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INSIDE

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Cognitive Epidemiology: IQ And The Rate of Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *To address studies that indicate an inverse relationship between intelligence and mortality rates, Batty and colleagues capitalized on a large cohort of Swedish men who, upon entry into military service in Sweden were subjected to an assessment of intelligence quotient (IQ) by comprehensive examination of cognitive function.*

Source: Batty GD, et al. IQ in early adulthood and later cancer risk: cohort study of one million Swedish men. *Ann Oncology.* 2007;18:21-28.

Nearly one million young Swedish military recruits were subjected to intelligence testing approximately 20 years ago. Within this cohort, there are now known to be approximately 10,000 incident cancers. In the current analysis, cancer development (all cancers, and each of 20 specific types) was examined in the context of the intelligence test scores. There were a few minor trends detected (some up, some down) with only one reaching a level of statistical confidence; a positive correlation of skin cancer and intelligence test result. However, the subjects in this cohort are currently only in their early forties, well below the peak incidence of cancer, and future studies might find more substantial associations where currently there are only trends.

Several studies have indicated an inverse relationship between intelligence and mortality rates, yet little is known about this association and specifically whether it relates to cancer deaths. To address this, Batty and colleagues capitalized on a large cohort of Swedish men who, upon entry into military service in Sweden were subjected to an assessment of intelligence quotient (IQ) by comprehensive examination of cognitive function. The data for 959,540 men born between the years 1952 and 1976 and tested between 1970 and 1994 (at age 18 or 19 years) were linked with cancer registry and/or mortality data to examine the association. Hazard ratios for the relation between IQ and cancer outcomes were computed using Cox regression.

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During the average follow-up of 19.5 years there were 10,273 new cancer cases. Although IQ showed few associations with most of the 20 cancer types catalogued, there was a suggestion of a positive correlation with lung cancer and an inverse relationship with stomach, esophageal, and liver malignancies. The only robust finding was the relationship between IQ and skin cancer (hazard ration [HR] 1.18; 95% confidence interval [CI] 1.13-1.24, $P < 0.01$).

COMMENTARY

Within the evolving literature in the field of cognitive epidemiology[1] there have been repeated demonstrations of an inverse association of intelligence and all-cause mortality (e.g., [2]). However, an explanation for this has not been conclusively forwarded. Furthermore, with regard to chronic diseases, such as cardiovascular disease or cancer, the impact of cognitive function has not been satisfactorily addressed. On the other hand, observations that low childhood IQ scores are associated with smoking[3], obesity[4] and heavy use of alcohol[5], are factors that might predispose to increased cardiovascular disease or cancer. Furthermore, low scores have been associated with deprived socioeconomic status[6] which might, over the long term, result in less adequate health maintenance and vulnerability to diseases that might otherwise be prevented.

The findings in this large analysis are intriguing, but modest. First the positive association, albeit weak, of IQ and lung cancer runs counter to at least one other report in which a negative correlation was found.[7] Second, the robust positive association with skin cancer (both melanoma and non-melanoma cancers) would seem related to socioeconomic factors as has been previously reported. However, when the current data is adjusted for socioeconomic status, the relationship between IQ and skin cancer remains significant, albeit somewhat muted.

The fact that any relationships were discovered by this analysis is in itself remarkable, and likely most attributable to the very large data base available. The individuals under investigation (all men) were only in their late forties; two to three decades younger than the peak incidence years for most human cancers, particularly those that seem modifiable by host behavior. Thus, for the emerging field of cognitive epidemiology, a repeat analysis of this valuable cohort is warranted in perhaps twenty or thirty years. At least until then, it's probably advisable to continue doing those crossword puzzles! ■

References

1. Deary I, Batty GD. J *Epidemiol Community Health.* 2005;59:656-663.
2. Whalley LJ, et al. *BMJ.* 2001;322:819-823.
3. Taylor MD, et al. *J Epidemiol Community Health.* 2003;57:464-465.
4. Chandola T, et al. *Int J Obesity.* 2006;30:1422-1432.
5. Batty GD, et al. *J Epidemiol Community Health*, in press.
6. Neisser U, et al. *Am Psychol.* 1996;51:77-101.
7. Hart CL, et al. *Psychosom Med.* 2003;65:877-883.

