available, however, there is the risk that patients with a diffuse, multifocal pattern of progression, or who have new lesions growing concurrently or appearing over

intervals of only months, may be subjected to multiple interventions. This may be inappropriate for what is truly a multifocal metastatic process, with a prognosis that is likely to be dictated by the diffuse, systemic nature of the disease, rather than by the effect of one or a few discrete lesions.

The danger of applying local therapy injudiciously for multifocal disease with multiple metachronous lesions, or oligoprogressive disease with several lesions demonstrating visible progression concurrently, is that patients may lose significant amounts of functional lung parenchyma from serial surgeries or radiation treatments. This approach may lead to overall harm if the patient experiences subsequent disease progression that causes further loss of functional lung parenchyma. It is unwise to recommend a pneumonectomy or the resection of multiple lung lobes, with the sacrifice of large amounts of uninvolved lung tissue, for a process that might have been readily foreseen to have a very high probability of subsequent multifocal recurrence/progression. The fact that patients with multifocal BAC may undergo resections and do well for several years afterward[11-14] should not lead us to presume that such patients have done well *because* of this surgery. In many cases, the background disease was so indolent that it may be fairer to conclude that the patients have done well *despite* the loss of so much functional lung parenchyma. Reports on these cases sometimes make a backward argument that these lesions are separate primary cancers because survival is favorable. In such a setting, it is important to make the distinction between what can be done and what should be done.

An unusual circumstance in which surgery may be appropriate (if unconventional) involves palliative surgery for multifocal BAC, most commonly for the mucinous subtype. We would not normally consider surgery, with its morbidity and rigors, as a palliative intervention. However, rare patients with a pneumonic form of BAC—characterized by extensive infiltration that appears remarkably similar to lobar pneumonia in 1 or more lung lobes—may benefit from palliative surgery.[15] Such patients may experience a severe productive cough with bronchorrhea and/or dyspnea caused by "shunting" of blood. In these cases, blood perfusing these extensively infiltrated but poorly aerated regions of lung parenchyma remains unoxygenated, diluting oxygenated blood from uninvolved lung areas. Surgery has rarely been employed as a palliative maneuver, even in patients known to have terminal, multifocal disease.[16,17] Unfortunately, but not surprisingly, patients who undergo such a procedure commonly experience disease progression shortly after surgery.[18]

Question 3: What Is the Optimal Systemic Treatment?

If BAC is multifocal and diffusely progressing at a clinically significant rate, the third key question is what systemic therapy should be used. Systemic therapy is the cornerstone of management of these patients, although one additional option that has been pursued rarely is lung transplantation. Lung transplantation has been described in isolated, small case series of patients with multifocal BAC or a pneumonic pattern of diffuse disease.[19-23] Such studies have generally reported favorable results in the short-term (a few years), though recurrence is common when patients are followed for longer.[24,25] Although a subset of patients do very well for years, the efficacy of this approach cannot be assessed because of the small series size and selection bias, plus the variability in natural history of multifocal LPA/BAC. The lack of data demonstrating a proven survival benefit, combined with the limited availability of transplantable lungs and economic considerations, limit the generalizability of this approach to a broad population. The potential role of lung transplantation for multifocal BAC remains undefined.

Systemic therapy with chemotherapy and/or targeted therapies remains the appropriate strategy for the vast majority of such patients, despite the prevalent view that BAC is unresponsive to conventional chemotherapy compared with other NSCLC histologic subtypes. This may be partially related to the generally accepted premise that faster-growing cancers are more responsive to chemotherapy than slower-growing cancers.[26] It is also likely that chemotherapy has in part been dismissed as ineffective against BAC because of the radiographic features of BAC, which often manifests as a poorly defined, consolidative pattern that may not demonstrate measurable response as readily as more invasive, discrete lesions that characterize most other forms of advanced NSCLC. However, limited, retrospective data directly comparing the efficacy of standard chemotherapy for advanced BAC vs other NSCLC subtypes challenge the view that it is more chemoresistant.[27]

