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Cyclosporine for Cytopenias in Chronic Lymphocytic Leukemia

ABSTRACT & COMMENTARY

Synopsis: This report deals with the use of Cyclosporin A in 31 CLL patients with autoimmune anemia or thrombocytopenia. A response was seen in 69% of patients with anemia and 66% of patients with thrombocytopenia. They also were durable with a median duration of 10 months and occurred after a median of 3 weeks. Previous treatment with steroids, immune globulin (IVIG), or splenectomy did not affect the likelihood of a response to CsA. The most important toxicity was renal insufficiency, occurring in 19% of patients.

Source: Cortes J, et al. *Cancer.* 2001;92:2016-2022.

The management of chronic lymphocytic leukemia (CLL) can be complicated by autoimmune thrombocytopenia (ITP) and hemolytic anemia (AIHA). For those patients resistant to steroids, cyclosporin A (CsA) has provided encouraging data in case reports and small series. Cortes and associates therefore studied 31 CLL patients whose cytopenias were felt to be immune-mediated. All but 3 of the patients had received antileukemic therapy, with 15 patients exposed to 2 or more regimens. Anemia (hemoglobin < 11) was present in 52% and thrombocytopenia (platelets < 100) was observed in 94% of patients when CsA was started. The cytopenia was associated with fludarabine in 17 cases (55%).

A response was seen in 11 of 16 (69%) patients with anemia and 19 of 29 (66%) patients with thrombocytopenia. The responses were characterized as excellent in 9 anemic patients (hemoglobin rise > 3 to at least 12 g/dL) and 12 thrombocytopenic patients (platelet rise > 50 to at least 150×10^9/L). They were also durable with a median duration of 10 months and occurred after a median of 3 weeks. Previous treatment with steroids, immune globulin (IVIG), or splenectomy did not affect the likelihood of a response to CsA. CsA was effective in 76% of fludarabine-associated cytopenias and 57% of the patients without fludarabine exposure. The most important toxicity was renal insufficiency, occurring in 19% of patients.

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COMMENT BY KENNETH W. KOTZ, M

Cortes et al present what is likely the largest study of CsA for autoimmune cytopenias in CLL. AIHA is the most common hematologic autoimmune disease in CLL, occurring in 10-25% of patients, with ITP occurring in 2-5% and pure red cell aplasia being relatively rare.[1,2] Interestingly, the association of nonhematologic autoimmune disease and CLL may be overstated due to reporting biases and errors in study design.[1,3]

Diagnosing AIHA and monitoring response to therapy can be complicated by the multifactorial nature of the anemia in CLL, including therapy-related myelosuppression, marrow infiltration, and hypersplenism. Once diagnosed, the standard therapy is prednisone, usually started at 1 mg/kg daily. Responses occur as soon as 3 days or up to 3 weeks. IVIG has been recommended for patients not responding after 7-10 days,[1] but Diehl and colleagues point out that responses to IVIG are limited and may be best for those patients requiring a rapid result.[1] CsA has been recommended as second-line therapy for AIHA while reserving splenectomy for those patients with ongoing hemolysis.[1,4] Surprisingly, the data supporting the use of splenectomy for AIHA in CLL are relatively sparse.[1,3,4] Nevertheless, either CsA or splenectomy could be used in selected patients as second-line therapy.

Diagnosing ITP in CLL can be complicated by myelosuppression, marrow infiltration, or hypersplenism. Of the 31 patients enrolled, 29 had thrombocytopenia perhaps reflecting the cutoff used (platelets < 100) and the imprecise eligibility requirements ("suspected immune etiology"). Treatment of ITP in CLL starts with prednisone 1 mg/kg daily. Cortes et al report ITP responds to CsA 66% of the time. They also reference articles showing similar or better response rates to splenectomy. The choice of second-line therapy for ITP in CLL could probably be individualized.

