Treating Nasopharyngeal Cancer: Raising the "Barr"

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Nasopharyngeal carcinoma (NPC) is distinguished from other head and neck malignancies by virtue of its unique clinical and pathologic characteristics. NPC is an epithelial tumor with a distinct geographic distribution that is uncommon in Europe and North America but common in southern China (1). Multiple factors play a role in the pathogenesis of NPC, including genetic predisposition, environmental factors, and Epstein-Barr virus (EBV) infection (2–4).

Histopathologically, NPC is separated into the following three categories by the World Health Organization (WHO) (1,5): 1) keratinizing squamous-cell carcinoma similar to other head and neck tumors (type I); 2) nonkeratinizing epidermoid carcinoma (type II); and 3) undifferentiated carcinomas referred to as lymphoepithelioma or Schminke tumors (type III) (1). In most parts of the world, NPC occurs sporadically due to both genetic and environmental factors. However, endemic EBV-associated NPC is usually categorized as type II or III.

In dividing, cultured human B lymphocytes infected with EBV, the EBV genome expresses 11 genes, six of which are essential for efficient transformation (4,5). This fact, coupled with the close association of EBV and NPC, has prompted the designation of EBV as a human DNA tumor virus. However, most viral transforming genes are not expressed in NPCs, suggesting that transformation results from a combination of viral and altered cellular proto-oncogenes and/or tumor suppressor genes (1). The viral genome is clonal in dysplastic cells and cells in carcinoma in situ, indicating that the tumor originated from a single infected cell and that EBV infection is an early event in the development of NPC (5). The presence of EBV in preinvasive and tumor cells of EBV-associated cancers appears to be a useful marker for this subset of patients. Thus, EBV may provide both a mechanism and marker for NPC.

Chan and colleagues (6) have previously shown that EBV-associated RNA was elevated in the plasma of patients with NPC, that these levels returned to zero in 10 of 10 patients by the end of radiation therapy (7,8), and that pretreatment EBV plasma levels correlated with tumor stage and with the overall survival of NPC patients (8,9,10). In this issue of the Journal (11), Chan et al. designed a prospective study to determine whether the plasma level of EBV-associated RNA after treatment was associated with disease recurrence. The results show that elevated EBV levels 6–8 weeks after therapy were strongly associated with both progression-free and overall survival. When these results are combined with previous work from this group, plasma EBV DNA levels can be viewed as a prognostic factor for outcome after radiation therapy. In addition, the results of Chan et al. raise several interesting questions related to therapeutic strategies.

The level of plasma tumor DNA is one of many promising tumor markers, but its clinical utility is diminished by the substantial heterogeneity in genetic abnormalities among malignancies. In contrast, viral genomes are more homogenous and, thus, viral DNA is well suited to be a sensitive marker for viral-associated tumor cells. Plasma EBV DNA could originate from several latently infected cell types; however, in nonkeratinizing NPC, the viral molecules are primarily derived from the tumor. Although the exact mechanism responsible for releasing viral DNA into the plasma is unclear, possible mechanisms include tumor cell apoptosis, small fragmented viral DNA release, and viral DNA release caused by lytic replication in the rapidly dividing NPC tumor cells (4,5). Regardless of the exact mechanism, it appears that levels of plasma EBV DNA before and after treatment are closely associated with the number of tumor cells or, clinically speaking, the tumor load. This idea has been well described by this group, establishing a relationship between plasma levels of EBV DNA and tumor stage (8–10). The fact that plasma levels of EBV DNA before and after therapy are associated with clinical end points of local control, distant disease-free survival, and overall survival makes it a useful prognostic marker. However, the use of plasma levels of EBV DNA for clinical management will require additional information, including whether levels of plasma EBV DNA decrease during therapy as the tumor burden decreases and whether such information can be used to effectively guide and appropriately alter therapy.

Serum markers can be classified as prognostic and/or predictive. If the marker merely informs patients and physicians of outcome (a prognostic marker), such information is useful for generating new hypotheses and for developing novel interventions but is of limited benefit to the patient. Of course the assay must be reliable, reproducible and, ideally, readily available at reasonable cost, so that it can be used to accurately monitor treatment. Plasma EBV DNA levels could be investigated in an effort to customize therapy to individual patients. Although the level of plasma EBV DNA has the statistical power to predict outcome (11), the more readily available clinical information was able to predict local recurrence and/or persistence and distant recurrence. For example, a Cox regression analysis showed that the tumor stage was associated with local recurrence and the lymph node stage was associated with distant recurrence (12). Additionally, NPC is often treated with a combination of radiation therapy and chemotherapy, a therapy that is associated with an improved outcome for patients with advanced stages of NPC in most (13,14) but not all (12,15) studies. Thus, the applicability of the results in Chan et al. (11) to combined modality therapy is unknown, as the authors recognize.

Although these results show that the level of plasma EBV DNA has potential as a molecular marker, do the results also show that EBV DNA has potential as a molecular target? A unique feature of nonkeratinizing NPC is the presence of large numbers of inflammatory cells, suggesting a substantial host immune response (3,4). Although the exact mechanism for this

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immune response is unknown, virally expressed antigens on the surface of NPC cells are likely targets for cytotoxic T lymphocytes and would explain the accumulation of lymphoid and other inflammatory cells in such tumors (4). These observations raise two questions. First, what mechanism is used by NPC cells to evade the host immune response and continue proliferating? Second, are NPC tumors amenable to treatment with immunotherapy? Furthermore, the observation that EBV may be directly involved in transformation (16–18) may define new therapeutic targets. Antiviral therapy might be used along with combined modality therapy (19).

The era of molecularly targeted cancer treatment requires both correlative and mechanistic studies to define novel treatment approaches. Ultimately, molecularly targeted therapy must be validated by evidence that the initial treatment and/or mid-course corrections can be effectively tailored to the individual patient. That the measure of plasma EBV DNA is associated with outcome makes it an intriguing potential molecular target for this patient population, with the possibility of raising the “Barr” for more effective and less toxic treatment.

REFERENCES