Understanding the Lethal Variant of Prostate Cancer: Power of Examining Extremes

Ana Aparicio, Christopher J. Logothetis, and Sankar N. Maity

Summary: Small cell prostate carcinoma is a lethal variant of castration-resistant prostate cancer. Beltran and colleagues identified overexpression and amplification of both aurora kinase A (AURKA) and the MYCN proto-oncogene in the small cell prostate carcinomas and propose Aurora kinase A as a potential therapeutic target in this disease subset. Cancer Discovery, 1(6), 466-68. ©2011 AACR.

Commentary on Beltran et al., p. 487(4).

Poorly differentiated neuroendocrine carcinoma (NEPC, also known as small cell carcinoma of the prostate) is a morphologic variant of prostate cancer linked to a distinct and aggressive clinical phenotype. NEPC morphology predicts for frequent nonosseous visceral metastases, predominantly lytic bone disease, poor response to androgen ablation, and frequent but fleeting responses to chemotherapy. Although rare as a primary diagnosis, NEPC often emerges in the castration-resistant progression of the disease (1). The role of the biology that drives NEPC may be greater than appreciated; we have observed that clinical features characteristic of NEPC are present in approximately 25% of men with chemotherapynaive prostate cancer (A. Aparicio, C.J. Logothetis, and S.N. Maity, unpublished data). This number is in line with the frequency of NEPC elements detected at autopsy. As with Small cell variants in other cancers, the Small cell variant in prostate cancer has been linked by association to neuroendocrine features. Because NEPC is an androgen receptor (AR)-negative variant, it can be viewed as representative of mechanism(s) implicated in AR-independent progression. Understanding this subtype will lead to the elucidation of mechanism(s), to the complexity of the clinical setting.

Small cell carcinomas of the prostate and other organs grow rapidly and are highly metastatic. Investigators have shown that, aside from neuroendocrine secretory proteins (such as chromogranin A), small cell carcinomas typically express high levels of transcription factors characteristic of neural precursor cells (such as ASCL1) (2, 3). These clinical and basic observations suggest a link between neural development biology and this phenotype. In this issue of Cancer Discovery, Beltran et al. (4) provide additional evidence to support this notion. Using RNA sequencing and single-nucleotide polymorphism arrays, they found NEPC-specific overexpression and amplification of MYCN, a member of the MYC protooncogene family that encodes a 60- to 63-kDa transcription factor expressed at high levels in early embryogenesis and is implicated in the developmental control of neural stem cells. MYCN is amplified or overexpressed in cancers that originate from embryonic and/or neuroendocrine tissues (in which MYCN is normally expressed) such as neuroblastoma and small cell lung cancer (5). In addition, Beltran et al. (4) observed overexpression and amplification of Aurora kinase A (AURKA), an essential mammalian protein that localizes to centrosomes and regulates mitotic entry, mitotic spindle assembly, and chromosome separation. AURKA is amplified or overexpressed in a number of malignancies, including breast and colon cancer (6). Furthermore, in normal development, mitotic proteins have been implicated in cell fate determination. Of particular interest is the observation that overexpression of either AURKA or MYCN in prostate cancer cell lines induced neuroendocrine marker expression. These data further support the hypothesis that mitotic and neural development pathways are implicated in the progression to the androgen-independent NEPC.

Based on their studies, Beltran et al. (4) conclude that AURKA is a therapeutic target in NEPC and show that PHA-739358 (or danusertib, an inhibitor of AURKA, AURKB, ABL, RET, TRKA, and FGFR1) (7) inhibits the growth of NEPC models more effectively than AR-expressing castration-resistant prostate cancer (CRPC) cell lines. A similar effect of danusertib on the transgenic adenocarcinoma of the mouse prostate model has been described. However, despite these promising experimental data, only 2 of 58 (4%) of CRPC patients displayed a prostate-specific antigen (PSA) response to danusertib in a phase II clinical trial (8). The result of this initial clinical experiment illustrates the difficulty in moving from an experimental system, optimized to understand mechanism(s), to the complexity of the clinical setting. Several plausible explanations may account for the discordance: (i) the model system does not reflect human prostate cancer, (ii) the study patients were not appropriately selected, or (iii) AURKA is not a driver of human prostate cancer.

