What’s in a Name—Neoadjuvant

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The use of chemotherapy initially in patients with localized solid tumors with the intent of (a) increasing the potential for local control by surgery and radiotherapy and (b) delivering the earliest possible treatment to micrometastatic disease (neoadjuvant chemotherapy) is an opportunity whose time has come (1). It is not new, in that pioneering studies, particularly in pediatric solid tumors, were conducted over 20 years ago (2). However, for most cancers, particularly the common epithelial tumors, the effectiveness of chemotherapy was too limited in the past to have promise in the neoadjuvant setting. In the past 10 and particularly the past 5 years, that situation has changed to the point where for many primary tumors, neoadjuvant chemotherapy has major potential and represents a therapeutic research challenge. Because of this trend and for the reasons presented below, I proposed in 1981 the use of neoadjuvant chemotherapy as a new term for this therapeutic approach (1). While it has achieved a major measure of acceptance (e.g., the Second International Congress of Neoadjuvant Chemotherapy was held in February 1988), the term remains controversial, and in fact, many competing or related terms are used. These terms include “upfront” chemotherapy, anterior chemotherapy, primary chemotherapy, protochemotherapy, protoadjuvant chemotherapy, induction chemotherapy, preoperative chemotherapy, and preradiotherapy chemotherapy. This plethora of terms is confusing, leads to communication problems, and is not optimal for the development of the field. Can we unite around a single, precise, acceptable term?

Let us consider the merits of the various competing terms for neoadjuvant chemotherapy. Upfront chemotherapy, anterior chemotherapy, protochemotherapy, and induction chemotherapy lack precision. What do we do, for example, in the leukemias, lymphomas, and metastatic cancers if it is not upfront chemotherapy?

“Upfront” chemotherapy lacks dignity. Imagine an International Congress of Upfront Chemotherapy. An International Congress of Outback Chemotherapy could follow. Other more salubrious terms come to mind. Anterior suggests anatomy. If there is anterior chemotherapy, there presumably must be posterior chemotherapy, which could mean chemotherapy for rectal carcinoma. Finally, anterior chemotherapy and protochemotherapy are not distinct from remission induction chemotherapy, a time-honored concept and approach, which is biologically very distinct from neoadjuvant chemotherapy (as presented below).

Preoperative chemotherapy and preradiotherapy chemotherapy are too specific. Neoadjuvant chemotherapy for surgery and radiotherapy may be similar and deserve an encompassing term. Moreover, in many protocols, surgery and/or radiotherapy may be employed for local treatment, rendering the specific term, e.g., preoperative, misleading.

Induction chemotherapy or remission induction chemotherapy was introduced some 30 years ago for the acute leukemias. It has universal acceptance and is a precise term. The distinction between remission induction chemotherapy and treatment during remission was a major conceptual and operational advance (3-6). Remission induction in that setting had to do with a two-log or greater reduction in a systemic tumor cell burden. The biological and medical implications here are thoroughly different from those involved in regression of the primary localized epithelial tumor. Thus the extension of an older term from the hematologic cancers to primary solid tumors, a situation which is superficially similar but fundamentally profoundly different, is not wise. Finally, induction chemotherapy is imprecise. Such chemotherapy is generally thought to precede chemotherapy during remission and not surgery or radiotherapy. Induction chemotherapy for solid tumors is emerging in the form of the treatment of patients with overt metastatic disease prior to autologous bone marrow transplantation. In that setting, it is a more acceptable term. What would be included in the program of an International Congress of Induction Chemotherapy?

Primary chemotherapy is an attractive term, since it indicates that chemotherapy is first in time and suggests that it is first in importance. The latter suggestion may make the term difficult to accept by our surgical and radiotherapy colleagues. Most particularly, as with anterior chemotherapy, protochemotherapy, and induction chemotherapy, the term primary chemotherapy lacks precision.