Oncologists unaccustomed to using CsA should remember that the several available brands are not bioequivalent (although they are all spelled "cyclosporine" in the PDR). The drug should be given twice a day with the CsA level drawn right before the morning dose. Be aware that CsA levels can be measured by different assays that are in general use. Also, CsA is associated with thrombotic microangiopathy that might be confused with progressive autoimmune cytopenias. Hypertension can be managed with diltiazem, but calcium channel blockers can interfere with CsA metabolism, as does grapefruit (and grapefruit juice), which should be avoided. Remember to check for the multiple drug interactions, watch the renal function carefully, and watch for hypomagnesemia. Starting doses in the literature range from 5-8 mg/kd/d although Cortes et al used "300 mg p.o. daily" which would best be given as 150 mg every 12 hours.[1,4]

The AIHA in CLL is related to polyclonal antibodies rather than the malignant clone itself.[4] Therefore, one theory holds that AIHA occurs in CLL as the progressive immune dysregulation allows re-expression of normally suppressed auto-reactive T cells.[1,3] This may explain the association of immune complications and purine analogs, which cause prolonged lymphopenia mainly affecting T cells. It has been recommended that CLL patients recovering from fludarabine-associated AIHA not be rechallenged due to life-threatening recurrence of the hemolysis.[3,4] Because fludarabine has also been associated with ITP,[3] it is interesting that Cortes et al re-treated 3 fludarabine-associated ITP patients and report that subsequent cycles had improved platelet nadirs with CsA. Nevertheless, extreme caution should be taken when considering reexposure to fludarabine after any autoimmune complication.

Several reports, referenced by Cortes et al, have described antileukemic responses during treatment with CsA. By design, concurrent chemotherapy was not

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administered with CsA in this study. Amazingly, there were 6 responses which included a sustained (8+ months) reduction in the leukocyte count in 1 patient and transient but major improvement in measurable lymphadenopathy in 2 patients. Although treating physicians should be aware of this phenomenon, the benefit is modest in degree and duration, and standard anti-CLL therapy should be instituted concurrently if appropriate. Perhaps elucidating the mechanism of action will translate into newer therapeutic approaches. ❖

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Tumor Bed Boost After Whole-Breast Radiotherapy Leads to Improved Local Control

ABSTRACT & COMMENTARY

Synopsis: Although there have been many published reports supporting postoperative radiation therapy to optimize local control following breast conservation surgery, a consensus regarding the optimal total dose and fractionation has not been reached. The EORTC undertook a randomized trial in women with lumpectomies for stages I or II carcinoma to determine whether a boost to the tumor cavity following whole-breast radiotherapy improved local control and survival in comparison to whole-breast treatment alone. A statistically significant benefit was identified favoring the boost arm.

Source: Bartelink H, et al. *N Engl J Med*. 2001;345: 1378-1387.

The european organization for research and Treatment of Cancer (EORTC) set out to determine whether a boost dose of radiation to the excision site of T1 or T2 breast cancers offered a local control and/or survival benefit to women who were candidates for breast conservation surgery. Their starting point was 50 Gy to the whole breast, based on the earlier published results from the NSABP B06 trial. They designed a randomized trial powered with a 90% probability of detecting a 5% improvement in 10-year survival. After a median follow-up of 5 years, the data monitoring committee decided to publish its first preliminary analysis of the results based on differences in local control favoring the boost arm.

Between 1989 and 1996, 5569 women in 31 centers in 9 participating European countries had lumpectomies resulting in gross total resections of tumors which were T1-2 on palpation or mammogram. There were 5318 women whose final microscopic margins were negative, 24% of whom needed a re-excision to achieve the clean margins. Ninety-nine percent of patients had an axillary dissection performed. Postoperatively, those patients with microscopically negative margins, disease limited to one quadrant, < 70 years old, with an ECOG status < 2 were enrolled in a randomized trial evaluating the effect of a 16 Gy boost on tumor control in the breast, and on survival. Patients received 50 Gy whole-breast RT in both arms, followed by the boost in the investigational arm. All tumor specimens were reviewed in a central lab. Patients were stratified by age, menopausal status, intraductal component, tumor size, nodal status, and treating center.

Median age was 55 years (r, 23-84). Sixty-two percent of patients were postmenopausal. Twenty-one percent had nonpalpable lesions. Fifty-two percent were T1 and 48% were T2. Ninety percent were node-negative. The median number of lymph nodes dissected was 12 (r, 0-49). The intention at the time of lumpectomy was to take a 1 cm margin of normal tissue around the tumor. In general, tamoxifen was given to postmenopausal node-positive patients, and adjuvant chemotherapy was administered to premenopausal node-positive patients. According to the protocol, patients were to commence radiotherapy within 9 weeks of surgery if no chemotherapy was planned, and within 6 months of surgery if chemotherapy was given.