One possibility is that the mechanisms described in the experimental models used do not have a similar role in human prostate cancer. The limited value of established prostate cancer cell lines in predicting clinical outcomes is well known.
rate underestimated the effect of danusertib: an additional 15% of patients had disease stabilization lasting 6 months or longer. If correct, the overall “benefit rate” approximates the predicted rate of NEPC expression in unselected CRPC patients that we have observed (Fig. 1). However, given the short duration of response, the clinical experience also suggests that AURKA is not a principal driver, once again highlighting the discordance between conclusions drawn from a preclinical experience and the clinical results.

The data to date are insufficient to claim that AURKA is a validated therapy target, but clearly it is worthy of further study. The consequences of specific inhibition of its enzymatic activity need to be examined in a broader panel of models. Because AURKA is part of a broader signaling network, a better understanding of the effects on this network is required so that we can arrive at rational combinations. For instance, if the proposed function of AURKA in NEPC is thought to be mediated at least in part by its stabilization of MYCN (which has been shown to be independent of its kinase activity) (10), specific enzymatic inhibitors of AURKA could help elucidate the relative contributions of the mitotic versus the neural developmental program to the phenotype. This, in turn, will lead to a new label for this subset that can reflect its driving biology and catalyze the biologic classification of prostate cancer.

One likely reason for this limitation is that the number of tumors from which they are derived is small and, therefore, the diversity of the disease is not represented. A recent study reported that the activity of MLN8237 (a specific AURKA inhibitor) in 23 cell lines and 49 xenograft models of childhood malignancies showed no correlation to AURKA copy number or expression (9). Because the enzymatic activity of AURKA depends not only on the amount of protein present but also on the activity of several cofactors (such as TPX2, BORA, and Ajuba), and because its substrates are numerous (including several proteins involved in cancer, such as p53, BRCA1, and even AR), it is likely that the effects of AURKA (and thus the impact of its inhibition) are dependent, at least in part, on the activity of the cofactors and the role of its substrates in a given cell. To overcome some of the cell lines’ limitations, we and others have developed human NEPC xenografts, which not only preserve the three-dimensional tumor architecture and retain the biologic complexity of the tumor of origin, but also offer the opportunity to increase the number of models to recapitulate the heterogeneity of the cancers.

It is possible that the absence of patient selection based on biologic insight accounts for the clinical results. According to the results of Beltran et al. (4), only patients with cancers that express NEPC-associated factors will benefit from AURKA inhibition. An alternative explanation is that the PSA response

---

**Figure 1.** Top, NEPC biology is estimated to drive approximately 25% of the lethal prostate cancers indicated by the blue zone. Bottom, mitotic and neural development pathways have been implicated in the progression to the androgen-independent NEPC and offer targets, such as small-molecule inhibitor of AURKA, that might change the course of the disease by inhibiting both the mitotic and neural program. Because NEPC is often found mixed with AR-positive adenocarcinoma, an understanding of adaptive AR signaling in this context is also needed.
In conclusion, the findings by Beltran et al. (4) add to the clinical and preclinical data supporting the view that NEPC is a unique and important subset of prostate cancer and that its underlying biology is implicated in the lethal progression of many prostate cancers. The ambiguities of the reported clinical experience emphasize the need to urgently apply biologic insight to the clinical experimentation. The need to develop and characterize model systems that reflect NEPC is also apparent. This line of research will lead to the reclassification of prostate cancer that will frame therapy. However, we have not yet identified the "driver events" that must be prioritized for study. A better understanding of the underlying biology of NEPC is required to identify therapy targets efficiently. Furthermore, NEPC is frequently found in a mixed phenotype consisting of both AR-negative NEPC and AR-positive adenocarcinoma of prostate (Fig. 1). An understanding of the role of adaptive AR signaling present in association with NEPC is also needed to better define the underlying biology of NEPC, which could then efficiently identify therapy targets.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received October 6, 2011; accepted October 7, 2011; published online November 17, 2011.

REFERENCES

Understanding the Lethal Variant of Prostate Cancer: Power of Examining Extremes

Ana Aparicio, Christopher J. Logothetis and Sankar N. Maity

Cancer Discovery 2011;1:466-468.