Head and Neck Cancer: Meeting Summary and Research Opportunities


Abstract

Head and neck squamous cell carcinoma (HNSCC) is the most common malignant neoplasm arising in the mucosa of the upper aerodigestive tract. Nearly two thirds of patients present with advanced (stage III and IV) disease. Fifty percent of HNSCC patients die of their disease, and 5% of HNSCC patients per year will develop additional secondary tumors. Currently used therapeutic modalities (surgery, radiation, and/or chemotherapy) have been associated with rather modest improvements in patient survival. The Head and Neck Cancer: Research and Therapeutic Opportunities Workshop (held in Washington, DC, May 24–26, 2004) was organized by the Division of Cancer Biology at the National Cancer Institute to identify research areas and directions that will advance understanding of HNSCC biology and accelerate clinical translation. The primary goal of the workshop was to identify the barriers that impede basic science discovery and the translation of these developments to the clinical setting. Over a 2.5-day period, experts in both HNSCC and other cancer-related fields met to identify and prioritize the key areas for future research. The overall consensus was that HNSCC is a relatively understudied malignancy and that investigations that focus on the biology of this tumor have the potential to impact significantly on the prevention and treatment of epithelial malignancies. The chief objective is to communicate these research goals to the cancer biology community and encourage more interest in HNSCC as a tumor model to test translational research hypotheses.

Workshop Symposia

Three overview talks set the stage of the introductory session by summarizing the current status of medical oncology, surgery, and radiation oncology approaches for head and neck squamous cell carcinoma (HNSCC) prevention and management. W. K. Hong (University of Texas M. D. Anderson Cancer Center, Houston, TX) summarized his 30-year experience by highlighting the multistep oral carcinogenesis progression model and discussed the major clinical studies that have emerged from his translational research program. Given the cumulative negative results of the single-agent retinoid prevention trials, an emphasis was placed on biochemoprevention using multiple agents that target several pathways and on the complete characterization of individual lesions so that they can optimally be treated.

G. Wolf (University of Michigan, Ann Arbor, MI) acknowledged that there had been significant advancements in surgery for HNSCC over the past few decades; however, these have not translated into significant improvements in survival. The failure of these discoveries to result in improved patient survival is due to the heterogeneous nature of HNSCC, the significant comorbidities present in the patient population, a high rate of synchronous and metachronous primary tumors, and the significant immune impairment of HNSCC patients.

Surgical innovations have included microvascular reconstructions, endoscopic laser resection, and conservation laryngeal surgery. With combined modality treatment using both chemotherapy and radiation playing an increasingly important role as an alternative to primary surgery, improved surveillance is required with an emphasis on quality of life and functional outcomes as primary end points.

R. Weichselbaum (University of Chicago, Chicago, IL) discussed radiation therapy advancements in defining optimal fractionation regimens and focused dose delivery with the goal of sparing normal tissue. He focused on transcriptional targeting of a radioinducible/chemoinducible gene therapy strategy and enhancing oncolytic viral gene therapy. By combining viral gene therapy with radiation therapy, preliminary results suggest that cellular stress kinases induced by radiation “power-up” the virus by enhancing viral replication (2). In addition, strategies using MnSOD-plasmid gene therapy for the protection of normal tissues are another approach.

The molecular alterations that characterize HNSCC were addressed in the second session. D. Sidransky (Johns Hopkins University, Baltimore, MD) summarized the early detection and risk models of HNSCC with an emphasis on preneoplastic lesions as the ideal targets for therapeutic/preventive intervention. Studies analyzing the genetic and epigenetic changes in premalignant lesions as well as invasive cancers have allowed the identification of those alterations that can predict progression to more advanced disease. He noted that 46% of HNSCC tumors demonstrate mutations in mitochondrial DNA and that the clinical application of this finding will be facilitated by the imminent availability of a mitochondrial DNA chip for hybridization.

