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INSIDE

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Molecular Tests Discriminate Prognosis in Normal Karyotype AML

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

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Dr. Artz reports no financial relationships relevant to this field of study.

Synopsis: *Acute myeloid leukemia in the elderly has a poor prognosis using standard therapy. Lenalidomide is a thalidomide analogue with activity at low doses for low-risk MDS harboring a 5q-. Two institutions using different protocols evaluated high-dose lenalidomide induction (35-50 mg daily for 14-21 days, 14-30 days of rest) followed by lower dose maintenance (10 mg daily). Out of 33 patients, four patients had a complete response. Interestingly, the two evaluable patients with AML and a trisomy 13 both achieved a complete cytogenetic remission lasting 8-9 months. Lenalidomide has activity in AML. Further study will be needed to confirm if certain cytogenetic subsets of AML have higher response rates to lenalidomide.*

Source: Fehniger T, et al. Single-agent lenalidomide induces complete remission of acute myeloid leukemia in patients with isolated trisomy 13. *Blood*. 2009;113:1002-1005.

ACUTE MYELOID LEUKEMIA (AML), PARTICULARLY IN OLDER ADULTS, has dismal long-term outcomes.[1] These poor results relate to worse disease features such as multi-drug resistance, a tendency to arise from myelodysplastic syndromes (MDS), and adverse karyotypes. Further, worse performance status of older adults diminishes tolerance to chemotherapy. While outcomes have improved for younger adults with AML, the poor survival among older AML patients remains unchanged. Novel approaches are sorely needed that have a different mechanism of action than standard chemotherapy and/or have improved tolerability.

Lenalidomide is an oral thalidomide analogue that shows considerable activity in multiple myeloma and low-risk MDS accompanied by the 5q- cytogenetic abnormality.[2] Lenalidomide-related myelosuppression

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has limited the dose to 10 mg per day for MDS. These lower doses result in plasma concentrations much lower than that achieved from the higher doses for multiple myeloma.[3] Fehniger et al report two cases from separate institutions and protocols of AML harboring a trisomy of lenalidomide-induced complete remissions.

The first case was a 71-year-old man who presented with de novo AML without known MDS treated at Washington University. Metaphase cytogenetics only revealed a trisomy 13. He received lenalidomide at 50 mg per day for 14 days, with 30 days of rest followed by cycle 2 of 50 mg per day for 21 days. The peripheral blood blasts improved, and the marrow showed aplasia and residual blasts. After one month of rest following cycle 2, low-dose therapy at 10 mg daily for 28-day cycles was begun. At the end of the first cycle of consolidation (124 days from initial treatment), blood counts normalized and a bone marrow demonstrated a complete cytogenetic response with 60% cellularity, less than 5% blasts, and no cytogenetic abnormalities (CRc). CRc was confirmed six and 16 weeks after this. He remained on maintenance lenalidomide but relapsed nine months after the initial CRc.

In a second case, a 68-year-old man treated at Ohio State University had AML arising from MDS in first relapse after 3.5 years. While a normal karyotype was present at diagnosis, a trisomy 13 was detected at relapse. Lenalidomide was started at 35 mg/day for 21 days followed by seven days of rest. After cycle 1, he remained pancytopenic, transfusion dependent, and the marrow had residual disease and persistence of the trisomy 13. After four days of cycle 2, an infection required holding therapy. After four weeks, the counts recovered while therapy remained on hold. A bone marrow showed a CRc. The patient was consolidated with two cycles of lenalidomide at 35 mg per day, but was later reduced to 10 mg per day for 21 of 28 days because of myelosuppression; he relapsed nine months after the initial CRc.

Importantly, among other patients treated at Washington University with lenalidomide, none of the 13 non-trisomy 13 AML patients achieved CR. One patient had a trisomy 13 with additional cytogenetic abnormalities; lenalidomide was only given for six days because of infection. At Ohio State University, two of 18 non-trisomy 13 AML patients had responses. One 74-year-old patient with AML and a normal karyotype in second relapse with skin involvement at relapse achieved a third CR lasting eight months. In another case, a 61-year-old male with AML and a monosomy 7 received an allogeneic hematopoietic transplant in CR2 from an unrelated donor. Relapse followed nine months later, and he achieved CRc after three cycles of lenalidomide and continues on therapy.

■ COMMENTARY

Fehniger et al report two complete cytogenetic remissions among older adults with AML and a trisomy 13 using high-dose lenalidomide. The patients maintained the remissions 8-9 months with low-dose consolidation lenalidomide. The data are intriguing in that older adults with AML generally have a poor prognosis even using induction chemotherapy. Moreover, rare karyotypic abnormalities such as trisomy 13 usually predict a poor prognosis.[4] Finally, many older adults are not eligible for intensive therapy due to co-existent health limitations.