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Aspirin Use And The Thrombocytic Cancer Patient with Acute Coronary Disease

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Aspirin can be life saving in patients with acute coronary events, but its use in patients with cancer, particularly in those with thrombocytopenia, is often avoided, presumably for fear of hemorrhagic complications. In this retrospective review of 70 patients who sustained an acute coronary event while at MD Anderson Cancer Center, over a one year period, aspirin treatment was associated with significantly better survival and this was true for the subgroup with normal platelet counts and the group with thrombocytopenia. Furthermore, there was no observed hemorrhagic complication in the aspirin treated patients.*

Source: Starkiss MG, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. *Cancer.* 2007;109:621-627.

OVER THE YEARS, THE BENEFIT OF ASPIRIN AND beta blocker therapy in the treatment of Acute Coronary Syndrome (ACS) has been well documented.[1] However, the evidence has been drawn on well conducted clinical trials that, for the most part, were devoid of patients with cancer and also those with thrombocytopenia. Thus, in the setting of an acute coronary event in a patient with cancer and thrombocytopenia, it has not been clearly demonstrated that aspirin or other antiplatelet therapy would have the same benefit and be without substantial additional risk. In fact, aspirin therapy has often been withheld in ACS patients who happen to also have cancer with or without thrombocytopenia, presumably for fear of hemorrhagic complications.

The current study, a retrospective analysis of patients with acute coronary syndrome during an inpatient stay at MD Anderson Cancer Center during the year 2001 was designed to evaluate the impact of aspirin therapy on relevant clinical outcomes including overall survival. For the diagnosis of an acute coronary syndrome (ACS), at least two of three criteria had to be documented. These included chest pain, characteristic EKG changes and elevation in cardiac enzymes. Seventy patients during the one-year stay met these criteria.

ACS patients were examined in the context of their platelet count (above or below 100 x106/ul) at the time of coronary event. Once categorized this way (those with normal platelet counts and those with thrombocytopenia), an examination of baseline risk factors for adverse outcomes from coronary disease revealed no significant differences. Of the total 70 ACS patients, 43 had "normal" platelet counts and 27 had thrombocytopenia (mean platelet count for this group was 32 x106/ul). The 7-day survival rate was significantly better for those with normal platelets (77% vs 37%). In both groups, the survival of patients who received aspirin was significantly higher than that in patients who did not receive aspirin. In the thrombocytopenia group, the overall 7-day survival for those who received aspirin was 90% compared with 6% for those who did not receive aspirin. Similarly, in the group with normal platelet counts, the overall survival for those who received aspirin was 88% compared with 45% for those who did not.

Importantly, no significant bleeding was observed in any patient, including those with low platelet counts.

COMMENTARY

Physicians are commonly confronted with difficult decisions for which hard evidence is unavailable. We frequently face this when making treatment decisions for cancer patients who, for any of a number of reasons (eg, functional impairments or co-morbidities) have little in common with the patients entered on the clinical trials that ultimately are used to define treatment standards. The current report is representative. The cardiology literature is rife with data about the life saving effects of aspirin in the acute coronary setting. Yet, these data are derived from trials on which cancer patients and patients with thrombocytopenia have been excluded. Internists, conservative by nature, will often rely on clinical judgment when the intervention is risky and the published guidelines not totally applicable. In this regard, the current report may be of great value. Although the series was small, the therapeutic benefit of aspirin was clearly demonstrated in a consecutive series of cancer patients, with or without thrombocytopenia, who were experiencing an acute coronary event. Furthermore, anticipated hemorrhagic complications were not observed, even in those with thrombocytopenia. Oncologists often find themselves caring for very ill patients and some quite possibly will develop acute coronary events. The take home message from the MD Anderson experience is that cancer patients with acute coronary events have a high rate of fatality that can be reduced in the acute setting by aspirin. Furthermore, when aspirin was used in patients with thrombocytopenia, there was significantly less mortality and, at least in this series, no observed hemorrhagic complications. ■

Reference

1. Braunwald E, et al. *J Am Coll Cardiol.* 2002;40:1366-1374.

Comorbidity Predicts Outcome for AML in Older Adults

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD, MS

Section of Hematology Oncology, University of Chicago

Dr. Artz reports no financial relationship to this field of study.

Synopsis: *AML most commonly occurs in older adults. Predictors of chemotherapy tolerance are sorely needed. The haematopoietic cell transplantation comorbidity index (HCT-CI) has been validated to predict outcomes after allogeneic hematopoietic transplant. Using this index, Giles and colleagues studied 177 adults 60 years*

and over who received a uniform induction regimen of idarubicin and cytarabine. HCT-CI scores of 0, 1-2, and 3 were found in 22%, 30% and 48% of participants. Early death occurred 3% scoring a 0, 11% scoring 1-2, and 29% scoring a 3 or higher (P < 0.001). Lower median overall survival also correlated with higher HCT-CI scores. More comorbidity as defined by the HCT-CI is predicted for more early death and inferior overall survival for older AML patients receiving induction chemotherapy. Future studies are needed to validate this index and assess the additive value of functional status.