C. Arteaga (Vanderbilt University, Nashville, TN) emphasized the need for new models to verify targets and therapeutic efficacy of molecular targeting agents. Interval assessment of cellular activity of the target in the tumor tissue in breast cancer has provided an opportunity to predict clinical utility and subsequently prioritize the use of targeting agents. He strongly encouraged the HNSCC community to consider a new paradigm: delivery of an experimental therapy for a short term (e.g., 2 weeks) followed by surgery and analysis of the tissue to assess response. The application of signal transduction paradigms to cancer progression models was presented by M. Weber (University of Virginia, Charlottesville, VA). Studies have shown that cancer cells expressing kinase-dead epidermal growth factor receptor (EGFR) still signal through mitogen-activated protein kinase, implicating EGFR as a platform for integration of intracellular signaling pathways. The widespread expression of EGFR in HNSCC and the wealth of information from clinical trials to date using EGFR targeting agents, this area is ripe for investigation. T. Carey (University of Michigan, Ann Arbor, MI) discussed the VA larynx trial as a paradigm for prospective specimen collection to determine markers of response. Expression of Bcl-xL, an antiapoptotic protein, was associated with failure of laryngeal preservation in this trial, providing the rationale for Bcl-xL as a therapeutic target in HNSCC. Gossypol, a naturally occurring polyphenolic yellow pigment present in cottonseed products, was discovered via small molecule screens to bind to Bcl-xL and the levorotatory isomer and is now in development for...
clinical application as an inducer of apoptosis in cisplatin-resistant HNSCC.

Invasion of local and regional tissues is responsible for tremendous morbidity and mortality in HNSCC. R. Kramer (University of California San Francisco, San Francisco, CA) presented a model of stepwise invasion in which epithelial cells dissociate from neighboring cells, elaborate proteases, and motility factors and initiate downstream signaling through integrin receptors to activate the cytoskeleton and trigger cell locomotion. Cumulative evidence suggests that laminin 5 is a key stimulus for HNSCC migration and may represent a robust therapeutic target (9). G. Clayman (University of Texas M. D. Anderson Cancer Center, Houston, TX) summarized the development of adenosine p53 gene therapy for HNSCC treatment and prevention. Prior studies have demonstrated therapeutic efficacy in preclinical models and a good safety profile with intratumor injection in early-phase clinical studies (10). Two phase III clinical trials are under way in addition to topical and intraluminal approaches for oral premalignant lesions. Human papilloma virus (HPV) infection is emerging as a potential risk factor and vaccine target for HNSCC. N. Kiviat (University of Washington, Seattle, WA) reported that 20% to 25% of all HNSCC (and 40% of tonsillar HNSCC) are associated with HPV (11). She emphasized the need for more rigorous methods to ascertain HPV infection because the simple presence of HPV DNA does not implicate active or prior infection. The proportion of HPV-positive precursor lesions in HNSCC needs to be defined in light of the early encouraging results of HPV vaccines in cervical cancer prevention. T. C. Wu (Johns Hopkins University, Baltimore, MD) presented an analysis of cellular immune responses against HPV in HNSCC (12). These data provide the rationale for a planned phase I clinical trial to study the safety and immunogenicity of repeated vaccination in HPV-positive HNSCC patients.

The third session focused on applications of advanced technology and bioinformatics. W. Yarbrough (Vanderbilt University, Nashville, TN) presented the promise and pitfalls of proteomics for application in HNSCC. Proteomics can be used to identify protein markers of early disease in surrogate specimens (such as serum and saliva) as well as new biomarkers from primary tumors to predict clinical behavior. Limitations include a limited mass range and difficulty in identification of proteins for some commonly used proteomic platforms, as well as the inability to correlate relative levels of proteins between multiple samples. E. Petricoin (United States Food and Drug Administration, Rockville, MD) presented the concept of molecular profiling to individualize patient care. He presented recent discoveries suggesting that biomarkers of importance may be bound to more highly abundant serum proteins (e.g., albumin). New strategies are in place to enrich serum samples for these key proteins. In addition, phosphoproteomics is being developed as a way to interrogate select signaling pathways in tissues. To date, his group has validated over 300 phospho-specific antibodies for use on a protein chip platform.5 HNSCC specimens from patients treated with agents that target signal transduction pathways can be assessed using this approach.