Several prospective trials have tested the utility of conventional chemotherapy in patients with advanced BAC. A multicenter trial of single-agent paclitaxel administered over a 96-hour infusion to 58 patients with advanced BAC[28] demonstrated a response rate (RR) of 14%, with another 40% of patients achieving stable disease as the best response; the median overall survival (OS) of the study population in this trial was 12 months. A smaller Italian trial of single-agent paclitaxel administered over 3 hours[29] reported an RR of 11%, stable disease in 50% of patients, and a median OS of 8.6 months. Finally, the French IFCT-0401 (Intergroupe Francophone de Cancérologie Thoracique-0401) trial[30] reported outcomes with a range of chemotherapy regimens administered to 43 of 47 patients whose disease had progressed after first-line gefitinib for advanced BAC. Of these 43 patients, 38 received platinum doublet chemotherapy (with a taxane in 29 patients, and gemcitabine in 9) and 5 received single-agent chemotherapy (gemcitabine

in 3 patients, pemetrexed in 2). Aggregate results for the range of chemotherapy regimens included an RR of 21% and median progression-free survival (PFS) of 3 months. The small numbers of patients receiving specific regimens preclude meaningful comparison of one chemotherapy approach with another, but it is notable that the RR for platinum-taxane regimens was 28%, compared with 0% for recipients of platinum-gemcitabine, while the 2 patients receiving single-agent pemetrexed also appeared to do especially well (PFS of 10 months and 32 months, respectively). Anecdotal case reports have corroborated the potential for particular efficacy with pemetrexed in some patients with advanced BAC, including those with mucinous BAC that demonstrates a pneumonic pattern.[31,32] Overall, in contrast with the common and incorrect perception that chemotherapy is ineffective in BAC, the data support the activity of conventional chemotherapy with a platinum doublet that includes either a taxane or pemetrexed. In fact, the efficacy is objectively comparable to that seen for platinum doublet chemotherapy in other NSCLC subtypes.

Enthusiasm about systemic therapy for multifocal BAC centered around the early anecdotal reports and some retrospective data suggesting that such patients were among those most likely to demonstrate profound and prolonged responses to oral EGFR tyrosine kinase inhibitors (TKIs), specifically gefitinib and erlotinib at the time.[33,34] This led to prospective trials of both agents in multifocal BAC. A 4-center trial of 101 patients (74 previously untreated) who received erlotinib (150 mg PO daily) demonstrated an RR of 22% and a median OS of 17 months.[35] A multicenter trial by the Southwest Oncology Group (SWOG) of 136 patients with advanced BAC (101 untreated) who received gefitinib (500 mg PO daily) revealed an RR of 17% in previously untreated patients and 9% in patients previously treated with chemotherapy, with a median OS of 13 months in both groups.[36] The IFCT also administered gefitinib (250 mg PO daily) to 99 previously untreated patients with advanced BAC, demonstrating an RR of 13%, with stable disease in an additional 16%.[37]

More recently, however, it has become clear that the molecular features of a lung cancer override clinical features such as histology in predicting the benefit of targeted therapies like EGFR or ALK inhibitors, particularly in light of the IPASS (Iressa Pan-Asian Study) results. The IPASS trial[38] compared gefitinib vs standard chemotherapy with carboplatin-paclitaxel in Asian patients with advanced lung adenocarcinoma (94%) or a light prior smoking history (6%), and demonstrated that in a clinical population with clinical features highly associated with benefiting from EGFR TKIs, the RR and PFS were markedly superior with gefitinib alone in the 60% of patients whose cancer harbored an *EGFR* mutation. In fact, the remaining 40% of patients without an *EGFR* mutation demonstrated far better outcomes with first-line chemotherapy. In other words, adenocarcinoma histology (presumably including the BAC subhistology of adenocarcinoma) and other identified factors such as never-smoking or minimal prior smoking status appear to be proxy identifiers for a higher probability of a tumor harboring an activating *EGFR* mutation, which is the truly relevant factor predictive of benefit from EGFR TKI therapy.

Data on the association of *EGFR* mutation with BAC subtype remain limited but support the premise that the efficacy of EGFR TKIs in advanced BAC is likely predicated on the relatively high prevalence of an activating *EGFR* mutation in such patients,[39,40] particularly those with nonmucinous BAC.[36,40-43] Within a series of 86 patients with advanced BAC, 26% were demonstrated to have an *EGFR* mutation. All 22 of the mutations occurred in patients with nonmucinous BAC, whereas none occurred in patients with mucinous BAC.[39] Furthermore, a study of molecular features in Japanese patients with BAC or adenocarcinoma with BAC features demonstrated that an *EGFR* mutation was present in 58% of patients with nonmucinous BAC vs 15% of those with mucinous BAC, while a *KRAS* mutation was present in 29% vs 70% of these subgroups, respectively.[44]