Source: F. Giles, et al. *Br. J. Haematology.* 2007;136:624-626.

The incidence of AML rises steeply with advancing age. Older age also portends a worse prognosis for AML, in part due to adverse biologic disease characteristics including prior MDS, unfavorable cytogenetics, and increased expression of the multidrug resistance protein.[1, 2] A recent cooperative group analysis of AML in adults 60 years and over reported 5 year survival at only 6.6%.[3] The results probably paint an overly optimistic picture since cooperative group trials of intensive chemotherapy exclude many older and less fit patients.

The poor long-term outcome is compounded by concerns about acute toxicity and mortality related to intensive chemotherapy in older adults who frequently have complicating health conditions. Surprisingly, there has been scant data defining factors that increase the risk toxicity and death for receiving chemotherapy for AML.

Comorbidity indexes have been frequently used to summarize relevant medical conditions and predict toxicity and long-term survival. Typically, a numerical score is generated from known medical conditions. Higher scores reflect a greater burden of comorbid conditions. One of the first and most widely applied tools was the Charlson Comorbidity Index (CCI).[4, 5] A modified instrument based upon the CCI was developed by researchers at the Fred Hutchinson Cancer Research Center to better predict toxicity from allogeneic hematopoietic cell transplantation. This hematopoietic cell transplant comorbidity index (HCT-CI) incorporated additional comorbid conditions and objective laboratory parameters and thus detected at least one abnormality in five times more patients than the CCI alone.[6] Higher HCT-CI scores independently predicted for mortality related to transplant and overall survival.

In this study, researchers from the MD Anderson Cancer Center examined the HCT-CI among adults 60 years old who were undergoing induction chemotherapy for AML at their center since 1990. They evaluated 177 patients who received an idarubicin and cytarabine regimen. The median age was 70 years, 26% had an ECOG performance status of 2 or greater, and 90% had unfavorable cytogenetics.

Across all patients, scores of 0, 1-2, and 3 or greater were detected in 22%, 30%, and 48%, respectively. The most common comorbid diseases included cardiac (41%) and infectious (24%). The three strata of HCT-CI scores predicted outcomes for complete remission (CR), early death (death within 28 days of starting), and overall survival (OS). The CR rates were 64%, 43%, and 42%, and early death was 3%, 11%, and 29% ($P < 0.001$) based upon HCT-CI of 0, 1-2, and 3 or greater. A higher HCT-CI score also predicted worse overall survival ($P = 0.04$). Median overall survival was 45 weeks in those with an HCT-CI score of 0 as opposed to only 19 weeks in those scoring 3 or greater.

COMMENTARY

This short report addresses the common problem for the practicing oncologist of determining whether an older adult with AML will tolerate intensive chemotherapy. Giles and colleagues, using standard intensive chemotherapy of idarubicin and cytarabine, showed that the HCT-CI can be useful in predicting not only early death but also overall survival.

For those harboring 3 or more conditions on the HCT-CI, a critical threshold reported in the original description of the HCT-CI, overall survival was only 19 weeks and early death was 29%. Alternatively, the early death rate was only 3% in the low risk group defined as having no comorbid conditions by the HCT-CI. The median OS was still only 10 months in this low risk group, reiterating the poor prognosis in older AML patients.

Several shortcoming in the HCT-CI tool itself warrants discussion. At least one of the elements of the tool (infections after therapy requiring treatment) cannot be assessed at baseline and thus must be revised in future studies. Second, the original HCT-CI required pulmonary function studies, which are not routinely performed before chemotherapy. Third, how one scores malignancy must be clarified. Most have advocated not scoring the hematologic condition for which therapy is being pursued (ie, no points would be given for AML). However, in older patients, a considerable fraction may have had a recently treat-

ed prior malignancy resulting in therapy related AML. Prior malignancy not only represents a comorbid condition to be scored by the HCT-CI, but also could be associated with more aggressive AML. Thus, we must determine if the HCT-CI has independent utility in therapy related AML.

Finally, the curious lack of adjustment for known prognostic factors, such as disease factors or performance status, limits our ability to independently attribute HCT-CI score and outcome.

