20. PATHOBIOLOGY OF ANTINEOPLASTIC THERAPY IN UNDIFFERENTIATED THYROID CANCER

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INTRODUCTION

Undifferentiated thyroid carcinoma is a descriptive term often applied to the rare subset of thyroid cancers classified as anaplastic; however, there is a broad spectrum of tumors which show varying degrees of differentiated function and clinical aggressiveness. Among thyroid carcinomas derived from the thyroid follicular cell, differentiated functions include: expression and membrane localization of the sodium/iodide symporter (NIS; enabling intracellular concentration of iodide), expression of thyrotropin receptors (permitting both stimulation of the cell by rising thyrotropin levels and suppression of the cell by decreasing thyrotropin levels), organification of internalized iodide (enhancing iodide retention), and production of thyroglobulin (clinically useful as a specific tumor marker in thyroidectomized patients). Additional clinical features common to differentiated thyroid cancers include: a slow growth rate, limited metastatic potential (usually only local lymphatic spread in the majority of cases), and the ability of the host to tolerate a significant tumor burden for extraordinary lengths of time. As each of these functional features are lost and clinical aggressiveness is enhanced, therapeutic options decrease while, at the same time, the clinical situation becomes more desperate (1). This is epitomized by anaplastic carcinomas with median survival measured in months despite the most assertive therapeutic efforts (2, 3).

Although fewer than 400 cases of anaplastic thyroid carcinoma are expected in North America in a year, many-fold more patients will manifest poorly differentiated metastatic thyroid cancers with sufficient loss of differentiated function to make classical

treatments (surgery, radioiodine, and thyroid hormone suppression of thyrotropin) ineffectual. Also, disseminated medullary thyroid carcinomas and rare histologies, such as mucoepidermoid carcinomas and angiosarcomas, have no known effective systemic therapies and are usually lethal. Patients with these tumors need active antineoplastic agents that can evoke better outcomes without intolerable morbidity. To that end, it is necessary to critically review the clinical experience with current antineoplastic agents, address known mechanisms for resistance to these agents, and consider alternative therapeutic approaches to systemic therapy.

SYSTEMIC CHEMOTHERAPEUTICS, BY CLASS OF AGENT

Antimetabolites

Antimetabolites encompass compounds that have sufficient structural similarity to naturally occurring intermediates critical to the synthesis of key molecules, such as RNA and DNA, as to interfere with normal metabolism and take advantage of metabolic differences between normal and malignant cells for therapeutic specificity. Although most antimetabolite chemotherapeutic agents are nucleoside analogs, interfering with nucleic acid synthesis, some may also interfere with other critical cellular processes, such as glycosylation, organelle activities, or phospholipid synthesis. These drugs have proven most useful in hematological malignancies. Pyrimidine analogs, hindering the synthesis of cytidine, thymidine, or uridine, include the fluoropyrimidines (notably 5-fluorouracil) and cytidine analogs (cytarabine and gemcitabine). There is some preclinical single agent activity with these compounds in anaplastic thyroid carcinomas, but somewhat greater promise for their contribution to combination chemotherapy. Purine analogs, interfering with adenosine and guanosine synthesis, include the thiopurines (6-mercaptopurine and 6-thioguanine) and the adenosine analogs (fludarabine, pentostatin, and cladribine); however, these agents have not proven useful in solid tumors. Methotrexate is the most clinically useful antifolate compound, although agents such as raltitrexed (ZD1694) and edatrexate have been showing promise. These agents inhibit dihydrofolate reductase, depleting cells of reduced folates and resulting in decreased purines, thymidylate, amino acids (methionine and serine), and effects on gene methylation (4, 5).

Among the pyrimidine analogs, the only agent with any clinical experience in thyroid carcinoma is 5-fluorouracil. In all cases, it was used as part of a drug combination, with dacarbazine in advanced medullary thyroid carcinoma for modest partial responses in three of five patients (6), in combination with many drugs for a rare partial response in anaplastic carcinoma patients (7), and with three other agents in 49 patients with poorly-differentiated non-anaplastic thyroid cancers resulting in negligible clinical activity (8). This poor effect was presaged in preclinical studies using poorly differentiated or anaplastic thyroid cancer cell lines (9), although concomitant Bcl-2 antisense nucleotides (10), but not radioiodine (11), seem to enhance antineoplastic effects. Initial anaplastic thyroid cancer monolayer studies with gemcitabine were promising (12, 13) but were not followed by confirmatory reports using xenograft model systems, suggesting this agent to be less impressive than originally suggested. These deficiencies