Small-Cell/Neuroendocrine Prostate Cancer: A Growing Threat?

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Treatment-emergent small-cell/neuroendocrine prostate cancer is likely to become of increasing clinical relevance in the era of widespread use of potent androgen receptor-targeted therapies.

Source:

In the accompanying review article, Drs. Aparicio and Tzelepi present a series of clinical vignettes that highlight the salient clinical features of small-cell prostate cancer, including frequent visceral and bulky soft-tissue metastases and limited duration of response to both hormonal therapy and cytotoxic chemotherapy.[1] These vignettes offer insight into the frequently aggressive clinical course of this disease entity and serve to highlight the need for novel targeted therapeutic approaches to improve outcomes for this lethal disease subset. Interspersed among the vignettes, several of the molecular and histopathologic features associated with small-cell/neuroendocrine differentiation are nicely summarized by the authors. In considering the body of literature on small-cell prostate cancer and the conclusions presented by Drs. Aparicio and Tzelepi, there are several points worth highlighting.

It is important first to note that the majority of published molecular analyses of small-cell prostate cancer represent analyses of primary prostate tissues and models of neuroendocrine prostate cancer that are based on primary prostate cancer cell lines.[2-4] In the published literature, the total number of human metastatic castration-resistant tumors with small-cell features that have undergone thorough molecular analysis remains quite limited. Given the different potential for evolution in the genomic makeup of metastatic vs primary tumors, and the discordance in patterns of gene/protein expression between primary and metastatic tumors observed in other cancer subtypes, it is critical in the coming years to define the molecular characteristics of metastatic small-cell prostate tumors (as well as their circulating tumor cells and nucleic acids) as these tissues become increasingly available. Efforts to obtain and analyze metastatic small-cell prostate cancer tissues are underway, including the multi-institutional research project funded by the Stand Up To Cancer-Prostate Cancer Foundation (http://www.standup2cancer.org/dream_teams).

Secondly, the cellular origin of treatment-emergent small-cell/neuroendocrine prostate cancer remains to be defined. The authors of this review suggest a transdifferentiation event (adenocarcinoma → small-cell/neuroendocrine), which is supported by evidence of shared TMPRSS2-ERG gene fusions and the frequent presence of pathologic specimens admixed with adenocarcinoma and small-cell/neuroendocrine features.[5] It is equally plausible, however, that there is clonal selection of a subset of cancer cells with small-cell/neuroendocrine features; this hypothesis is supported by the reports of small populations of neuroendocrine cells observed in primary prostate cancer tissues at the time of diagnosis.[6] Clarifying the origin of small-cell prostate cancer is not just of academic interest; this may have future implications for the sequencing and timing of therapy, and could potentially make it possible to reverse the small-cell phenotype if a transdifferentiation phenomenon is found to predominate. In patients with EGFR-mutant non–small-cell lung cancer who develop small-cell features as a mechanism of resistance (adenocarcinoma → small-cell/neuroendocrine), which is supported by evidence of shared TMPRSS2-ERG gene fusions and the frequent presence of pathologic specimens admixed with adenocarcinoma and small-cell/neuroendocrine features.[5] It is equally plausible, however, that there is clonal selection of a subset of cancer cells with small-cell/neuroendocrine features; this hypothesis is supported by the reports of small populations of neuroendocrine cells observed in primary prostate cancer tissues at the time of diagnosis.[6] Clarifying the origin of small-cell prostate cancer is not just of academic interest; this may have future implications for the sequencing and timing of therapy, and could potentially make it possible to reverse the small-cell phenotype if a transdifferentiation phenomenon is found to predominate. In patients with EGFR-mutant non–small-cell lung cancer who develop small-cell features as a mechanism of resistance to EGFR inhibition, the discontinuation of the EGFR inhibitor results in reversal of the small-cell phenotype.[7] It is not known whether such plasticity exists in small-cell/neuroendocrine prostate cancer.

Thirdly, while it is clear that small-cell/neuroendocrine prostate cancer has been increasingly described in the era of highly potent novel agents that target the androgen receptor, it is not known whether its growing prevalence can be fully attributed to selection pressure, with treatment-emergent disease following abiraterone or enzalutamide resistance.

Fourth, the use of clinical features alone to define small-cell/neuroendocrine prostate cancer and to make treatment decisions is not sufficient to optimize treatment outcomes. Prior studies, including the single-arm phase II prospective trial led by Dr. Aparicio, used a series of clinical features to define aggressive phenotypic disease (previously called “anaplastic” prostate cancer, a term that is now discouraged, since “anaplastic” carries pathologic connotations); these features included the presence of visceral metastases, low serum prostate-specific antigen (PSA) level in relation to bulk of...
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Small-cell/neuroendocrine prostate cancer, elevated serum markers of neuroendocrine differentiation, lytic bone metastases, and bulky pelvic soft-tissue disease.[8] However, these clinical features lack specificity and sensitivity for the detection of small-cell prostate cancer. Drs. Aparicio and Tzelepi recommend that patients with aggressive phenotypic features, with or without small-cell/neuroendocrine differentiation, should be treated with combination chemotherapy, since there is no evidence that distinguishing the particular histologic subtype (small-cell prostate cancer vs poorly differentiated adenocarcinoma) impacts treatment outcomes. While this may be currently true in an era of cytotoxic chemotherapy without the availability of targeted anticancer therapies, as the molecular features of small-cell/neuroendocrine prostate cancer are defined and therapeutic targets identified, histologic confirmation of small-cell/neuroendocrine prostate cancer (or the use of noninvasive diagnostic biomarkers that accurately identify small-cell prostate cancer) will be increasingly important as a means of patient selection for clinical trials and ultimately to guide the choice of systemic therapy. Finally, there is unlikely to be a “one-size-fits-all” optimal approach to the treatment of small-cell prostate cancer. As pointed out by Drs. Aparicio and Tzelepi, there is frequently significant intratumoral heterogeneity that is evident at the histologic level, with pathologic specimens often showing adenocarcinoma admixed with small-cell/neuroendocrine differentiated tumors. It will be important to determine whether intra- and intertumoral heterogeneity are also found at the molecular level, as this will have implications for the development of targeted therapies for small-cell prostate cancer. A high degree of molecular heterogeneity argues for combination treatment strategies and for the development of monitoring strategies that can provide early detection of treatment-resistant subclones, in order to optimize outcomes for this high-risk subset of prostate cancer.

In summary, treatment-emergent small-cell/neuroendocrine prostate cancer is likely to become of increasing clinical relevance in the era of widespread use of potent androgen receptor–targeted therapies. The current review highlights the most frequently observed clinical features of this disease entity, but further research is needed to define the optimal treatment approach. The molecular characterization of this entity is predicted to significantly enhance our ability to develop novel targeted treatment approaches for this uniformly lethal subset of prostate cancer.

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References:

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