The results must be put in perspective. Essentially, four of 33 (12%) patients achieved a complete remission. While lenalidomide could be viewed as non-intensive therapy, the high doses used for induction likely lead to considerable myelosuppression and may result in other serious toxicities. Further therapies such as hypomethylating agents or clofarabine probably have more activity. At a minimum, high-dose lenalidomide, followed by lower-dose consolidation, has some activity in AML and certainly warrants continued study.

The largest question these data raise is whether the responses in two patients with AML and trisomy 13 are coincidence or a unique biology. While Fehniger et al postulated the association of mutation in the RUNX1 gene and increased expression of the FLT-3 tyrosine kinase gene (which is located on chromosome 13), the exact reason that lenalidomide would inhibit these specific targets is not addressed. Because the mechanism of lenalidomide is not well appreciated, and may relate to multiple pathways,

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a uniform hypothesis, or target, is unlikely. Lenalidomide has activity in MDS, including non-5q minus, so it is not surprising to see some activity in AML, especially since AML in older adults often arises from MDS. Further investigation of high-dose lenalidomide, particularly in AML with rare cytogenetic abnormalities, is of great interest. ■

References

1. Appelbaum FR, et al. Age and acute myeloid leukemia. *Blood*. 2006;107:3481-3485.
2. List A, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med*. 2005;352:549-557.
3. Richardson PG, et al: A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood*. 2006;108:3458-3464.
4. 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.

Pre-Treatment CBC and the Prediction of Myelotoxicity

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Capitalizing on data from a rather homogenous population of breast cancer patients treated with a single chemotherapy regimen (FEC), Jenkins and Freeman found that pretreatment absolute neutrophil and absolute lymphocyte counts, examined together, were highly predictive of risk for all neutropenic events, including febrile neutropenia, dose delays, and overall reduced dose intensity over the six cycle course of treatment.*

Source: Jenkins P, Freeman S. Pretreatment haematological laboratory values predict for excessive myelosuppression in patients receiving adjuvant FEC chemotherapy for breast cancer. *Ann Oncology*. 2009;20:34-40.

Neutropenia and associated neutropenic events (NE), such as febrile neutropenia (FN) and treatment delays, are a major untoward effect of many chemotherapy regimens. In addition to the life-threatening aspect of infection in a myelosuppressed patient, there is also the issue of delays or reduction in chemotherapy dose, both of which diminish the intensity of a planned chemotherapy regimen, and such reduced intensity has been associated with reduced treatment effectiveness.[1] Thus, identifying factors that might predict NE prior to treatment might prove of clinical value, such that prophylactic measures could be undertaken.

The current research was undertaken to determine if the pretreatment complete blood count (CBC) might be used to predict NE. Jenkins and Freeman analyzed a large cohort (n = 741) of breast cancer patients who received adjuvant or neo-adjuvant FEC (5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 intravenously every three weeks) for a planned six cycles. Capitalizing on an electronic database patient management information system employed at the Gloucestershire Cancer Center, all FEC-treated breast cancer patients were identified between the years 2001-2005 and because a dose-banding algorithm was employed by the Center's pharmacy; the actual doses employed were within 5% of those calculated based upon body surface area (BSA). Each cycle of treatment was delivered if the absolute neutrophil count (ANC) was > 1.5 x 10^9/l and the platelet count > 100 x 10^9/l. If not, chemotherapy was delayed for one week. If chemotherapy had to be delayed on two occasions due to inadequate blood counts, a dose reduction of 20% was made for all agents and maintained for the rest of the treatment course. Greater dose reductions were instituted if the patient experienced further myelosuppression despite these modifications. After an episode of FN, doses were also reduced by 20%. Granulocyte colony-stimulating factors (G-CSFs) were not employed as either primary or secondary prophylaxis during the period of this study. No patient received concomitant radiotherapy, and endocrine treatment was only commenced after completion of chemotherapy. A NE was defined as either an episode of FN or a dose delay > 1 week caused by prolonged myelosuppression. Dose intensity was defined as (dose received/dose planned)/(overall treatment time/planned treatment time) over six cycles of treatment.[2] This was considered to be suboptimal if it fell < 0.85 (DI < 85%).[3]

Of the 741 consecutively treated patients, 192 had a schedule interruption on the basis of myelotoxicity. Of these, 53 had an episode of FN (three patients had two episodes) and 160 experienced one or more treatment delays due to myelosuppression. In total, 104 (17.3%) patients had a dose intensity (DI) of < 85% and 10 (1.6%) a DI < 65% due to myelosuppression. While treatment delays were evenly spread throughout the planned six cycles of chemotherapy, FN was most common in cycle 1 (25 of 53, 47%). Of note, 83% of patients who experienced a neutropenic event in cycle 1 went on to receive a

DI of < 85%, whereas, of the 29 patients with FN in cycles 2-6, only two (7%) had experienced a previous treatment delay due to neutropenia.