The HCT-CI may have value now to account for patient health in comparative studies. Also, the HCT-CI may guide clinicians when providing prognostic information to patients and their families about treatment, particularly regarding early death rates.

Ultimately, prospective validation using a larger number of patients and various treatment regimens will be necessary to validate the HCT-CI in older AML patients. In the future, treatment could be dictated by not only the risk group defined by the disease (ie, cytogenetic risk groups), but also by patient health status. Nevertheless, more precision will be needed before we can allocate patients to different treatment regimens based upon a health score. It is likely that precise prognostic information mandates inclusion of functional status as well as comorbid conditions as even using performance status, a crude functional status measure, is a consistent and powerful adverse prognostic factor across cancers and treatments. Whether other novel prognostic factors such as measures of C-reactive protein (CRP) will further refine estimates of induction tolerance requires study.

In summary, the HCT-CI significantly predicted outcome among uniformly treated older AML patients. ■

References

1. Leith CP, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood.* 1997;89:3323-3329.
2. Appelbaum FR, et al: Age and acute myeloid leukemia. *Blood.* 2006;107:3481-3485.
3. Farag SS, et al. Pretreatment cytogenetics add to other prognostic factors predicting complete remission and long-term outcome in patients 60 years of age or older with acute myeloid leukemia: results from Cancer and Leukemia Group B 8461. *Blood.* 2006;108:63-73.
4. Charlson ME, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373-83.
5. Charlson M, Szatrowski TP, Peterson J, et al: Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47:1245-1251.
6. Sorror ML, et al: Hematopoietic cell transplantation-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106:2912-2919.

ALLO Transplants And Second Malignancies

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *The risk for solid tumor development in prior recipients of allogeneic hematopoietic stem cells at the Leukemia/Bone Marrow Transplantation Program of British Columbia was found to be 3.1% at ten years of follow up. Older recipients (40 years and older) and those who received their graft from female donors were particularly susceptible. Extended follow up will be needed to assess more fully the magnitude of second cancers among transplant recipients.*

Source: Gallagher G, Forrest DL. Second solid cancers after allogeneic hematopoietic stem cell transplantation. *Cancer.* 2007;109:84-92.

IMPROVEMENTS IN OUTCOMES AFTER TRANSPLANTATION have resulted in increased long-term survival, and now there is concern that marrow recipients, cured of their primary disease have more frequent or accelerated chronic diseases that are more typically seen in late life. Gallagher and Forrest reviewed the case files of 926 consecutive patients who received allogeneic hematopoietic stem cell transplant (allo-HCST) between the years 1985 and 2003 at the Leukemia/Bone Marrow Transplantation Program of British Columbia (Vancouver). Twenty-eight patients developed 30 solid malignancies at a median of 6.8 years after allo-HSCT for a 10-year cumulative incidence of 3.1% (95% confidence interval [CI], 2-5%; all solid tumors) and 2.3% (95% CI 1-4%, excluding basal cell carcinoma and carcinoma in situ of the cervix). The risk ratio of developing a second solid

malignancy after allografting, compared with the general population of British Columbia, adjusted for age and sex, was 1.85 (95% CI, 1.04-3.06; P = 0.019). The variables examined with regard to developing a second malignancy included: age at the time of transplant (< 40 years vs > 40 years), sex, diagnosis (AML vs ALL vs CML vs MDS vs lymphoma vs other), interval between diagnosis and transplant (< 6 months vs > 6 months), history of prior radiotherapy, donor age (< 40 years vs > 40 years). HLA disparity between donor and recipient, type of transplantation (related vs unrelated), conditioning regimen (TBI-based vs chemotherapy only), source of stem cells (bone marrow vs peripheral blood), year of transplant (before or after 1995), whether the stem cells underwent T-cell depletion, the presence of acute graft vs host disease (GVHD), and the presence of chronic GVHD. Of these, in univariate analysis only, recipient age at the time of allo-HCST (P = 0.02) and donor sex (P = 0.005) were significant risk factors. These same factors (age > 40 years at time of transplant [P = 0.005], and having a female donor [P = 0.0008]) were risk factors for developing a second solid cancer after multivariate analysis.

The pattern for increased risk based upon recipient age was examined by additional subgroup multivariate analysis. Compared to those less than 30 years, for those aged 30-40 years at the time of transplant, the relative risk (RR) was 2.06, and for those 40 years, 4.75 (P = 0.005). Compared with the general population, the RR for those aged < 40 years and those > 40 years at allo-HCST was 3.42 (95% CI, 1.37-7.05; P = .005) and 1.32 (95% CI, 0.57-2.61, P = 0.26), respectively.

