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INSIDE

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Dasatinib Highly Effective for Imatinib Intolerant/Resistant CML

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD, MS

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

Synopsis: *The prognosis for CML blast crises remains poor even with imatinib therapy. Dasatinib is an oral multi-targeted tyrosine kinase inhibitor of BCR/ABL and Src with clinical activity against imatinib-resistant CML. Cortes and colleagues report preliminary phase II data pooled from two studies of dasatinib for imatinib resistant or intolerant CML in either myeloid blast crises (MBC) or lymphoid blast crises (LBC). Among the 116 patients, 64% had MBC and 36% had LBC. Dasatinib induced major hematologic responses in 34% and 31% of MBC and LBC, respectively. Major cytogenetic responses were achieved by 31% and 50% of MBC and LBC, respectively. At 8 months of follow-up, 88% of MBC and 46% of LBC maintained their responses. Cytopenias and GI toxicities were common. Six percent had serious pleural effusion. Dasatinib is active for imatinib resistant or intolerant blast crises CML. Longer term follow-up data is needed to determine the response duration.*

Source: Jorge Cortes, et al. *Blood.* 2007; 109:3207-3213.

Chronic myeloid leukemia (CML) has become the prototypical disease for targeted therapy. The BCR/ABL fusion protein derived from a translocation between chromosomes 9 and 22 has been successfully targeted using Imatinib (Gleevec™).[1] The large randomized IRIS study, confirmed significantly enhanced activity and reduced toxicity compared to interferon,[2] moving imatinib to front-line therapy for CML.

Nevertheless, imatinib resistance can emerge, often due to point mutations in the BCR/ABL[3] and less often through the Src kinase pathway. Resistance is particularly problematic in advanced stages of CML and the prognosis remains dismal. Although Imatinib achieves hematologic responses in over 50% of imatinib naïve

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CML blast crises patients, cytogenetic responses are uncommon and relapse is the rule.[1]

New more potent inhibitors of BCR/ABL hold promise to be effective against BCR/ABL mutations conferring imatinib resistance. The two drugs most advanced in clinical development are dasatinib (Sprycel, formerly BMS-354825) and nilotinib.[4,5] Point mutations at T315I remain resistant.

Cortes and colleagues report the preliminary results of dasatinib for imatinib intolerant or resistant blast phase CML. These data were pooled from two phase II open label international trials of dasatinib for myeloid blast crises (MBC) and lymphoid blast crises (LBC).

Imatinib resistance required progression to blast crises from chronic phase on at least 400 mg daily or from accelerated phase on at least 600 mg daily. Alternatively, patients may have been intolerant to these doses.

Standard response definitions were employed. Specifically, cytogenetic responses were defined by the percent of Philadelphia positive metaphases from the bone marrow. Cytogenetic responses were evaluated by once-monthly bone marrow aspirates/biopsies for the first 3 months and every 3 months thereafter. Complete cytogenetic response (CyR) mandated 0% Philadelphia Chromosomes, whereas 1-35% defined partial CyR. Major CyR encompassed those having a complete CyR or partial CyR.

The initial Dasatinib dose of 70 mg orally twice daily could be escalated to 100 mg twice daily for poor response or could be reduced for toxicity. Treatment continued until disease progression or toxicity. No other disease treatment was permitted except for supportive care which included anagrelide or temporary hydroxyurea.

Among the 116 patients, 74 had MBC and 42 LBC. Data were presented for 6 month and 8 month follow-up. Most were enrolled for resistance (91%), rather than intolerance. The median age was 47 years and 33% had a prior stem cell transplant.

In the MBC cohort, major hematologic responses at 8 months occurred in 34%. Major CyR were induced in 31%, with the majority being complete CyR (27% of all MBC patients). Among the LBC patients, 31% achieved a major hematologic response. Dasatinib induced a major CyR in 20/42 (50%) of LBC patients, most of which were complete CyR (18/42, 43% of total LBC cohort).