Gene discovery in HNSCC was discussed by S. Gutkind (National Institute of Dental and Craniofacial Research, Bethesda, MD), who highlighted the Head and Neck-Cancer Genome Anatomy Project, which began in 1998 as a collaborative effort to create a complete database of genes (both novel and known) expressed in HNSCC cell lines and tumors. To date, libraries have been created from >600 tumors, and >150,000 sequences have been entered into the database.6 Use of this database can aid in elucidating the function of novel and known genes in HNSCC. S. Ramaswamy (Harvard University, Cambridge, MA) presented a new model for studying metastasis. In contrast to prior stochastic views, this model is based on the assessment of gene expression profiles in primary tumors and metastases, which suggests that the propensity to metastasis can be determined by the gene profile of the primary tumor (13). Given the relative accessibility of primary HNSCC tumor and paired metastases from cervical lymph nodes, additional gene expression studies using these tissues should be informative. Bioinformatics is essential for collecting and analyzing clinical and laboratory data, especially in this era of Health Information Portability Accountability Act regulations. There is a tremendous need for standardization of tissue collection and processing techniques including developing standard operating procedures (SOPs) for serum to facilitate proteomic studies. M. Becich (University of Pittsburgh, Pittsburgh, PA) emphasized the role of the National Cancer Institute (NCI) in developing SOPs and the importance of the tissue bank and pathology tools workspace on the NCI cancer bioinformatics grid (CaBIG).

The obstacles present in imaging and targeting the tumor tissue were the topic of the fourth session. D. Hallahan (Vanderbilt University, Nashville, TN) presented the use of radiation-inducible neoantigens as a mechanism to deliver drugs to HNSCC tumors. Using phage-display methodology, his group has identified peptides that selectively bind to irradiated tumors (14). These peptides can be conjugated to drug containing liposomes (e.g., cisplatin), thereby providing a new model to target delivery of cytotoxins or radiation to the tumor while sparing nontumor tissue and reducing systemic toxicity. Functional and molecular imaging for cancer applications was discussed by K. Krohn (University of Washington, Seattle, WA), who emphasized that biological processes at the cellular and molecular level can be characterized using remote imaging detectors. Technology requires the availability of probe molecules that can be detected by imaging. Whereas 2-[18F]fluoro-2-deoxy-D-glucose (FDG) has been studied as an imaging tool in HNSCC, he emphasized the need to go beyond FDG to incorporate new probes that can theoretically image proliferating cells [e.g., the thymidine analog 3-deoxy-3-[18F]fluorothymidine (FLT)] or apoptotic cells (e.g., annexin 5; ref. 16). C. Chao (University of Texas M. D. Anderson Cancer Center, Houston, TX) discussed targeting hypoxic tumor cells with radiotherapy. The development of intensity-modulated radiation therapy (IMRT) allows for dose painting with high precision to spare normal tissue and target tumor cells. However, even with IMRT, there is a 25% to 40% local failure rate within the high-dose region of treatment. He discussed potential strategies to address this problem including use of hypoxia-specific chemotherapeutic agents (e.g., tirapazamine) and blockade of hypoxia inducible factor-1α in conjunction with cytotoxic therapy (17). The tumor vasculature has emerged as a critical component for the delivery of therapeutic reagents. The importance of key integrins in the process of tumor angiogenesis was discussed by J. Varner (University of California San Diego, San Diego, CA). These integrins (αvβ3, αvβ6, and αvβ1) exert their angiogenic effects by regulating key cells including endothelial cells, pericytes, circulating progenitor cells, monocytes, and stromal cells (18). She emphasized the exciting prospects for the clinical use of integrin antagonists (generally antibodies) to block angiogenesis and tumor development/progression.

Finally, the status of clinical research was the focus of the fifth session. A. Forastiere (Johns Hopkins University, Baltimore, MD) presented the progress of the HNSCC studies conducted under the auspices of the Eastern Cooperative Oncology Group. She summarized the status of ongoing trials and noted the importance of planning for correlative biomarker studies at the time of trial design so that tissues can be optimally collected and stored for future analyses. The

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status of the HNSCC trials in the Radiation Therapy Oncology Group was presented by K. Ang (University of Texas M.D. Anderson Cancer Center, Houston, TX), who emphasized the benefit of prospective tissue collection in conjunction with clinical and pathological information on patients treated on these trials. Such collection efforts allowed the Radiation Therapy Oncology Group to demonstrate that EGFR expression is a negative prognostic indicator and a robust predictor for radiation response for HNSCC. J. Myers (University of Texas M.D. Anderson Cancer Center, Houston, TX) presented the more recently established American College of Surgeons Oncology Group, which focuses on the development of clinical trials to address surgical questions. The major American College of Surgeons Oncology Group study to date is an ongoing trial of lymphatic mapping and sentinel node lymphadenectomy for patients with T2Nx or T3Nx oral squamous cell carcinoma. He emphasized the need to collect specimens for correlative studies to facilitate the design of the subsequent studies. An alternative chemoradiotherapeutic approach for advanced HNSCC was presented by M. Posner (Dana Farber Cancer Institute, Boston, MA), who suggested sequential therapy as a model. This treatment regimen includes induction chemotherapy followed by combined chemoradiotherapy followed by surgery if there is residual disease. Recent evidence supports improved efficacy for a three-drug (versus two-drug) combination (19). He noted that the toxicity of such an approach requires intensive support and rehabilitation of the patient.