There were 2657 women randomized to the standard treatment arm and 2661 women randomized to the boost arm. The 2 groups were demographically similar. Median time to initiation of RT was 39 days for patients not receiving chemotherapy (r, 3-156), and 52 days for patients given chemotherapy (r, 14-468). The whole-breast RT was either via linear accelerator or cobalt unit, and the boost was accomplished with electrons, tangential photon fields, or interstitial iridium-192 brachytherapy. The boost target was 1.5 cm around the tumor resection bed unless an extensive intraductal component was noted, in which case the boost margin

was 3 cm. The median RT dose in the standard arm was 50 Gy (r, 2-73), and 66 Gy in the boost arm (r, 23-79). Treatment was prescribed to the isocenter of the fields.

Most patients were treated per protocol. Only 2% of patients in the standard arm received a boost, and 1% in the boost arm did not get a boost. For patients who were boosted, 63% received electrons, 27% photons, 8% interstitial, and 1% unknown. A total of 272 women were treated to the locoregional lymph nodes, either because their axilla was not dissected, or they had metastases to the highest lymph nodes dissected. There were 1089 patients who received RT to the internal mammary lymph nodes, although Bartelink and colleagues did not specify the number by treatment arm.

There were 479 deaths at a median follow-up of 5.1 years. Deaths from breast cancer were identical at 7% in either treatment arm. There were 291 local recurrences, including 182 (7.3%) in the standard arm, and 109 (4.3%) in the boost arm ($P < .001$). Five-year overall and distant metastasis-free survival was 91% and 87% in both groups. Among the local recurrences, 47% occurred in the tumor bed, and 9% in the lumpectomy scar. The hazard ratio for local recurrences was 0.59 with the boost. Local recurrences were lower in the boost arm in every age category. The largest clinical benefit was seen in patients < 40 years, where local recurrences occurred in 19.5% of patients in the standard arm, vs. 10.2% in the boost arm ($P = .001$). The smallest benefit was seen in the 51-60-year-old group, where there were 20% fewer local recurrences in the boost arm (P = NS). Breast cosmesis was good or excellent in 86% of patients in the standard arm, and 71% in the boost arm.

Bartelink et al concluded that the addition of a boost dose of radiation nearly halved the odds of a local recurrence, but that the absolute benefit varied with individual risk factors. A multivariate analysis determined that age < 50 years was the only factor which could be linked to the extent of the benefit afforded by the boost. They recommended that boosts be given to women < 50 years. The explanation offered in terms of why younger women benefited more from a boost than older patients did was that local control with 50 Gy alone is excellent in older patients. Finally, Bartelink et al felt that at least 10 years of follow-up was needed before any difference in overall survival emerges.

COMMENT BY EDWARD J. KAPLAN, MD

The preliminary results from this EORTC randomized trial add to our knowledge about postoperative care of the breast. By looking at the figure showing actuarial local control in the ipsilateral breast published in the article, one can see that the curves for the 2 treatment arms continue to diverge. There are 741 patients who have been followed for 8 years. Thus, it is likely that the results will remain robust as the data mature. This is in agreement with early published results from a French randomized study of 1024 women which showed that a 10 Gy boost following 50 Gy to the whole breast led to a significant reduction in local recurrences ($P = .04$).[1]

There are several interesting issues related to the way this study was conducted. First, the study excluded purely intraductal lesions, and women > 70 years were ineligible to participate per the protocol criteria, although some actually made it into the trial. Given the effect of age on the results, had there been more elderly women included, the significance of the trial results may not have held up for the entire study population. In fact, several recent retrospective studies looking at local control outcomes following breast conservation surgery also concluded that younger women, usually defined as < 35-40 years, have significantly higher local recurrence rates than their older counterparts.[2-5] Despite the fact that the boost group did better than the standard treatment group for every age level in the EORTC trial, so far there is no statistically significant difference for women > 50 years.

The techniques permitted for boosting in the Bartelink paper are also worthy of discussion since they were heterogeneous. Although Bartelink et al do not give any detail about how the location of the resection bed was determined, it was probably by clinical inspection. This sounds straightforward, but sometimes is not, especially when a surgeon has "burrowed" to the tumor and the scar is not directly over the resection cavity. Boost technique was not a significant factor in terms of local failures, according to the multivariate analysis done by Bartelink et al. Although little has been published on this topic, Frazier's recent retrospective study assessing the same 3 methods of boosting did not find any differences in local recurrence rates by method.[6]

It remains to be seen whether the local control differences will translate into a survival benefit with longer follow-up. One caveat should be borne in mind. There were 1089 patients who received treatment to their internal mammary lymph nodes, but we are not told the breakdown by treatment arm. This may be an important confounding factor since we know that IMN irradiation has been responsible for an increase in cardiac deaths in previous trials.