The 10 year cumulative incidence of developing a second solid cancer in patients who received a graft from a female donor and a male donor was 4.6% (95% CI, 2.5-7.6%) and 1.8% (95% CI, 0.8-3.8%), respectively (P = 0.008). The influence of sex matching on second cancer risk (donor/recipient: M/M, M/F, F/F, F/M) was examined in both univariate and multivariate analysis. As mentioned, having a female donor was associated with a significant risk (RR, 3.8; P = 0.0008). This risk was particularly high when the recipient of a female graft was a male (RR: M/M, 1.0; M/F, 0.97; F/F, 1.87; F/M, 4.7; P = 0.005).

COMMENTARY

It is a testament to the procedural advances in stem cell transplantation that we are now facing long-term consequences. The 39% estimated 10-year disease free survival of the approximate 1000 patients transplanted in Vancouver between 1985 and 2003 reflects the remarkable advances in transplant biology and supportive care made possible by prior decades of careful laboratory and clinical investigation. Now, we are becoming increasingly aware of the risk of second cancers over the long-term in patients cured of their primary disease by transplantation.[1, 2] Retrospective analysis, such as this from Vancouver, can provide clues as to where to focus to better understand and ultimately intervene to reduce second malignancy risk.

One might have the impression that the estimates from Vancouver are low. The experience with Hodgkin's disease and solid tumor risk (ie, in contrast to myelodysplasia or leukemia risk) would suggest a long latency period and thus extended surveillance beyond ten years, and perhaps for life. In fact, for Hodgkin's disease, the risk of second malignancy increases at a rate of approximately 1%/year, indefinitely.[3, 4] Thus, the relatively short follow up for the Vancouver transplant patients (of the 420 alive at the time of report, the median duration of follow up was 7.0 years, and only 30% of these were out beyond 10 years) would allow prediction that the rate of solid tumor development in this cohort could increase significantly over the next decades.

That age was found to be an independent risk factor comes as no surprise. Older patients are theoretically more likely to harbor pre-malignant lesions that might accelerate with the intense preparative regimens involved in transplantation, or age-sensitive host factors, such as DNA repair mechanisms might render the older recipient more susceptible.[5] However, if the marrow procedure itself is associated with carcinogenesis, it might be expected that solid tumor incidence in the younger recipients will catch up to that of the older cohort, but only after a longer latency, well in excess of what is currently available in the Vancouver series.

The unexpected finding of an increased risk when the donor is female had not been previously reported, and if confirmed from data at other marrow transplant centers, warrants in-depth analysis.

Thus, Gallagher and Forrest have presented an excellent summary of second tumor risk observed at their transplant center. The estimated rate of 3.1% at ten years of follow-up significantly exceeds what would be observed in the general population (age and sex matched) but probably is a harbinger of an even greater risk after longer follow up. However, it is important to remember that the incidence of these solid tumors would not be a concern for those leukemia patients not transplanted, as

the great majority will have died years before from their primary disease. Second malignancies in this setting are an unwanted but not unexpected complication of prior life-saving treatment. It is inherent upon us now to identify the modifiable risks and reduce them, as possible.

References

1. Baker KS, et al. *J Clin Oncol.* 2003;21(7):1352-1358.
2. Curtis RE, et al. *The New England journal of medicine.* 1997;336(13):897-904.
3. Longo DL. Radiation therapy in the treatment of Hodgkin's disease—do you see what I see? *Journal of the National Cancer Institute.* 2003;95(13):928-929.
4. van Leeuwen FE, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *Journal of the National Cancer Institute.* 2003;95(13):971-980.
5. Evans MK, et al. *Mutation research.* 1994;314(3):221-231.

Intraperitoneal Chemotherapy for Ovarian Cancer: The QOL Trade-Off

By William B. Ershler, MD, Editor

ABSTRACT & COMMENTARY

Synopsis: *Recent advances in ovarian cancer management include the demonstration of improved progression-free and overall survival with intraperitoneal (IP) chemotherapy in the adjuvant setting. For example, the Gynecologic Oncology Group (GOG) has reported an increase by 15.9 months in IP vs standard dose intravenous (IV) chemotherapy for good performance status in stage III patients after debulking. However, the added months come at significant impingement in quality of life, as apparent in the GOG trial and detailed in this report.*

Source: Wenzel LB, et al. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol.* 2007;25:437-443.