Regarding the pretreatment CBC as a predictor of neutropenic events (NEs), it was found that both the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were strongly associated with the risk of febrile neutropenia (FN), dose delays, and receiving suboptimal chemotherapy dose intensity (DI < 85%). On the basis of ANC and ALC, the total population was divided into quintiles, and it was found that the risk of any NE varied by 2.8-fold (from 18% to 52%) between the separate groups, the risk for a DI of < 85% varied four-fold (9% to 36%), and the risk for FN by 5.3-fold (4% to 21%) between the groups.

■ COMMENTARY

FEC chemotherapy at these doses is not considered a high risk for producing myelotoxicity, but 26% of patients still had scheduled interruptions, and 13% had dose reductions because of NEs. Using pretreatment differential white blood cell count to identify patients at an increased risk of significant myelosuppression, whether such a model can be extrapolated to other chemotherapy regimens or other clinical settings, will require additional investigation. Certainly, the concept is a good one and, if substantiated, would provide an inexpensive method of predicting those patients at risk for neutropenic events and for whom primary prophylaxis with granulocyte colony stimulation factor (G-CSF) would be warranted. ■

References

1. Budman DR, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J *Natl Cancer Inst*. 1998;90:1205-1211.
2. Longo DL, et al. The calculation of actual or received dose intensity: a comparison of published methods. *J Clin Oncol*. 1991;9:2042-2051.
3. Bonadonna G, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med*. 1995;332:901-906.

Sunitinib Improves Overall Survival in Patients with Renal Cancer

By William B. Ershler, MD

Synopsis: *In a population-based retrospective review of first-line treatment of metastatic renal cell carcinoma, sunitinib was shown to double overall survival when compared to interferon alpha. The unique circumstances allowing the connection of tumor registry data with chemotherapy treatment and outcomes allowed a clear (albeit retrospective) demonstration that improvements in progression-free survival observed in clinical trials are likely to be reflected in improved overall survival as well.*

Source: Heng DYC, et al. A population-based study evaluating the impact of sunitinib on overall survival in the treatment of patients with metastatic renal cell cancer. *Cancer*. 2009;115:776-783.

For patients with metastatic renal cell carcinoma (mRCC), standard chemotherapy has proven ineffective, and immunotherapeutic approaches, such as interferon alpha or interleukin-2, offered only modest benefit in terms of progression-free and overall survival.[1-3] However, in recent years, anti-angiogenic agents such as sunitinib, sorafenib, and bevacizumab have demonstrably improved the outlook for RCC patients.[4-6]

In the pivotal, randomized, phase 3 trial, sunitinib treatment resulted in progression-free survival (PFS) of 11 months, comparing favorably to five months associated with interferon alpha treatment ($p < .001$).[6] Overall survival (OS) for that trial was also better for the sunitinib-treated patients (26.4 vs 21.8 months) ($p = .051$). The less striking difference in OS compared with PFS was considered possibly related to the crossover of many of the patients initially randomized to IFN to sunitinib upon recognition of progressive disease.

The current research aimed to compare overall survival in a population-based analysis comparing two cohorts of mRCC patients, those treated with IFN and those treated with sunitinib.

For this, the British Columbia Cancer Registry was cross-referenced with the Provincial Pharmacy Database to identify all patients with mRCC who were treated with IFN and/or sunitinib in the province of British Columbia between January 2000 and September 2007. The IFN group consisted of all patients who received IFN alone between January 2000 and October 2005. The sunitinib group included all patients treated with first-line sunitinib from October 2005 to September 2007, when sunitinib became available as standard therapy.

Patients who received first-line IFN followed by second-line sunitinib were excluded.

Before October 2005, patients with mRCC were treated with IFN^{9}x10^{6} international units (IU) three times per week on nonconsecutive days. After October 2005, patients were treated with sunitinib at a starting dose of 50 mg daily for four weeks, followed by a two-week break each cycle. There were 131 and 69 patients in the IFN and sunitinib groups, respectively. The median follow-up of those still alive was 12.6 months. Despite the different years of treatment, the groups were comparable with regard to age (mean 62 vs 63 years), Memorial Sloan Kettering Cancer Center (MSKCC) prognostic criteria (poor in 19% vs 30%), and proportion with > 1 metastasis (53% vs 62) between the IFN and sunitinib groups, respectively.

