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Rationale for Neoadjuvant Chemotherapy in the Management of Malignant Disease

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1. Introduction

In the earliest days of the modern anti-neoplastic chemotherapeutic era the focus of such therapy in solid tumor oncology was on the management of recurrent or metastatic cancer. Over the past several decades the outcomes of such treatment, both an improvement in survival and a reduction in the toxicities associated with this strategy have made some form of drug therapy routine care in most advanced human malignancies.

Subsequent efforts demonstrated the effectiveness associated with the administration of anti-neoplastic agents in the *adjuvant setting* prior to the documentation of the existence of metastatic cancer. Such therapy was justified where there was a recognized known unacceptable risk that the disease may still be present within the individual patient despite appropriate local therapy (e.g., surgery, radiation therapy, or both).

2. Rationale for neoadjuvant chemotherapy in the management of malignant disease

The concept of *neoadjuvant chemotherapy* is a newer addition to the anti-neoplastic drug strategies employed in routine cancer management. The several important and unique goals associated with this approach in contrast to chemotherapy delivered as adjuvant therapy or as treatment of metastatic disease are outlined in Table 1.

It is reasonable to suggest the initial use of the therapeutic concept of neoadjuvant therapy developed in settings where individual oncologists believed local disease control would simply not be able to be achieved due to the extent of local tumor (e.g., large locally-advanced

breast, bladder or esophageal cancer), where the signs/symptoms of the cancer increased the risks associated with attempting to accomplish this goal (e.g., rapidly accumulating ascites in a patient with extensive intra-abdominal carcinomatosis from ovarian cancer), or when existing co-morbidity precluded consideration of such surgery (e.g., recent history of myocardial ischemia).

However, in recent years investigators have begun to speculate that rather than simply being a reluctantly delivered less effective alternative, the successful use of an initial neoadjuvant approach (chemotherapy alone or combined with external beam radiation) may actually permit the subsequent undertaking of definitive local/regional treatment to a substantially larger percentage of patients who present with a particular clinical scenario [1-7].

Thus, the advanced ovarian cancer patient with extensive intra-abdominal cancer who would have required a very extensive operation of quite uncertain value performed at a time of nutritional/protein depletion (secondary to massive fluid present within the peritoneal cavity in addition to poor appetite) may be able to successfully undergo surgery to remove all visible cancer following the administration of chemotherapy that substantially reduces tumor volume. In fact, a published landmark phase 3 randomized trial has now confirmed that the administration of neoadjuvant chemotherapy (carboplatin plus paclitaxel) in this exact clinical setting not only results in an identical overall survival outcome, compared to primary surgery in women with advanced ovarian cancer, but actually accomplishes this goal with less morbidity and surgery-associated mortality [4].

And in the setting of locally advanced breast cancer the administration of neoadjuvant chemotherapy designed to reduce the extent of tumor involvement may permit disease control in this region to be achieved without the requirement for a cosmetically unacceptable outcome (due to the extent of the otherwise necessary surgery) [6,7].

A particularly attractive feature of the concept of neoadjuvant chemotherapy is the ability to define the inherent chemosensitivity of an individual cancer *in vivo* within a particular patient. In certain clinical settings where the biological activity of available chemotherapy is unfortunately anticipated to be quite modest (at best), knowledge that the specific cancer has decreased in size prior to surgical resection can be one critically relevant component in the decision to continue adjuvant therapy with the same drug(s) in that individual.

Similarly, the failure of a neoadjuvant chemotherapy regimen to produce the anticipated biological and clinical outcome in a particular patient (e.g., advanced ovarian cancer with an objective response rate of 70-80%) should result in very serious questions being raised about the wisdom of continuing with the original plan to subject the patient to an attempt at maximal surgical cytoreduction. In fact, if the patient has failed to respond to the best chemotherapy available when delivered in the neoadjuvant setting, it is most difficult to see the benefits of surgery considering the very small changes a second line chemotherapy approach will have a favorable impact on the course of the illness. It should be noted that in some circumstances surgical intervention for the specific purpose of providing palliation of distressing cancer-related symptoms may still be considered appropriate in carefully selected patients even if definitive surgical resection is realistically no longer a viable therapeutic option.

With increasing evidence supporting a role of molecular testing in the selection of an optimal management strategy one could envision a novel role for the neoadjuvant therapy strategy. Following the performance of such testing, the selection of a novel treatment and the observation of an outcome (e.g., tumor regression, progression), the *re-biopsy and re-analysis of changes in the molecular profile of the residual cancer might help inform decisions regarding future therapy*. It is reasonable to anticipate that there will be considerable clinical cancer research undertaken in the future that employs this basic paradigm. Finally, it is not unreasonable to anticipate that this approach will someday become a component of standard-of-care medical management in some malignancies.

1. Reduce the risk of serious treatment-related morbidity or treatment-related mortality associated with attempting to achieve definitive local disease control
2. Enhance the chances definitive local disease control will be associated with an optimal quality-of-life outcome
3. Increase the proportion of patients in a particular clinical setting who will be candidates to undergo a realistic attempt to achieve definitive local disease control
4. Demonstrate the relative chemo-responsiveness of a particular cancer or, conversely, chemo-resistance. (Note: Such data can be helpful in the decision as to whether an aggressive and successful attempt to achieve local disease control can realistically also be associated with long-term survival).
5. Help determine the potential clinical utility associated with the continued delivery of *adjuvant chemotherapy* following the surgical removal/primary radiation treatment of all viable local tumor (in the absence of knowledge of the existence of any metastatic disease).
6. Avoid a negative impact on outcome in settings where the performance of definitive surgery/radiation unfortunately must be delayed (for example, due to limited personnel, operating room time/space, or equipment)
7. Obtain tissue prior to and following chemotherapy to determine changes in the molecular profile of residual cancer with the goal that such information may help predict which therapies might be most beneficial to administer.

Table 1. Rationale for neoadjuvant chemotherapy of malignant disease

3. Conclusion

As outlined in this chapter there is a strong rationale for the delivery of systemic therapy prior to definitive local/regional treatment of a malignancy. It is relevant to note that not all of the justifications for this approach highlighted in Table 1 will be operative in a particular clinical setting. Further, it is important to acknowledge the actual benefits associated with this therapeutic approach in specific situations will likely ultimately need to be examined in well-designed evidence-based clinical trials.

However, the genuine opportunity to both increase the patient populations able to undergo definitive local cancer control while at the same time optimizing quality-of-life outcomes that are inherent in the general concept of the neoadjuvant approach should serve as a strong

stimulus to encourage clinical investigators to actively address the use of this strategy as an important component of routine cancer management.

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