Response to Chemotherapy Necessary in G2 and G3 Neuroendocrine Carcinomas

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Introduction/Background

Although approaches to treatment of G1 and G3 neuroendocrine carcinomas are generally agreed upon, treatment of G2 disease and residual disease from treated G3 is problematic. As the most threatening component is the higher proliferating component, therapy should be initially directed to that constituent of the disease.

Heterogeneity of Tumor Cell Populations: The tumor cell population can be conceived of in several different ways. In the simplest form the tumor cell population could be homogeneous and have variable rates of proliferation yielding a discrete proliferation fraction that may measured in individual tumors over a wide range. Currently the KI-67 index and number of mitoses per 10 high power fields are considered to represent this proliferation rate. Alternatively the tumor mass may of at least two populations of cells with different proliferation rates. The evidence indicates that many cytotoxic therapies result in little effect in low proliferative cells. On the other hand there is ample evidence that cytotoxic therapy has its major effect on proliferating cells. Current practice accepts that neuroendocrine carcinomas with high Ki67 (>20%) are often sensitive to chemotherapy and should be offered that modality. It could be contended that the model may be in fact be irrelevant if chemotherapy affects mainly cells that are actively proliferating.

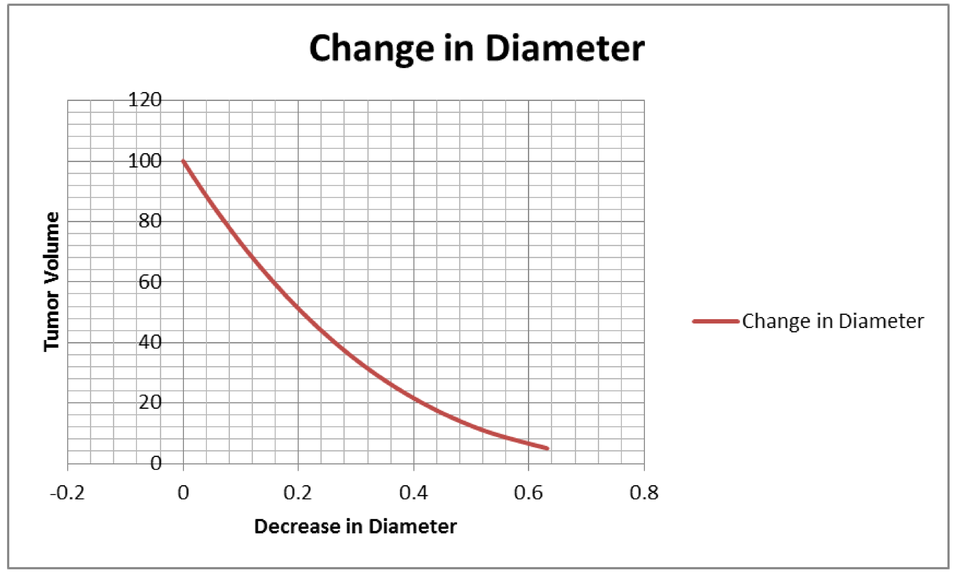
Heterogeneity in G2 Disease and Sequential Therapy: It is suggested that the treatment of tumors with intermediate Ki67 indices in the G2 range, especially those with Ki67 > 10%, could be approached as sequential treatments for respective cell subpopulations. The most proliferative cells could be treated with chemotherapy to maximum response with the goal of greatest achievable eradication of that cell compartment. Residual cells could then sequentially be treated with the modalities relevant to that G1 tumor such as PRRT. In the case of radioisotopes, therapy can not only benefit the slowly proliferating cells but may also be cytotoxic to any remaining higher proliferative cells as a "bystander effect". In this scheme of multi step therapy, a challenge would be the determination of extent of effect on the rapidly proliferating component. What degree of response therefore should be accepted utilizing chemotherapy for the rapidly proliferating component and how could this be quantitatively determined ?

Aims

The aim was to determine the expected response of tumor to therapy using RECIST 1.1 criteria of decrease in one diameter when the proliferative tumor fraction was successfully treated, leaving the low proliferative cell compartment intact.

Materials and Methods

The mathematical determination of tumor volume related to tumor diameter was considered assuming that the perfectly spherical tumor was the least sensitive case. As volume can be calculated with $\mathbf{V=4/3\pi r^3}$, the diameter then can be calculated with respect volume by $\boldsymbol{D = \sqrt[3]{1.91V}}$. Varying the total fraction of tumor volume that was of high proliferation and assuming that all of that tumor compartment was eradicated by chemotherapy, the expected change in tumor diameter was calculated. The change in volume required for 10%, 20% and 30% decrease in diameter. The latter is the defined value required for declaration of partial response by the RECIST 1.1 criteria.