There have now been three randomized trials demonstrating superior survival with intraperitoneal (IP) vs intravenous (IV) cisplatin for adjuvant treatment after successful debulking of ovarian cancer.[1-3] The Gynecologic Oncology Group (GOG) recently reported their phase III trial in which patients were randomly assigned to receive either IV paclitaxel plus cisplatin or IV paclitaxel plus IP cisplatin. The improvement in median overall survival was 15.9 months for the IP treated patients, but this was associated with a greater infringement on quality of life (QOL). The current report details the QOL results from this trial.

Patients (n = 415) with stage III ovarian cancer or primary peritoneal carcinoma who had no residual disease greater than 1 cm in diameter and met other eligibility criteria were enrolled onto GOG 172 and received paclitaxel 135 mg/m2 IV over 24 hours followed by either cisplatin 75 mg/m2 IV on day 2 (IV arm) or cisplatin 100 mg/m2 IP on day 2 plus paclitaxel 60 mg/m2 IP on day 8 (IP arm). Treatment cycles were every 3 weeks for a total of 6 cycles.

QOL, neurotoxicity, and abdominal discomfort were assessed by questionnaires administered on four occasions; before randomization, before chemotherapy cycle 4, approximately one month after treatment, and one year after completion of treatment. For QOL, Functional Assessment of Cancer Therapy (FACT)-Trial Outcome Index (which includes physical, functional, and ovarian subscales) was utilized. Neurotoxicity was assessed by FACT/GOG-Ntx, which is an 11 item scale used to assess short- and long-term symptoms of neurotoxicity. Symptoms of abdominal discomfort were captured by two additional questions added to the above instruments specifically for this study.

Physical and functional well being and ovarian cancer symptoms were significantly worse in the IP arm before cycle 4 ($P < 0.001$) and at one month after treatment ($P < 0.001$). Patients in the IP arm also reported significantly worse abdominal discomfort before cycle 4 ($P < 0.001$) and significantly worse symptoms of neurotoxicity at one month and twelve months after completion of treatment. There was evidence that QOL in general improved over time in both groups upon completion of therapy.

COMMENTARY

For women with optimally debulked ovarian cancer and good performance status, recent data indicates a significantly improved progression-free and overall survival with the more intensive IP drug administra-

tion. However, the more intensive regimens carry increased toxicity and associated negative impact on quality of life. It would seem the findings are consequential, as 98 patients in the IP arm vs only 30 patients in the IV arm had dropped off study by cycle 4.

A 15.9 month survival advantage is not inconsequential either, and, at the moment, the precise role for IP treatment as the initial post surgical adjuvant approach remains controversial. And, as usual, the practicing oncologist finds him/herself in the middle, weighing the latest advances measured in added months of life against those more subjective but equally important factors that influence the QOL in those remaining months. Hopefully the GOG and/or other groups will focus future studies on reducing toxicity and improving QOL while not slipping back on those added months of life for those with ovarian cancer. ■

References

1. Markman M, et al. *J Clin Oncol.* 2001;19:1001-1007.
2. Alberts D, et al. *N Engl J Med.* 1996;335:1950-1955.
3. Armstrong D, et al. *N Engl J Med.* 2006;354:34-43.

CME Questions

9. Regarding the association of IQ scores and cancer, for which of the following tumor types did Swedish military recruits who scored high on intelligence testing have a significantly higher risk of developing?
a. lung cancer
b. gastric cancer
c. skin cancer
d. non-Hodgkin's lymphoma
e. laryngeal cancer

10. In this study of older AML patients undergoing induction chemotherapy, more comorbid conditions based upon the hematopoietic cell transplantation comorbidity index (HCT-CI) predicted for what?
a. better response rates
b. more early deaths (ie, deaths within 28 days of treatment)
c. more falls
d. better quality of life

11. Among allogeneic hematopoietic stem cell recipients, risk factors for the development of solid tumor (second malignancy) include:
a. older age
b. being female
c. having ALL (as opposed to AML)
d. all of above

12. Regarding the quality of life for patients who receive IP vs IV chemotherapy for ovarian cancer, as per the GOG 172 protocol, overall differences observed during treatment or at one month after treatment were virtually gone by one year after treatment except for:
a. abdominal discomfort
b. symptoms of neuropathy
c. fatigue
d. anorexia
e. none of the above

Answers: 9(c); 10(b); 11(a); 12(b)

CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

In Future Issues:

PSA at 40, Can It Predict Prostrate Cancer at 70?

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

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any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■