Neoadjuvant chemotherapy represents a concept and an approach whose time has come; it provides a unique and major clinical research opportunity and thus deserves a new and unifying term. What is the regional biology of a primary solid tumor regressing under chemotherapy? What is the magnitude of tumor regression? Does the nature of the regression represent an implosion of tumor cells, a decrease in density of tumor cells, or both? What happens to the blood supply and the partial pressure of oxygen after regression? What is the interrelationship of such regression under chemotherapy to the optimal follow-up treatment with surgery and/or radiotherapy—to the choice of surgery or radiotherapy or both? These and other features represent major research challenges—challenges that are unique to neoadjuvant chemotherapy.

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The therapeutic opportunity provided by this approach is major. Combination chemotherapy, often including cisplatin, has been found to be significantly more effective for many epithelial tumors when it is employed in the neoadjuvant setting as compared with the same treatment in patients with advanced recurrent tumor. Indeed, for neoadjuvant chemotherapy of head and neck cancer or bladder cancer, overall response rates of 70%-90% have been achieved with complete response rates in the range of 20%-50%. This represents a major change from just 10 years ago and indicates that, at least in terms of initial response, some of the epithelial tumors have a chemosensitivity approaching that of the hematologic neoplasias (7). Diseases of current ferment in terms of neoadjuvant chemotherapy include the aforementioned head and neck cancer and bladder carcinoma; they also include osteogenic sarcoma, stage III breast cancer, stage III regional non-small cell lung cancer, and anal carcinoma. While a longer follow-up and definitive quantitative studies will be necessary to determine the impact of neoadjuvant chemotherapy on survival for the aforementioned diseases, this chemotherapy is widely recognized as a major opportunity. Perhaps the best evidence for this is the numerous studies of neoadjuvant chemotherapy for the above diseases currently extant, a situation that represents a remarkable change from 5 to 10 years ago (7-9). As above, major conferences have been held in the past several years concerning neoadjuvant chemotherapy, including an International Congress of Neoadjuvant Chemotherapy.

The term neoadjuvant chemotherapy has several derivations. Most particularly, it is derived from adjuvant chemotherapy. This term, which involves systemic chemotherapy in patients following control of the primary tumor by local treatment, was controversial at first. Many of us objected to the term because it suggested that the chemotherapy is less important than the primary treatment when in fact both are essential. However, the term adjuvant chemotherapy has gradually become, and is today, universally accepted and is precise. The use of chemotherapy prior to local treatment can be construed in part as an extension of adjuvant chemotherapy. As with adjuvant chemotherapy, it provides a systemic approach to the control of micrometastatic disease. However, it also provides the potential for “downstaging” the primary tumor and improving the effectiveness of the subsequent use of surgery and/or radiotherapy. In this sense, it is adjuvant, only more so. Therefore, the term protoadjuvant chemotherapy might be appropriate. However, this would suggest that the only difference from adjuvant chemotherapy was temporal. In fact, the unique biological setting (i.e., regression of a primary tumor) and the novel therapeutic opportunities suggested that the best term should emphasize the novelty of the concept and approach—hence “new” adjuvant or neoadjuvant. It is not an extension of an old term, such as induction, that has a different meaning; nor is it imprecise, such as anterior chemotherapy, protochemotherapy, or upfront chemotherapy.

Does a term make a difference? If your son is to play the left side of a line at Notre Dame, he might have a greater chance of success with a name like Mack Truck as compared to Casper Milquetoast. More seriously, if you want to give emphasis to a relatively new concept and approach to the experimental and clinical treatment of cancer, a new and precise name is important. While not everyone likes the term neoadjuvant chemotherapy, everyone knows immediately and unambiguously what it means. This is in contrast with the other competing terms. Winston Churchill pointed out that democracy was inefficient, expensive, contentious, and, in emergency situations, sluggishly adaptable. Its one compelling advantage was that it was better than any other form of government. In terms of nomenclature, this is true for neoadjuvant chemotherapy.

Neoadjuvant chemotherapy as a term recognizes the novelty for the approach. It is precise and thus allows for more effective communication. It is unifying, has gathering acceptance, and should strengthen and provide a banner for this highly important field of therapeutic research.

References