The median survival of the IFN and sunitinib groups was 8.7 and 17.3 months, respectively (log-rank p = .004). The median survival of patients with favorable, intermediate, and poor MSKCC prognostic profiles in the IFN group was 22.9, 8.7, and 4.1 months, respectively (p < .001), whereas, in the sunitinib group, median survival was not reached, or reached in 16.8, or 10.7 months, respectively (p = .006). The hazard ratio of death after adjusting for MSKCC criteria was 0.49 (95% confidence interval, 0.31-0.76; p = .001).

■ COMMENTARY

Sunitinib is an oral tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF) receptor types 1, 2, 3, platelet-derived growth factor receptors alpha and beta, c-kit, and FLT-3.[7] With impressive findings from the aforementioned phase 3 studies, sunitinib has become the standard first-line treatment for patients with mRCC. We learn from the current report that such has been associated with a doubling of overall survival compared with patients treated with IFN alone. The strength of this observation is based upon the well-constructed tumor registry in British Columbia and a health care system that standardizes treatment protocols (albeit for reimbursement purposes). Thus, it is likely that all, or nearly all, mRCC patients in this province who received treatment were included in this analysis. This includes older and frailer patients who might not have been candidates for a phase 3 trial, but received the treatment nonetheless. Indeed, the benefits from sunitinib were shown to extend to patients with poor MSKCC prognostic profiles; a group that has been underrepresented on clinical research protocols in general.

Furthermore, although the phase 3 clinical trial demonstrated impressive improvements in PFS, the improvement in OS was modest and not quite statistically significant. Other phase 3 trials with similar anti-VEGF agents have resulted in similar findings (impressive improvement in PFS, lesser effect on OS).[4,5] The unique circumstances provided by the British Columbia health care system and the fairly abrupt change in "standard" therapy has allowed for a real-world analysis of the effects of the two different treatments, albeit at the risk of studying two cohorts separated by time. Even so, the findings are quite clear: first-line mRCC treatment with sunitinib, compared with INF, enhanced OS by a factor of two.

Nonetheless, despite this impressive move in the right direction, one cannot lose sight that we are talking about differences in months, not years. Anti-VEGF targeted treatments represent the beginning, not the end of the quest to control this difficult disease. ■

References

1. McDermott DF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23:133-141.
2. Negrier S, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med*. 1998;338:1272-1278.
3. Negrier S, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer*. 2007;110:2468-2477.
4. Escudier B, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356:125-134.
5. Escudier B, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007;370:2103-2111.
6. Motzer RJ, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007; 356:115-124.
7. Hutson TE, Figlin RA. Evolving role of novel targeted agents in renal cell carcinoma. *Oncology (Williston Park)*. 2007;21:1175-80.

Vitamin D Level and Prognosis in Patients with Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Calcidiol (25(OH)D) levels were measured in a series of 160 Norwegian prostate cancer patients, and the results correlated with cancer-specific and all-cause mortality. Compared to those with low levels, patients with medium or high levels experienced less cancer-specific mortality, and this was particularly notable in those who received some form of hormonal treatment.*

Source: Tretli S, et al. Association between serum 25(OH)D and death from prostate cancer. *Br J Cancer*. 2009;100: 450-454.

It has long been held that there is a relationship between insufficient sun exposure and cancer death.[1,2] Indeed, the mortality rates for breast, prostate, lung, skin, and lymphoma have each been shown to vary in accordance with sun exposure. Experimental studies have demonstrated an effect of vitamin D on key cell-cycle processes, including proliferation and apoptosis,[3] and it has been proposed that vitamin D influences cancer progression.

Vitamin D levels are dependent on a number of factors, including sunlight. The most active form, calcitriol (1,25(OH)2D), is produced in the kidney from calcidiol (25(OH)D). The amount of vitamin D in the body is closely associated with the concentration of calcidiol in the blood.