My overall impression of the trial results is that they lend support to the current standard of care in this country, and may help to further refine our approach. Prescribing 50 Gy to the isocenter at 2 Gy per fraction per the EORTC is essentially equivalent to my habit of

prescribing 46.8 Gy to the breast volume within the 95% isodose envelop at 1.8 Gy per fraction. Similarly, a 16 Gy boost prescribed to a point is the equivalent of a 14.4 Gy boost prescribed to the 85% isodose line. Based on the EORTC results and the other data mentioned, an area that bears further study is dose escalation in younger patients. In terms of the older age population, it is too soon to tell whether a boost can be omitted. ❖

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A Pooled Analysis of Adjuvant Chemotherapy for Resected Colon Cancer in Elderly Patients

ABSTRACT & COMMENTARY

Synopsis: The balance of chemotherapy efficacy with side effects among elderly colon carcinoma patients continues to spur debate. Results from 7 randomized trials comparing surgery alone to postoperative fluorouracil-based regimens for stage II and III colon carcinoma were pooled to investigate the presence of interactions between chemotherapy use and age. Adjuvant therapy provided a significant overall and recurrence-free survival benefit that persisted in each age category, with no reduction in efficacy among older age groups. While leukopenia was significantly increased among patients older than 70 years of age (P = 0.001 with levamisole; P = 0.05 with leucovorin), no other interaction between age and toxicity was observed. These data support the conclusion that selected elderly colon cancer patients at high risk for recurrence may experience adjuvant treatment benefits equivalent to those enjoyed by younger patients with similar disease.

Source: Sargent DJ, et al. *N Engl J Med.* 2001;345: 1091-1097.

As the post-world war ii generation ages, swelling the ranks of Americans older than age 65 by 57% between 2000 and 2025, physicians can expect to treat substantially increasing numbers of elderly patients.[1] Moreover, according to the Surveillance, Epidemiology, and End Results database of the National Cancer Institute, the largest increases in cancer incidence are occurring among older age groups. Between 1973 and 1991, for example, overall cancer incidence rates for age groups 65-74 and > 75 increased by 35% and 28%, respectively. Given these changing demographics and evidence of ongoing questions regarding age-related use of adjuvant treatment,[2] Sargent and colleagues undertook a pooled analysis of randomized trials comparing postoperative fluorouracil-based therapy for Stage II/III colon carcinoma to treatment with surgery alone, and assessing benefits and toxicities among age categories.

A systematic search of Medline and bibliographies was performed, followed by discussions with primary investigators of identified appropriate trials. Seven studies met inclusion criteria, yielding 3351 total eligible patients.[3-7] Five studies randomized patients to receive postoperative fluorouracil plus leucovorin for 1 year (4) or 6 months (1) vs. surgery alone, while 2 randomized to fluorouracil plus levamisole for 1 year. Doses of fluorouracil ranged from 370-450 mg/mL^2. Leucovorin dose was 200 mg/mL^2 in 4 studies and 20 mg/mL^2 in one study. Levamisole dose was 50 mg/mL^2 in the remaining 2 studies. All studies identified overall and recurrence-free survival as primary end points, recorded toxicities per World Health Organization or National Cancer Institute grading scale, and followed patients for more than 5 years. Patients were initially divided into age groups of equivalent size. After statistical analysis revealed identical results when divided into age groups of 10-year increments, results were reported by decade (< 50 yr, 51-60 yr, 61-70 yr, > 70 yr).

Not surprisingly, while the probability of death with recurrence of cancer was roughly equivalent among age groups (29-33%), probability of death without known recurrence monotonically increased with older age group. Among patients < 50 years of age, death rate without recurrence was 2%, contrasted to a 13% death rate in the > 70 year age group.

Studies were examined for differences in treatment effect and found to have no heterogeneity for either primary outcome. Although 4 studies did not reach statistical significance, the pooled analysis revealed improved 5-year survival rates for subjects undergoing adjuvant treatment compared with surgery alone (71% vs 64%, respectively; P = 0.001). Similarly, although 2 studies did not reach statistical significance, pooled analysis of patients in the adjuvant arm experienced improved 5-year recurrence free survival rates (69% vs 54%; P =

0.001). When stratified by age, no significant interaction between age group and primary outcome could be identified.