These associations appear to correlate with the clinical activity of EGFR TKI therapy, at least based on the scant evidence directly available. In the aforementioned 4-center trial of erlotinib for advanced BAC,[35] the RR among patients with an *EGFR* mutation was 87% and median PFS was 13 months, contrasting with 7% and 2 months, respectively, for those patients with wild-type *EGFR*. Further analysis of patients in the same trial revealed that the presence of a *KRAS* mutation, long identified as associated with a low probability of significant benefit from EGFR TKI therapy,[45-47] followed the opposite pattern, with an RR of 32% for those with wild-type *KRAS* but 0% for those with a *KRAS* mutation. With the data suggesting that the benefit of EGFR TKIs in this population is driven by the enrichment for activating *EGFR* mutations, current recommendations for systemic therapy in multifocal LPA/BAC and adenocarcinoma with a lepidic pattern of spread are not based on histologic findings but rather on the presence or absence of an activating *EGFR* mutation.[48,49]

There also may be a role for the addition of bevacizumab to EGFR TKI therapy, though this remains an open question. In a follow-up to the SWOG trial of gefitinib for advanced BAC,[36] the SWOG 0635 trial tested the erlotinib-bevacizumab combination in 78 patients with advanced BAC,[50] demonstrating an RR of 18%, a median PFS of 5 months, and a median OS of 17 months. These results, while not remarkably superior to those of the preceding trial with gefitinib, are perhaps

more notable for the small proportion of never-smokers; these subjects were preferentially enrolled in a concurrent, competing trial of the same combination for never-smokers with advanced lung adenocarcinoma. As noted above, the most relevant issue with regard to optimal first-line therapy is likely to be dictated by molecular marker status. A recently reported Japanese randomized trial of *EGFR* mutation–positive patients with advanced lung adenocarcinoma demonstrated a statistically significant improvement in PFS of greater than 6 months with the addition of bevacizumab to erlotinib compared with erlotinib alone[51]; this strongly suggests a clinically significant incremental value of combining bevacizumab with EGFR TKI therapy in such patients.

Finally, another relevant driver mutation for which a specific targeted therapy exists is the *ALK* rearrangement, which has been noted in approximately 4% of patients with NSCLC. The ALK inhibitor crizotinib (Xalkori, Pfizer) has demonstrated significant efficacy in these patients[52] and has received approval from the US Food and Drug Administration for this purpose.[53] Because *ALK* rearrangements are both uncommon and newly discovered as a clinical target, we have yet to learn the prevalence of the *ALK* rearrangement among different adenocarcinoma subtypes. Early reports, however, have suggested that an *ALK* rearrangement may be disproportionately seen in patients with adenocarcinoma with bronchioloalveolar features.[54,55]

Taken together, this work on patients within the AIS/BAC spectrum, which has typically included LPA and even adenocarcinoma with BAC features, has consistently demonstrated that these cancers have a high probability of harboring a relevant molecular marker that can serve as a driver mutation to guide selection of targeted therapy vs conventional chemotherapy. The optimal systemic therapy for patients with multifocal, progressing BAC is not defined specifically by the cancer's histology, but rather by its molecular features or the absence thereof.

Future Directions

The clinical entity of multifocal LPA/BAC and the wider spectrum that includes adenocarcinoma with BAC features—essentially a lepidic pattern of cellular spread along the periphery of an invasive lung adenocarcinoma—are unlikely to be studied in a dedicated way in the future, as they are no longer formally recognized as well-defined types of lung cancer. Instead, the blurring of the lines of demarcation with the new definitions of adenocarcinoma, combined with the growing consensus that the optimal systemic therapy for patients with progressing multifocal BAC is guided by the molecular characteristics of the cancer, obviates the potential for dedicated trials for this undefined population. Nevertheless, clinical trials of various novel therapeutic approaches continue to be subdivided by histologic findings, which, along with clinical observations published as case series, may provide further insights in the clinical management of BAC patients based on subgroup analyses.

In addition to *EGFR* mutation and *ALK* rearrangement, the *ROS1* gene rearrangement is a target that has been identified as a clinically relevant marker in approximately 1% of NSCLC cases. It is highly associated with adenocarcinoma histology and never-smoker or minimal prior smoking status, as well as a high probability of significant response to crizotinib.[56] It remains to be determined whether it is likely to be disproportionately associated with BAC histologic findings and clinical syndrome.