The current report is from Norway where, during winter months, typical exposure to sunlight is very low, and this is reflected by low blood levels of 25(OH)D in the general population during these months. Curiously, Tretli et al have discovered that patients who were diagnosed with cancer of the breast, colon, prostate, lung, or lymphoma during the summer or autumn were found to have better prognosis (15%-50%) than patients diagnosed during winter months.[4,5] To more directly relate these observations to vitamin D sufficiency, pretreatment 25(OH)D levels were determined in prostate cancer patients and associated with clinical outcome. The study capitalized on an outstanding national registry and serum bank (the Janus serum bank, established in 1973). A total of 160 patients with prostate cancer were included in the analysis. Of these, 37 had received hormone therapy for a median of 2.4 years prior to the vitamin D blood sampling, and this cohort (Group 1) was considered separately from the remaining 123 patients who had vitamin D levels determined at the time of diagnosis and prior to therapy. All patients received some form of therapy for their prostate cancer, including radiation, surgery, and/or hormonal therapy. In total, 97 of the 160 patients received hormone therapy, most frequently with leutinizing hormone-releasing hormone (LHRH) or orchiectomy. Additional variables, including patient age, ECOG performance status, and tumor grade were factored into the analysis.

The serum level of 25(OH)D was classified as low (< 50 nmol/L), medium (50-80 nmol/L), or high (> 80 nmol /L). A Cox proportional hazard regression model was used to assess the association between serum 25(OH)D and cancer mortality. During follow-up, 61 deaths occurred, of whom 52 died of prostate cancer. The median time of follow-up was 44.0 months (range, 1.2-154.6). Serum 25(OH)D at medium or high levels were significantly related to better prognosis (RR 0.33; 95% CI 0.14-0.77, RR 0.16; 95% CI 0.05-0.43), compared with the low level. Analysis restricted to those 97 patients receiving hormone therapy gave a stronger association (RR 0.18, 95% CI 0.07-0.46 and RR 0.09, 95 % CI 0.03-0.27, respectively, for those with medium or high 25(OH)D levels, compared to those with low levels.

■ COMMENTARY

Thus, there was a clear association of serum 25(OH)D level and cause-specific mortality in prostate cancer. Although it is doubtful that such is unique to Norway, perhaps it is likely to be most demonstrable in such a northern environment where sunlight exposure varies strikingly in a seasonal manner. Nonetheless, in this series of 160 patients, the association was quite strong. Yet, as Trietl et al point out, association studies do not set out to prove causality, and the findings should not be extrapolated to indicate vitamin D replacement in prostate cancer treatment strategies in anything but a controlled clinical trial.

Whereas there are mechanisms postulated to account for the protective effect of vitamin D, there are also reports that high levels of this vitamin may be associated with an increased risk for prostate cancer development[6] or more aggressive disease.[7] It is quite clear that there is a lot we don't know about vitamin D and cancer in general. Certainly, the data presented would indicate that serum levels might prove to be useful in prognosis. Whether supplementation for those with low levels will be useful in prevention or treatment should be the subject of well-constructed clinical trials. ■

References

1. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*. 1980;9:227-231.
2. John EM, et al. Vitamin D and breast cancer risk: the NHANES I Epidemiologic follow-up study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev*. 1999;8: 399-406.

3. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol*. 2006;92:49-59.
4. Porojnicu AC, et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? *Lung Cancer*. 2007;55:263-270.
5. Porojnicu AC, et al. Season of diagnosis is a prognostic factor in Hodgkin's lymphoma: a possible role of sun-induced vitamin D. *Br J Cancer*. 2005;93:571-574.
6. Tuohimaa P, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int J Cancer*. 2004;108:104-108.
7. Ahn J, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst*. 2008;100:796-804.

Strategies to Preserve Larynx Function in Patients with Head and Neck Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a randomized, phase 3 trial of two different schedules of chemotherapy and radiotherapy for patients with advanced larynx or hypopharynx cancer, no difference was observed in progression-free survival, overall survival, or the maintenance of laryngeal function. Future studies are called for to define the optimal management of patients with locally advanced head and neck cancer.*

Source: Levebvre JL, et al. Phase 3 randomized trial of larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst*. 2009; 101:142-152.

The European Organization for Research and Treatment of Cancer (EORTC) published results from its first trial addressing the issue of preservation of laryngeal function in patients with cancer of the hypopharynx, employing induction chemotherapy followed by radiation therapy in 1996.[1] That trial, comparing three cycles of cisplatin plus 5-flurouracil, followed by radiotherapy with laryngopharyngectomy alone, found that the larynx could be preserved in 42% of patients at three years, but survival between the two groups was not different. Although that trial did not include patients with laryngeal carcinoma, an earlier trial conducted by the Department of Veterans Affairs demonstrated similar findings.[2] These studies established this particular treatment strategy in an effort to preserve laryngeal function for patients with locally advanced head and neck cancer of either hypopharynx or laryngeal origin. Subsequent trials indicated that concurrent administration of chemotherapy and radiation resulted in a statistically significant improvement in larynx preservation but was associated with more serious acute toxicity and possibly long-term side effects.[3]

The currently published trial (EORTC 249540) addresses the question of whether the standard sequential (ie, chemotherapy followed by radiotherapy) could be improved upon by a slightly more complicated alternating schedule. Patients (n = 450) with resectable advanced squamous cell carcinoma of the larynx (tumor stage T3-T4) or hypopharynx (T2-T4), with regional lymph nodes in the neck staged as N0-N2, and with no metastasis, were randomly assigned to treatment in the sequential (or control) or the alternating (or experimental) arms.