Because studies did show significant heterogeneity for toxicities, analyses of grade 3 or higher toxicities were performed separately for levamisole and leucovorin regimens. The only severe toxicity associated with increased age was leukopenia among patients > 70 years who were treated with either fluorouracil plus levamisole (P = 0.001) or fluorouracil plus leucovorin (P = 0.05).

Sargent et al assert that a perception of greater toxicity or poor treatment tolerance may mitigate use of chemotherapy among the elderly. Based on the data presented, they conclude that selected elderly patients at high risk for recurrence of colon carcinoma will derive the same survival benefit as younger patients, without a significant increase in treatment-associated toxicity.

COMMENT BY ARDEN MORRIS, MD

Fluorouracil-based adjuvant therapy has become the standard of care for patients with Stage III colon cancer. However, practitioners (and possibly patients themselves) have been reluctant to treat elderly patients with the same regimens as younger patients,[2] presumably due to concerns regarding decreased benefit and/or high toxicity. Furthermore, physicians may be reluctant to risk severely toxic side effects in a patient who may have a shorter prognosis simply due to advanced age. While these concerns are certainly valid in the setting of selected malignancies and regimens,[8] no evidence exists that colon tumor biology differs within different age groups. Age-related toxicity data for adjuvant treatment among colon cancer patients remains sparse. Additionally, in the face of increasing life expectancy and population growth of elderly Americans, concerns that adequately aggressive treatment may not be provided deserve attention.

Using pooled data from rigorously conducted phase III trials, Sargent et al have provided important information regarding appropriate treatment for elderly colorectal cancer patients. Overall, patients experienced no significant difference in survival benefit with increasing age. Type II error, or inability to demonstrate a significant effect where one truly exists, is a risk among underpowered studies. Sargent et al addressed this potential issue with power calculations demonstrating that the pooled data achieved 80% power to discern a significant interaction at a hazard ratio of 1.4, or a risk reduction of 40% in younger patients and no risk reduction in elderly patients. It should be noted that fluorouracil-based chemotherapy use in high-risk Stage II and Stage III colon cancer patients conferred an overall risk reduction of one third that of surgery alone, or a hazard ratio of 1.5 for those undergoing surgery alone.[5] Patient results were not stratified by stage, possibly due to issues of power loss due to decreased sample size.

Among the limitations of pooled data are potential bias due to differences in accrual, application of regimen, and follow-up techniques. Sargent et al attempted to control for these issues by communicating closely with investigators in each study included and by testing for and finding no significant heterogeneity in treatment effects. Moreover, results among the studies themselves justified pooling despite some of the protocol differences. For example, 6- vs. 12-month duration of treatment was shown to have no association with survival time.[7]

Because toxicities were significantly different among different studies, protocols using leucovorin were analyzed for toxicity separately from those using levamisole. Contrary to other chemotherapeutic regimens,[8] little significant increase in toxicity manifested as age increased. A highly significant increase in leukopenia was seen with levamisole use among patients of age > 70 years, however.

Lastly, pooled data certainly inherit limitations of the original studies. Although phase III trials are the criterion standard for controlling confounding, pragmatic issues cannot be ignored. As Sargent et al acknowledge, patients selected for these protocols met inclusion criteria that required a minimum performance status and support system. Especially among the elderly, potentially subject to higher rates of mental illness, poverty, and debilitation, these results may not be entirely generalizable but are important to consider among normally or highly functioning patients. ❖

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DNA Ploidy as a Prognostic Factor in Renal Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: Renal cell carcinoma (RCC) has an extremely variable clinical course that is only partially described by current staging and grading systems. Even in the presence of metastatic disease, some patients will have long survivals with preservation of performance status. In general, performance status and sites of metastatic disease have predicted prognosis and response to immunotherapy-based treatment regimens for stage IV disease, but the prognosis for earlier stage disease has relied heavily on tumor stage. This paper identified ploidy, carefully assessed in multiple sections of primary tumors, as a stronger independent predictor of recurrence and survival than tumor stage.

Source: Abou-Rebyeh H, et al. *Cancer.* 2001;92: 2280-2285.