KRAS mutation remains the most common mutation seen in advanced NSCLC, occurring in approximately 20% to 25% of cases. As noted above, it is a potential target in a subset of patients with advanced BAC, particularly the mucinous subtype. One report of a randomized phase 2 trial revealed a striking improvement in efficacy with a combination of the investigational MEK (MAPK-ERK kinase) inhibitor selumetinib with docetaxel vs docetaxel alone as second-line therapy in *KRAS* mutation–positive advanced NSCLC.[57] Thanks to these results, there is considerable excitement about the potential utility of selumetinib or perhaps other MEK inhibitors in *KRAS* mutation–positive NSCLC. Though there are no clinical trials specifically focusing on patients with BAC/LPA histology, patients with the BAC pattern and *KRAS* mutations may prove to benefit substantially from this class of agents.

Beyond these identified targets, the use of immune checkpoint inhibitors such as nivolumab, pembrolizumab, and others in advanced NSCLC has generated profound interest. This interest is based on these agents having demonstrated prolonged responses in a minority of patients with advanced and sometimes heavily pretreated NSCLC, often with modest or even minimal adverse effects.[58] Results with inhibitors of either the programmed death receptor or its ligand have demonstrated no clear association with NSCLC histology thus far,[58] but this field of immunotherapy for advanced NSCLC remains the subject of a wide range of studies that do not restrict inclusion on the basis of NSCLC histology. As with the work in *KRAS* mutation–positive patients, this work on immune checkpoint inhibitors includes a subset of patients with BAC/LPA, so we can expect to clarify whether there is an association of greater or lesser efficacy in this subtype.

Conclusions

The clinical entity previously recognized as BAC has undergone evolution over the more than 5 decades since it was

initially described. The new classification system for lung adenocarcinomas[2] removes this designation and characterizes unifocal, noninvasive, nonmucinous adenocarcinomas as AIS and multifocal, noninvasive, nonmucinous adenocarcinoma as LPA, with mucinous BAC now being classified as mucinous adenocarcinoma, whether unifocal or multifocal. Despite the reclassification and regardless of the terminology, experienced clinical oncologists continue to appropriately distinguish BAC as a clinical syndrome that merits special consideration compared with the majority of lung adenocarcinomas. This distinction is based on the extremely variable natural history of BAC, which can be so indolent that no therapy is necessary. The result is that any treatment may represent overtreatment, with a greater potential for harm than benefit.

Three central questions should be considered before undertaking interventions for these patients. First, is any area of disease demonstrating progression at a clinically significant pace likely to represent a threat to survival or quality of life in the relatively near future? This admittedly subjective measure can identify a subset of patients who can safely be observed over time for a new pattern of progression but who likely require no intervention.

Second, even if disease is technically multifocal, if clinically significant progression is noted, is that progression unifocal or limited in its geography such that local therapy may be considered? Although this challenges the central dogma against the value of local therapy in multifocal disease, the key issue is that nonprogressing or very indolent lesions in the background may be discounted, so that the only disease to address is what is growing at a rate fast enough to compromise survival or lead to cancer-related symptoms.

Third, if clinically threatening progression is identified, does it demonstrate a diffuse pattern of progression and if so, what is the optimal systemic therapy? Though limited, the evidence from studies of patients with advanced BAC indicates that the benefits of conventional chemotherapy are comparable to those seen in patients with other forms of NSCLC, perhaps with more promising activity with pemetrexed (Alimta, Lilly) or taxanes, typically paired with a platinum agent if chemotherapy is administered in the first-line setting. More generally, the data in advanced BAC suggest that management of systemic therapy options should follow the same principles as those now well established for invasive advanced lung adenocarcinoma. Specifically, it is most appropriate to test for a relevant biomarker such as an activating *EGFR* mutation or *ALK* rearrangement that would suggest optimal treatment being an EGFR TKI or ALK inhibitor, respectively; if an identifiable driver mutation with an associated inhibitor is not identified, then conventional chemotherapy emerges as the default optimal systemic therapy approach. Treatment decisions for subsequent lines of therapy should be directed by the same principles that apply to other NSCLC histologic subtypes.

Finally, just as the demographic and histologic features have now been recognized as serving as an imperfect proxy for the underlying biology of the cancer with regard to driver mutations, it is worth noting that the principles of individualizing therapy, potentially withholding treatment for extremely indolent cancers and considering local therapy for those with very limited progression, should not be considered unique to multifocal BAC. Instead, this setting serves as an exemplar for an approach to lung cancer management that clinical oncologists have recognized as valuable. We can hope and expect that as our understanding of the biology of lung cancer improves, we will be able to better select the precise strategies for all types of lung cancer that will avoid both overtreatment and undertreatment, recognizing the individualized features of each cancer rather than following a dogmatic approach by broad categories, especially when the definitions of such categories continue to evolve.

Disclosures

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