In the sequential arm, patients with a 50% or more reduction in primary tumor size after two cycles of cisplatin and 5-fluorouracil received another two cycles, followed by radiotherapy (70 Gy total). In the alternating arm, a total of four cycles of cisplatin and 5-fluorouracil (in weeks 1, 4, 7, and 10) were alternated with radiotherapy with 20 Gy during the three two-week intervals between chemotherapy cycles (60 Gy total). All non-responders underwent salvage surgery and postoperative radiotherapy.

The 450 patients were randomly assigned to treatment (224 to the sequential arm and 226 to the alternating arm). Median follow-up was 6.5 years. Survival with a functional larynx was similar in sequential and alternating arms (hazard ratio of death and/or event = 0.85, 95% confidence interval = 0.68-1.06), as were median overall survival (4.4 and 5.1 years, respectively) and median progression-free interval (3.0 and 3.1 years, respectively). Grade 3 or 4 mucositis occurred in 64 (32%) of the 200 patients in the sequential arm who received radiotherapy and in 47 (21%) of the 220 patients in the alternating arm. Late severe edema and/or fibrosis was observed in 32 (16%) patients in the sequential arm and in 25 (11%) in the alternating arm.

■ COMMENTARY

Thus, with a median follow-up of 6.5 years, there was no significant difference in clinical outcomes between the two treatment groups. Larynx preservation, overall survival, and progression-free survival were similar for patients treated with sequential and alternating chemotherapy and radiation. As described in an accompanying editorial,[4] several points regarding the interpretation of this trial warrant mention. First, there remains

some discrepancy in anatomic terminology of relevance. In Europe, tumors that occur on the medial wall of the pyriform sinus are considered "epilarynx," whereas the American Joint Commission on Cancer Staging would consider these hypopharyngeal. Accordingly, such distinction would leave only 21% of the current series as laryngeal, a number that might provide insufficient power to detect treatment-related difference to a degree of statistical significance between the two treatment groups. This is particularly relevant because tumors that arise in this region (pyriform sinus) are particularly aggressive and have a propensity for distant metastases.[5]

In the interval since this study was launched, additional trials have indicated that fewer than four cycles of chemotherapy would be as likely to produce the maximal pre-radiotherapy response[3] and that the addition of a taxane would improve chemotherapy responses.[6]

Thus, there remain a number of unanswered questions regarding the optimal approach to both preserve laryngeal function and improve survival for patients with larynx and hypopharynx cancer. The EORTC 24954 trial revealed no advantage for alternating chemotherapy and radiation when compared to the standard sequence of initial chemotherapy followed by radiotherapy. Nonetheless, the trial does reinforce the feasibility of sparing of laryngeal function for a large subset of patients with these locally advanced head and neck malignancies, and highlights the need for standardization of terminology and classification. ■

References

1. Lefebvre JL, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst*. 1996;88:890-899.
2. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med*. 1991; 324:1685-1690.
3. Forastiere AA, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091-2908.
4. Forastiere AA, Trotti AM. Searching for less toxic larynx preservation: a need for common definitions and metrics. *J Natl Cancer Inst*. 2009;101:129-131.
5. Kotwall C, et al. Metastatic patterns in squamous cell cancer of the head and neck. *Am J Surg*. 1987;154: 439-442.
6. Schrijvers D, et al. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I-II feasibility study. *Ann Oncol*. 2004;15:638-645.

CME Questions

11. What were the results for high-dose lenalidomide induction followed by lower-dose maintenance for AML?
a. Two cases of AML harboring an isolated trisomy 13 achieved a complete remission
b. Complete response rates among all 33 patients was over 50%
c. A high rate of deep venous thrombosis causes study discontinuation
d. Lenalidomide represents the new standard for elderly AML

12. Pre-treatment absolute neutrophil and absolute lymphocyte counts, examined together in patients with breast cancer treated with FEC chemotherapy, were shown to be highly predictive of:
a. Febrile neutropenia
b. Schedule delays
c. Lower dose intensity
d. All of the above

13. The population-based retrospective analysis of the effects of sunitinib vs. interferon alpha treatment of metastatic renal cell carcinoma clearly demonstrated that sunitinib treatment was associated with:
a. Improved PFS and OS
b. Improved OS
c. Improved PFS, no effect on OS
d. No effect on PFS or OS

14. Compared to those with low levels of 25(OH)D, prostate cancer patients with medium or high levels were:
a. More likely to be treated with hormonal therapy
b. More likely to die from prostate cancer
c. More likely to develop a second malignancy
d. Less likely to die from prostate cancer

Answers: 11. (a); 12. (d); 13. (b); 14. (d)

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: **Statins, Stem Cells, and Cancer**

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Liraglutide: Promise of the Incretin Class

Source: Nauck M, et al. *Diabetes Care* 2009;32:84-90.