Renal cell carcinoma is increasing in incidence at an annual rate of 2% worldwide and is often discovered incidentally in the absence of symptoms. One third of patients who undergo apparently curative resections will ultimately develop metastatic disease. DNA content has not previously been identified as a prognostic factor. However, these studies have been criticized because sampling methods may not have allowed for examination of all areas of the tumor. The study cited here examined 180 T1, T2, or T3 (8%, 51%, and 41% of the total, respectively) primary, nonmetastatic, fully resectable RCCs by sampling 8 different areas of the tumor for DNA ploidy. DNA content was measured in 300 tumor cell nuclei in each specimen and was defined as diploid or polyploid when it corresponded with the mean value of the standard diploid population (± 25%) or its multiple (± 25%). All cell nuclei with a DNA content outside of the diploid or polyploid ranges were termed as aneuploid. Tumors were thus classified as diploid (n = 56), polyploid (n = 20), or aneuploid (n = 104).

Of the 180 specimens, 41% were Grade I, 43% were Grade II, and 16% were Grade III. Although higher-grade tumors tended to more frequently exhibit aneuploidy, tumor grade did not reliably predict for ploidy (30%, 72%, and 100% aneuploidy for Grades I, II, and III, respectively). Ten-year survivals were available at the time of analysis and were typical for that reported elsewhere: pT1 85%, pT2 53%, and pT3 8%. However, 10-year survivals were 92%, 80%, and 0% for diploid, polyploid, and aneuploid tumors, respectively, regardless of tumor stage or grade. Univariate analysis showed that DNA ploidy, tumor stage, and tumor grade were significant predictors for tumor recurrence and progression. Multivariate analysis showed that only DNA ploidy ($P < .001$) and tumor stage ($P = .004$) were significant independent predictors of tumor progression whereas tumor grade ($P = .125$) was not.

COMMENT BY MICHAEL J. HAWKINS, MD

Since there is no adjuvant therapy that is of known benefit for patients with early stage RCC, at present the need to identify patients with greater risk of eventual recurrence is not necessarily compelling. In addition, the striking results of this study—using the extensive sampling procedures described—clearly need to be confirmed. Nonetheless, the results of this study are intriguing and could have major implications in the way these patients are managed in the future. Recent studies have shown a role for nephrectomy in patients with metastatic disease-increasing survival by 50% in selected patients. One of the more difficult clinical dilemmas in treating patients with metastatic disease is when to initiate treatment. IL-2 based regimens typically are associated with profound fatigue, loss of appetite, and decreased performance status. In patients who are feeling well, it is difficult to know when to subject them to treatment and a course of close observation to identify the aggressiveness of their malignancy is often appropriate. In the future, however, it may be possible to identify those patients whose tumors are destined to follow a more aggressive course by examining the DNA content and initiating therapy earlier for patients with aneuploid tumors. ❖

CME Questions

25. Levamisole-induced toxicity(ies) that significantly increased with increasing age include:

a. diarrhea.
b. stomatitis.
c. leukopenia.
d. All of the above

26. Nonmetastatic, fully resectable renal cell carcinomas with diploid DNA content were associated with a 10-year survival of ___% regardless of tumor stage.

a. > 90%
b. 70%
c. 50%
d. 25%

27. Which of the following is true?

a. Rechallenging CLL patients with fludarabine-associated cytopenias is safe.
b. In CLL, cyclosporine for autoimmune cytopenias will likely not be effective after splenectomy.
c. The malignant clone in CLL secretes monoclonal antibodies that recognize auto-antigens.
d. An important side effect of cyclosporine is renal insufficiency.

28. In the EORTC plus breast boost trial:

a. patients were ineligible for the study if there was invasive tumor at the surgical margin, but remained eligible if there was intra-ductal carcinoma at the margin.
b. patients in every age category benefited from a boost to the tumor bed.
c. those patients boosted with electrons did significantly better than patients whose boosts were administered by other means.
d. disease-free survival, but not overall survival, was shown to be better in the boost arm.

29. Which of the following is *false* concerning the EORTC plus breast boost trial?

a. Patients could receive their whole-breast radiotherapy on a cobalt unit.
b. Patients could receive their breast boost with interstitial iridium-192.
c. Patients could receive their breast boost up to 18 months post surgery.
d. Patients could receive radiotherapy to their regional lymph nodes if indicated.

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Expert Answers to Your Most Vexing Oncology Coding Questions

Medical Radiation

Question: *May we bill for the technical component with 77300-77334? If so, what documentation do we need?*

Colorado Subscriber

Answer: A number of services are included in 77300-77334 (*medical radiation physics, dosimetry, treatment devices, and special services*), and all of them include a professional and technical component.

