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Co-morbidities and their underappreciated impact on the conversion of oncology trial results into routine clinical practice

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"With the availability of these critically important trial results ... oncologists hopefully will be provided with the data they require to optimally manage their patients."

The relevance of clinical trials in defining optimal cancer care is undisputed. From the development of new antineoplastic agents and innovative management paradigms, to the documentation of the ineffectiveness or toxicity of established strategies, well-considered and -conducted studies have served the public and patients well in improving cancer-associated outcomes. Of particular importance in this arena has been the prominent role that randomized Phase III trials in oncology has played over the past half-century in providing the highest level of 'evidence' of clinical benefit.

Unfortunately, as fundamental concepts of cancer biology and treatment have evolved during the past several decades, with malignant disease in many settings being characterized by a requirement for management over a number of years rather than months (cancer managed as a 'serious chronic illness'), strong challenges have been raised to the objective relevance of the results of many cancer clinical trials to the far larger population of individuals who might be considered appropriate candidates to receive a given strategy outside the increasingly recognized rather artificial confines of a clinical study.

For example, consider the observation that while it is well-appreciated that the incidence of cancer increases with age, the elderly (e.g., individuals > 65 years of age) are remarkably poorly represented in the large majority of clinical trials initiated to define efficacy and toxicity [1]. As a result, it is appropriate to question the relevance of cancer clinical trial data (both utility and safety) for a 70+ year old and otherwise healthy individual when the median age for patients entered into an 'evidence-based' trial that resulted in the approval of a novel (but potentially toxic) antineoplastic agent was 20 years younger, and only a minor proportion (likely far less than 10%) of the participants in the study population were >70 years of age.

Added to the list of concerns related to translating clinical trial data into routine clinical practice is perhaps an even more problematic issue; that of the general absence of individuals from a large proportion of cancer studies with existing clinically-relevant co-morbidities (e.g., acute or medication-dependent chronic heart disease, chronic obstructive pulmonary disease resulting in exercise restrictions, insulin-dependent diabetes or severe obesity). While it is not difficult to explain the reasons for excluding such patients from these trials (e.g., the potential for serious side effects, a desire to carefully define toxicity of a

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strategy/drug isolated from the effects of pre-existing organ dysfunction or to minimize competing causes of death), the most unfortunate end result is that it may be very difficult, if not impossible, to translate the 'favorable results' of a given trial into a population of patients with pre-existing, clinically relevant co-morbidities.

And just how serious is this problem? What percentage of newly diagnosed cancer patients has a pre-existng co-morbid medical condition that may potentially impact their management?

A recent report from the American Cancer Society has provided an important response to these questions, highlighting the substantial and (in the opinion of this commentator) wholly underappreciated magnitude of the issue [2]. Through an examination of national cancer registry and Medicare claims data, investigators found that, overall, approximately a third of breast (32.2%) or prostate (30.5%) cancer patients >65 years of age had a co-morbid medical condition. This percentage was similar to that of Medicare patients without a diagnosis of cancer (31.8%). The corresponding percentage of patients with colon cancer (40.7%) or lung cancer (52.9%) with co-morbidity was even greater.

When specific co-morbid conditions are considered, the potential impact of such illnesses on cancer management and outcome is further highlighted. Overall, approximately 16% of patients with the four major cancers included in this analysis (lung, colon, breast and prostate) also had diabetes or chronic obstructive pulmonary disease, 10% were previously diagnosed with congestive heart failure and 6% had cerebrovascular disease. Particularly striking was the prevalence of co-morbid conditions in individuals with lung cancer, a common malignancy in both men and women. A third of these patients had chronic obstructive pulmonary disease (four-times the percentage of individuals without cancer) and more than 12% had congestive heart failure.

In addition, a recent report has noted the negative impact on cancer survival associated with even mild or moderate evidence of impairment of renal function, a common exclusion from clinical trials [3]. Furthermore, the prevalence of clinically relevant kidney disease has been reported to be 11% in the United States for individuals >20 years of age, increasing to almost 70% in the population >80 years of age [4].

The impact of the lack of objective data supporting the use of specific oncologic interventions relevant to large populations of patients with cancer can be profound. Note, for example, a recent report examining Medicare claims data that stated as many as 35% of patients >65 years of age in the USA who were receiving bevacizumab for a drug regulatory agency-approved cancer indication actually had a 'contraindication' to the use of the agent [5].

However, an alternative explanation for this rather striking finding is that oncologists caring for patients with both a cancer and one of these common co-morbid conditions were attempting to optimize cancer outcomes by employing this documented biologically active antineoplastic drug. Unfortunately, these efforts by individual oncologists on behalf of their 'real world' (nonstudy) patients have been made far more difficult in the absence of helpful and objectively valid clinical guidelines (e.g., optimal dose and schedule, clearly defined 'absolute contraindications' based on objective data) due to the general exclusion of patients with these so-called 'contraindicated' conditions from the trials that demonstrated the efficacy of the agent.

Several potential solutions to this increasingly relevant and unacceptable state-of-affairs in the arena of cancer clinical trials might be proposed. First, one might mandate that in the absence of objectively defined 'contraindications', patients with common co-morbid conditions be permitted to enter the definitive clinical studies designed to achieve regulatory approval, or perhaps be considered a unique subset to be analyzed separately from the larger study population. This will hopefully permit the safety and possible efficacy of a novel antineoplastic strategy to be defined (including potentially documenting a true 'contraindication' for a specific co-morbidity).

Alternatively, separate studies may be conducted (or perhaps even mandated by drug regulatory agencies) in patients with common co-morbidity conditions (e.g., chronic obstructive pulmonary disease, insulin-dependent diabetes, obesity or medication-dependent congestive heart failure). With the availability of these critically important trial results (which may be single-arm rather than randomized studies), oncologists will hopefully be provided with the data they require to optimally manage their patients with both cancer and relevant co-morbid medical conditions. And, after all, is this not one of the most important reasons for conducting cancer clinical trials: To inform treating physicians so they can more effectively manage their patients through this difficult journey.

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References

1 Hutchins LF, Unger JM, Crowley JJ *et al.* Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N. Engl. J. Med.* 341, 2061–2067 (1999).

2 Edwards BK, Noone A-M, Mariotto AB *et al.* Annual report to the nation on the status of cancer: 1975–2010, featuring prevalence of co morbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer* doi:10.1002/cncr.28509 (2013) (Epub ahead of head).

3 Iff S, Craig JC, Turner R *et al.* Reduced estimated GFR and cancer mortality. *Am. J. Kidney Dis.* 63(1), 23–30 (2014).

4 Qaseem A, Hopkins RH, Sweet DE *et al.* Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med.* 159, 835–847 (2013).

5 Hershman DL, Wright JL, Lim E *et al.* Contraindicated use of bevacizumab and toxicity in elderly patients with cancer. *J. Clin. Oncol.* 31, 3592–3599 (2013).