GLUCAGON-LIKE PEPTIDE-1 (GLP) IS A recently "rediscovered" endogenous hormone of the incretin class. GLP has diverse favorable metabolic effects that modulate excess glucose excursions, including enhancement of glucose-dependent insulin secretion, slowing of gastric emptying, blunting of glucagon, and increased satiety. "Natural" GLP has a fleeting (2 minutes or less) half-life, precluding its utility as a pharmacotherapeutic tool. Recently, we have captured some of the valuable activity of the incretins by employing agents that block the degradation enzyme of GLP, DPP-4. Subcutaneous liraglutide (LIR) is a synthetic GLP analogue with a half-life of 13 hours, allowing once-daily dosing.

Nauck et al performed a double-blind, controlled trial of LIR vs glimepiride or placebo added to maximum-dose metformin in more than 1000 Type 2 diabetics. Subjects were followed for approximately 6 months.

At the end of treatment, A1c reductions (about 1%) were similar for 2 different doses of LIR or glimepiride. Important differences, however, included changes in body weight and incidence of hypoglycemia. For instance, minor hypoglycemia was seen in only about 3% of LIR subjects, but 17% of glimepiride subjects. LIR was associated with modest weight loss (average 2.3 kg) compared to a 1 kg weight gain in glimepiride subjects. The most common adverse effect noted with LIR was nausea (11-19%), which has been commonly reported with another injectible member of the incretin class, exenatide. ■

Low-glycemic Index Diet in Type 2 Diabetics

Source: Jenkins DJ, et al. *JAMA* 2008; 300:2742-2753.

THE KNOWLEDGE THAT NOT ALL CARbohydrate sources provide a similar rate of glucose rise has been captured with the glycemic index metric; high-glycemic index foods (e.g., bread, potatoes, simple sugars) produce very prompt glucose rise compared with low-glycemic index items (e.g., beans, complex carbohydrate sources like cruciferous vegetables). In Type 2 diabetics, in whom first-phase insulin secretion (that component of insulin secretion intended to respond to prompt glucose rise) is lost, low-glycemic index foods are intuitively preferred. Unfortunately, confirming meaningful benefits from consumption of a low-glycemic index diet has been difficult.

In this trial, Jenkins et al studied Type 2 diabetics (n = 210) assigned to 6 months of a low-glycemic index diet or a high-cereal fiber diet. Both diets achieved A1c reduction, but the low-glycemic index diet was superior (0.5% vs 0.18%). An additional favorable effect of the low-glycemic index diet was a modest HDL increase.

Whether patients can and will sustain a low-glycemic index diet, and whether such A1c reductions will reduce diabetes-related endpoints, remains to be determined. In the meantime, there is no suspicion of any detrimental effect of the low-glycemic index diet: Most short and intermediate term data suggest salutary effects. ■

Glucose Control and Macrovascular Disease

Source: Duckworth W, et al. *N Engl J Med* 2009;360:129-139.

MOST CLINICIANS MAINTAIN A FAIRLY glucose-centric view of diabetes. That is, we have made the assumption that the most visible derangement in diabetes, hyperglycemia, is the culprit producing vascular disease. The next intuitive step is that if glucose is pathogenetic in the development of vascular disease, then glucose modulation should reduce it. Despite consistent favorable clinical trial data confirming the benefits of glucose control upon microvascular disease (retinopathy, nephropathy, neuropathy), no clinical trial (except a single trial with acarbose) has shown reduction in macrovascular risk (myocardial infarction or stroke).

The VA Diabetes Trial (VADT) follows close on the heels of the ACCORD and ADVANCE trials, which not only failed to show reductions in macrovascular disease, but in one trial (ACCORD) demonstrated increased mortality in persons with very tightly controlled diabetes.

The VADT enrolled almost 2000 veterans with Type 2 diabetes and randomly assigned them to standard vs intensive therapy. Since almost half had already sustained a CV event, other tools to reduce CV risk were already widely employed in both groups.