Conclusions of the Workshop

The conclusions of the workshop were framed in the context of issues, barriers, and solutions to the rather insignificant progress in head and neck cancer translational research. A summary of the most pertinent points raised during the discussion periods is provided in Table 1.

The overall consensus was that HNSCC represents an important tumor model that is eminently ripe for intensive investigation. Compared with other epithelial malignancies (such as breast, lung, and prostate cancer), there have been relatively few important advances, and none of these have translated into improved patient survival. It was generally agreed that the major accomplishments in the field of HNSCC during the past decade include the following: 1) improved delivery of radiation therapy including IMRT and altered fractionation; 2) multidisciplinary management as demonstrated by the increasing use of combined chemoradiotherapy as a primary treatment approach; 3) recognition of the importance of biomarkers as a means to identify therapeutic targets and response to treatment; 4) appreci-
progression with the identification of potential tumor antigens and vaccine strategies as well as the potential importance of HPV in various stages of tumorigenesis; and 5) standard use of FDG/pozitron emission tomography imaging with an appreciation of the importance of developing more robust noninvasive strategies to image tumor function. It was agreed that more intensive investigation of HNSCC biology could be rapidly translated into clinical benefit given the relatively unique accessibility of these lesions for biopsies and intra-tumoral administration.

Recommendations

Information about the basic biology of HNSCC must be enhanced. Tangible advances are likely to be accelerated by a more focused and cohesive effort encompassing multiple approaches. Interdisciplinary collaborations among different institutions and between basic scientists and clinicians at individual institutions should be encouraged. It is recommended that these collaborations focus on addressing the following needs:

1. Development of methods to reproducibly measure the expression profile of biomarkers in HNSCC and normal tissues as well as in surrogate material such as blood and saliva. This includes a comprehensive approach to identify patterns as well as a detailed analysis of the cell type expressing the gene/protein of interest.

2. Characterization of the molecular signatures of precursor lesions, established tumors, and metastatic disease to aid in designing therapeutic interventions.

3. Definition and integration of genomic, transcriptional, and proteomic profiling information of HNSCC lesions at various stages of development and progression to provide a comprehensive view of the molecular pathways and networks involved in HNSCC carcinogenesis.

4. Validation of relative prognostic predictive values of various biomarkers using specimens of well-characterized patients enrolled into large clinical trials who received well-defined therapy and had follow-up data.

5. Definition of interactions between tumor cells and host stromal cells and the role of inflammatory cells in the development and progression of HNSCC.

6. Encouragement of molecular and translational studies on the unique accessibility of these lesions for biopsies and intra-tumoral administration.

7. Development of new in vivo imaging approaches for tumor cell activity and tumor characteristics that predict a poor response to treatment (e.g., hypoxia and angiogenesis).

8. Creation of guidelines and SOPs for serum, saliva, blood, and tissue collection, so that results obtained at different institutions and placed into workspaces such as CaBIG can be directly compared.

9. Initiation of clinical trials using molecular targeting agents that emphasize tissue collection and analysis to validate new molecular targets and predict the efficacy of a given therapy.

These goals can be addressed through collaborative efforts with existing structures such as NCI-supported multidisciplinary programs and through continued and enhanced partnerships with pharmaceutical and biotechnology entities.

Summary

The explosion of information that has resulted in improved prevention, diagnosis, and treatment of cancer has not traditionally been applied to HNSCC. Specific issues and barriers to the clinical application of tumor biology have been explored, and potential solutions to the hurdles are proposed. There are clear opportunities to change the morbidity and mortality of this cancer. The complex biology of HNSCC and the substantial barriers to clinical translation require that future efforts enlist the participation of investigators with diverse yet complementary perspectives and expertise.

Appendix


References


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