Physiologic Evaluation in the Elderly Prior to Treatment With Chemotherapy

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H&O What is the purpose of conducting a physiologic evaluation in the elderly prior to treatment with chemotherapy?

MH In general, and particularly in my area of expertise, which is chronic lymphocytic leukemia (CLL), a significant number of elderly patients have severe comorbidities and disturbances of several organ systems. In CLL, physiologic evaluation is particularly important because the median age of onset for this disease is between 70 and 75 years. In these patients, the malignancy is often not the only disease. Therefore, it is extremely important to assess the patient's comorbidity and fitness before recommending chemotherapy or any other therapy.

H&O What are the methods used to evaluate patients?

MH There are several different methods used to assess the fitness of patients consisting of checks of different parameters. The International Society of Geriatric Oncology Chemotherapy Taskforce published consensus recommendations and a review of the literature regarding chemotherapy in the elderly in the May 10 issue of the *Journal of Clinical Oncology*. Several other articles in the same issue summarize techniques that can be used to assess a patient's fitness. One of the systems in use for decades is the Cumulative Illness Rating Scale (CIRS), which assesses, in a straight-forward manner, whether there is a comorbidity in different organ systems. If, for example, there is any condition that is disease-related, like heart disease, it is given a point value. The physician tabulates the number of points for a variety of systems on a single-page form. A high score indicates that a patient has considerable or severe comorbidities, and a score of zero indicates that a patient is very healthy. There are other measures that assess the intellectual fitness or physical mobility by simple scores, such as the Charlson score. In my opinion, it is not always necessary to assess every score, but it is important to bear in mind a picture of an individual patient's general fitness or comorbidities. The evaluation scores and a physician's intuitive assessment can complement each other, as long as a physiologic evaluation is made for every patient.

H&O In CLL, what recommendations are generally made based on the findings of the assessment?

MH A patient with CLL who has a high index of comorbidity should not receive standard chemotherapy at full dose and/or the agents should be chosen with great hesitation. The German CLL study group, as an example, is using physiologic assessment to influence the choice of chemotherapy in a given patient. Combination chemotherapies are administered to a patient with no comorbidities, the so-called "go-go" patient, who is very fit and can receive any chemoimmunotherapy at full dose. Dose-reduced monotherapy is administered to the so-called "slow-go" patient, who has relevant afflictions or disturbances of the renal or cardiac systems, for example. Research on what therapy to use in a given patient type should be done prospectively in clinical trials. The ideal combinations for each setting are not yet known because little research has been done. The relationship of comorbidity to drug pharmacokinetics is unknown and should probably be studied. Practically speaking, full-dose therapy can be recommended for the go-go patient and milder therapy for the slow-go patient.

H&O Does physiologic evaluation dictate whether a patient is a better candidate for chemotherapy alone or chemotherapy in combination with an antibody?

MH Yes, to some extent. In trials organized by the German CLL study group, a patient with severe comorbities may be recommended to receive chemotherapy without antibodies, whereas a patient with no relevant comorbidities will typically be recommended to receive chemoimmunotherapeutic combinations. However, there are no data from a prospective, randomized, double-blind trial to indicate whether these recommendations are the best choices; the recommendations are based on a commonsense decision. What should be done and has never been done is a randomized trial that actually compares treatments and assesses which is tolerated better or worse in patients who are frail or who have comorbidities. There has been some research elucidating when to use caution in treating elderly patients with CLL. Research from the University of Texas M.D. Anderson Cancer Center, led by Dr. Michael J. Keating, indicates that the novel chemoimmunotherapies used in the treatment of CLL, such as fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen Idec), are not well tolerated in patients older than 70 years. This finding indicates indirectly that severe comorbidity might be a condition in which a clinician should not choose chemoimmunotherapies in the first-line setting.

H&O How is assessment of gene expression used in this setting?

MH We are systematically conducting assessment of gene expression in the German CLL study group trials, but it is not known whether any markers exist for increased comorbidities. I would strongly encourage further studies on this subject, but at the moment we do not know whether and how prognosis is affected and whether there is any marker that could indicate comorbidity. There is one useful marker, outside of gene expression, which is renal function as determined by rate of creatinine clearance. We know that low creatinine clearance indicating poor kidney function correlates well with increased comorbidity. Thus, patients who have low creatinine clearance are potential candidates to receive modified doses of chemotherapy.

H&O Could you discuss ongoing research on the use of physiologic assessment in the elderly?

MH There are numerous clinical trials currently ongoing, and I think it is very important research. In the setting of CLL, we are currently conducting clinical trials in which we are selecting patients in a prospective manner according to their comorbidities. We are choosing different types of treatments for physically fit patients and not treating patients with serious comorbities. Before deciding whether to put a patient in a specific trial, we assess fitness by simple instruments such as the CIRS and Charlson score. After having undergone assessment, patients are enrolled under different protocols according to the findings of the assessment. There are comparator arms in some trials to find out whether the comorbidity assessment is correct and whether it is affecting prognosis. The entire management and stratification of our trials includes comorbidity assessment from the outset. I believe this sort of assessment should be conducted in nearly every trial done in cancer research now. Age alone is not a good qualification; there are very fit patients near the age of 70 and frail patients near the age of 55 or 60. Yet many trials have included patients either only older or younger than 65 years because that is the typical retirement age in western nations, even though 65 years of age does not have medical significance. There is a strong trend in the United States to eliminate age limits in trials endorsed by the National Cancer Institute both because it does not make sense medically and because of concerns about discrimination. In the future, I do not believe age limits in clinical trials will be seen as justified. More broadly, many researchers agree that assessment of fitness is highly important before administering chemotherapy, but more research is needed to find out what therapy is most appropriate in a given patient with a certain malignancy.

Suggested Readings

Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol*. 2007;25:1824-1831.

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Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4079-4088.

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