At the 5.6 year endpoint of the trial, the intensive therapy group attained a substantially lower A1c than the standard therapy group: 6.9% vs 8.4%. Disappointingly, there was no discernible reduction in CV risk or microvascular endpoints in this group. There was a reassuring contrast between VADT and ACCORD: No increase in mortality with tight control was seen, despite a greater incidence of hypoglycemia. Clinicians will have to rely upon diet, exercise, smoking cessation, lipid modulation, and blood pressure control to reduce CV endpoints in Type 2 diabetics. ■

Risks Associated with the Morning BP Surge

Source: Kario K, White WB. *J Am Soc Hypertens* 2008;2:397-402.

AMBULATORY MONITORING OF BLOOD pressure (BP) has demonstrated a pattern of BP change typified by an overnight reduction in BP of 10-20% and a "morning surge" in BP beginning closely around the time of awakening. Even in patients with hypertension, morning surge in BP is seen. And it's not only BP that surges in the morning: Blood coagulability, plaque vulnerability, platelet aggregability, and blood viscosity also increase at this time. Because CV events (MI, stroke, arrhythmia) also cluster disproportionately around this circadian phenomenon, experts have opined that modulation of the morning BP surge might provide benefits in clinical outcomes.

The relationship between the morning BP surge and CV risk is strengthened by the observation that it correlates with arterial wall stiffness, left ventricular hypertrophy, and carotid intima-media thickness.

Office blood pressure is typically measured several hours after the morning surge. Encouraging more widespread use of at-home BP self-monitoring is a reasonable first step to obtain more information about morning BP. Since we have not yet learned which, if any, antihypertensives might hold special benefits on morning BP, and we do not have a major clinical trial confirming risk reduction through morning BP control, we lack sufficient evidence to mandate control of morning BP surge as a specific entity at this time. ■

Simplifying Dosing for Actinic Keratoses

Source: Zeichner JA, et al. *J Am Acad Dermatol* 2009;60:59-62.

ACTINIC KERATOSES (AK) ARE AT BEST precancerous skin lesions, and at worst (a belief held by many leaders in the skin cancer field) skin carcinoma in situ. In either case, the combination of cosmetic burden, troublesome symptoms, and association with squamous cell cancer motivates their destruction. Although it is commonplace to utilize simple local destructive measures (e.g., cryotherapy) to destroy an individual lesion, it is becoming increasingly clear that field therapy (i.e., treating an entire region to include both evident and subclinical AK lesions) provides a better and more lasting service to the patient.

Imiquimod is an immune system upregulator that has shown excellent efficacy in eradication of AK. As with all other topical agents employed for this purpose, local adverse effects and complexity of dosing regimen are limitations for some patients. Typical dose regimens for imiquimod rely upon 2-3 times weekly application of 5% cream for 8-16 weeks. Less frequent dosing, if effective, would reduce cost, enhance compliance, and possibly be better tolerated.

In this small study (n = 20), subjects applied imiquimod 5% cream once weekly for 16 weeks to half of the face, and placebo to the other half. At 16 weeks, 47% of imiquimod recipients showed marked improvement or better. In contrast to 2-3 times weekly dosing regimens, local adverse effects were essentially absent.

Total clearance rates with more frequent dosing are much higher, but so are intolerance and adverse effect rates. The authors suggest that these favorable results should be stimulus for larger, longer-duration studies. ■

Aerobic and Resistance Training Effects in PAD

Source: McDermott MM, et al. *JAMA* 2009;301:165-174.

THE PRESENCE OF PERIPHERAL ARTERIal disease (PAD), confirmed by an ankle-brachial index of < 0.95, is often manifest by limitation in ability to walk, pain with walking, and limitation in performance of normal daily activities. For most patients, smoking cessation is the most important intervention. Pharmacotherapy is of limited value. Exercise training has been suggested as a method to improve oxygen utilization by the tissues and functional ability.

McDermott et al studied PAD patients (n = 156) who were randomized to aerobic training (treadmill), resistance training (weight training), or control. The treadmill group exercised 3 times weekly, beginning at a 2 mph walking speed for 15 minutes, working up to 40 minutes (with increases in treadmill speed and grade as tolerated). The resistance training group exercised 3 times weekly with knee extensions, leg presses, and leg curls. Both groups were followed for 6 months. The primary outcome was distance on the 6-minute walk.

Treadmill exercise improved the primary endpoint, but the control and resistance training groups did not significantly differ. Treadmill exercise also improved distant vascular health, as demonstrated by improvements in brachial artery flow-mediated dilation (no improvement was seen in the control or resistance training groups). ■

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Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■