Decrease in Diameter %	10	20	30
Decrease in Volume %	26	50	66

Results

The capability of tumor mensuration to resolve significant changes in tumor diameter considering potential sources of error including registration error, fuzzy tumor edges, inter-observer and intra-observer error is at minimum 10%. Experiments in such error measurement error yielded errors of 20%. In RECIST 1.0 a minimum of 20% change was required to declare progression in order to minimize these sources of measurement error. This represents a 50% change in tumor volume. Based on the RECIST 1.1 criterion of a decrease in diameter of greater than 30% required classification as response, the standard geometric calculation predicts that the threshold for partial response could not be satisfied unless the initial proliferative fraction is 66% or greater.

Implications

The treatment of G2 neuroendocrine neoplasms is problematic . Though the G2 grade of neuroendocrine neoplasms was reviewed at an international meeting in 2012, analysis of existing data led to the conclusion that this grade of disease exhibited widely different behavior depending on proliferative indices. Disease with a Ki67 of 5% was quite different from that with a Ki67 of 18%. However there was no data nor any proffered discussion on how to treat this group. There appears to be a need to further subdivide this group into behaviorally coherent subgroups. Nonetheless these patients exist in the present but without a clear conception on the best approach to treatment.

It is contended that an approach utilizing the notion of heterogeneous populations of patients with the most simple partition consisting of proliferating cell compartment and a constitutively low proliferative compartment could have therapeutic import. This intermediate grade of tumors may have an increasingly enlarging compartment of proliferating cells. Clearly such a compartment of cells could overtake the low proliferative cell constituents and become increasingly dominant. This would represent the most threatening part of the tumor. As such it would deserve priority in treatment. Chemotherapy could be employed to eradicate this component insofar as these cells are sensitive in terms of cytotoxicity. However, evaluation of change in subpopulations is difficult. This analysis suggests that the conversion of this tumor from progressing to stable disease is an adequate indication of therapeutic effect in higher proliferating G2 disease as well as in lower proliferating G3 disease where the initial proliferating compartment was less than 50%. To satisfy RECIST 1.1 criteria an initial proliferating compartment of 66% would be required.

Implications in Therapy Development

The concept of sequential treatment of high proliferative followed by low proliferative disease appears attractive and should bear testing. Our best current data indicates that the differential sensitivity of these subpopulations have little overlap and thus require separate considerations.

Considering a proliferative-therapeutic based paradigm, a further subdivision of G status might include a partition such as:

G2A: 3-10%, G2B: 11-19%, G3A:: 20-65%, G3B 66-100%.

In such a scheme the G2B and G3A subgroups would represent the grades of disease for which staged therapies may prove to be of advantage over "monotherapy". These issues and strategies deserve further consideration, discussion and ultimately testing.

Conclusions

Patients with G2 and low G3 disease should have at least stable disease to consider transitioning to treat residual disease as G1 disease. It is hoped that approaches such as these may serve as the basis for trials and further data greatly needed in these situations.

Abstract

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Introduction/Background

Although approaches to treatment of G1 and G3 neuroendocrine carcinomas are generally agreed upon, treatment of G2 and G3 disease is problematic. Therapy should initially be directed to the highest proliferating component with chemotherapy. Residual disease could then sequentially be treated with the modalities relevant to that G1 tumor such as PRRT. What degree of response therefore should be accepted utilizing chemotherapy for the rapidly proliferating component?

Aims

To determine the expected response of tumor to therapy using RECIST criteria when the proliferative tumor fraction was successfully treated

Materials and methods

A simple mathematical model of tumor volume related to tumor diameter was considered assuming that the perfectly spherical tumor was the least sensitive case.. Varying the total fraction of tumor volume that was of high proliferation and assuming that all of that tumor compartment was eradicated by chemotherapy, the expected change in tumor diameter was calculated as defined and utilized by the RECIST criteria

Results

Based on the RECIST criterion of a decrease in diameter of greater than 30% required classification as response, the model predicts that the threshold for partial response could not be satisfied unless the initial proliferative fraction is 66% or greater.

Conclusion

Patients with G2 and low G3 disease should have at least stable disease to consider transitioning to treat residual disease as G1 disease It is hoped that approaches such as these may serve as the basis for trials and further data greatly needed in these situations.