Following is key information for documenting the facility component. Code 77300 (*basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, as required during the course of treatment, only when prescribed by the treating physician*) defines basic radiation dosimetry calculations, and the technical component of this service is represented by a calculation sheet(s) completed by the dosimetrist and/or physicist.

The radiation oncologist must sign and date these calculations. Signing and dating the calculation sheet serves to bill the professional component of the services and to document that the calculations were used for patient treatment, which justifies the facility technical component billing.

Special dosimetry (77331) must be ordered in writing by the radiation oncologist and be medically necessary to be reimbursed. Documentation must include a report listing the method of special dosimetry employed (microdosimetry, diodes, etc.), which is signed and dated by the physician and physicist.

Codes 77305-77328 represent isodose plans created by the physics department at the request of the radiation oncologist, and are signed and dated by both the physicist and the physician. Documentation for the external beam isodose plans (77305-77315) and the brachytherapy isodose plans (77326-77328) is included in the patient record in the form of a printout that includes dose distribution information.

The special teletherapy isodose plan is similar to the special dosimetry service because it also requires a special patient-specific report requested by the radiation oncolo-gist and completed by the physicist. This service is generally medically necessary when special beams, such as electrons, are used for all or part of the treatment.

Codes 77332-77334 define treatment devices and are a documentation challenge for many facilities and professional practices. The simulation films will include physician drawings of devices to be constructed, but it is often difficult to produce legible copies of these films in an audit. As a result, facilities should include a "treatment device" form in the patient chart to record blocks constructed, as well as the use of wedges, boluses and patient positioning devices.

Treatment device documentation is widely audited by Medicare and commercial or managed care insurers, primarily due to the lack of medical records in many patient charts. One difference between facility and professional reimbursement for this service is that the facility is generally paid for each device constructed, but the physician may be reimbursed for each design completed.

Physicians can include device design information in the treatment plan, simulation or progress notes. This is one area of radiation oncology where the facility and physician may desire to capture and maintain separate documentation, because the service

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is reimbursed differently to each entity. Individual payer policies vary, so make sure to verify policy with local payers for all services. ❑

Blood Draws

Question: *Can a physician's office bill for a blood draw if it is done by a nurse employed by a hospital and not by the physician who ordered the procedure?*

Maine Subscriber

Answer: No. A practice may only bill for work performed by employees of the office and for supplies that they have purchased.

A good rule of thumb is that if the service did not represent an expense to the practice, it should not be billed. However, if the service was performed in the office by a nurse under the direct supervision of a physician, you may be able to bill.

More specifically, blood draws can be tricky. How a practice codes for them depends largely on whether it has its own laboratory or sends the specimen or patient to an outside lab.

Outside laboratory for blood draw and testing. If the patient is sent to an outside lab for blood draw and testing, the physician cannot bill for either procedure. However, if the test was ordered during a visit related to chemotherapy treatment, the practice can code the E/M service that describes the follow-up visit.

Collect specimen for testing at outside laboratory. Although testing is done by an outside laboratory, practices can bill for drawing blood. Most Medicare carriers allow for only one collection fee for each patient encounter, regardless of the number of specimens drawn. When a series of specimens is required to complete a single test, such as glucose tolerance (82951-82952), the series is treated as a single encounter.

Commercial insurers generally recognize 36415 (*routine venipuncture or finger/heel/ear stick for collection of specimen[s]*) for these services. Medicare, however, created G0001 (*routine venipuncture for collection of specimen[s]*), which replaces 36415 and prevents billing for minimal specimen collection costs (finger stick, throat culture, etc.).

Some carriers may not allow 36415 to be billed separately from an E/M visit and may bundle the blood draw into the office visit (99211-99215). Check with your individual carriers.

Collection and testing performed in the office. If the practice has a lab to perform a blood test such as a complete blood count (85022-85025), the specimen collection (36415 for non-Medicare, G0001 for Medicare) and the blood test may be billed. Again, some payers may bundle the collection code with the testing codes.

— *Answers to* You Be the Coder *and* Reader Questions *provided by* ***Elaine Towle, CMPE,*** *administrator for New Hampshire Oncology and Hematology in Hooksett, NH; and* ***Cindy Parman, CPC, CPC-H,*** *principal and co-founder of Coding Strategies Inc. in Dallas, Ga.* ❑

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