Mutation analysis found imatinib point mutations in 30/70 evaluable MBC patients and 24/40 evaluable LBC patients. Combing both MBC and LBC groups, no responses occurred in the six patients harboring E255K mutations or the eight found to have T315I mutations.

At the 8-month follow-up, 11% of MBC-CML patients discontinued therapy related to toxicity although dose interruptions occurred in 64%. Among LBC-CML patients, one patient discontinued therapy because of toxicity and dose interruptions occurred in 33%. Gastrointestinal disorders (including diarrhea, nausea, vomiting) were the most frequent events in both cohorts. Pleural effusions occurred in 31/116 (27%) of which 6% were at least grade 3. Cytopenias were common but drug related attribution was difficult as many patients had baseline cytopenias.

COMMENTARY

Even in the era of imatinib, blast crises developing on imatinib or de novo has a dismal prognosis. Allogeneic transplant and/or chemotherapy also lead to disappointing results. Imatinib resistance is the major cause of failure often mediated through BCR/ABL point mutations. Thus, more potent inhibitors of BCR/ABL hold promise for imatinib resistant (and intolerant) CML.

In this preliminary report of 116 patients having either myeloid (MBC) or lymphoid blast crises (LBC) CML, dasatinib induced hematologic remissions in approximately 1/3rd of patients with complete cytogenetic remissions in over 1/4th. Remissions occurred within 1-2 months of treatment and many were maintained (especially in MBC) at 8 months follow-up. These patients were heavily pre-treated, including a considerable number of prior stem cell transplants.

The results of BCR/ABL mutation analysis were

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informative. Activity occurred despite BCR/ABL point mutations. Mutations at T315I and E255K, however, were exceptions where no responses occurred. Nevertheless, in a considerable fraction, BCR/ABL mutations were not detected. This may relate to resistance mediated by another kinase pathway, such as Srk, which dasatinib also inhibits.

Dasatinib was generally well-tolerated. Serious toxicity leading to drug discontinuation only occurred in 1 patient. Toxicity did not appear greater in the imatinib intolerant cohort, suggesting these agents may have non-overlapping toxicity. Importantly, pleural effusions were relatively frequent and 6% were considered at least grade 3. The toxicity profile including pleural effusions was similar to prior reports.[5]

This study presents a compelling rationale for dasatinib in imatinib intolerance or resistant blast crises CML. A major limitation is the short study duration which precludes data on long-term response durability. Thus, it remains prudent to consider an allogeneic transplant in appropriate candidates if one can achieve a hematologic if not cytogenetic response. However, most patients will not be candidates for transplant or lack donors. The best strategy for imatinib naïve blast crises CML also remains unclear. While the standard approach has been imatinib at 600 mg daily, the lack of durable responses employing imatinib raises the question whether dasatinib might be better initial therapy. An important unanswered question is how dasatinib compares to nilotinib, another highly potent oral BCR/ABL inhibitor in late clinical development. Cytopenias are common with both drugs but otherwise the toxicities profiles differ. Unfortunately, neither agent shows activity against the T315I. Nilotinib may lead to elevated bilirubin and rashes.[4]

The activity of dasatinib also raises interest in upfront treatment for chronic or accelerated phase CML. Both nilotinib and dasatinib are being actively investigated for earlier stage CML as initial therapy and/or imatinib resistant/intolerant disease. Dasatinib may have serious toxicities, including pleural effusions, and we lack long-term follow-up data. In the IRIS study of chronic phase CML, most patients randomized to imatinib remained on imatinib at 5 years. Further, many cases of imatinib resistance can be salvaged with Dasatinib. Therefore, imatinib remains the initial therapy for most CML patients, especially those with chronic phase. The rapid emergence of cytogenetic and molecular monitoring of imatinib as well as progress in understanding the molecular pathogenesis of drug resistance should enable earlier transition to active agents rather than waiting for morphologic disease progression.

In summary, dasatinib is effective and well-tolerated for imatinib resistant/intolerance blast crises CML but long-term responses remain unknown. ■

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Doxil Maintenance of Ovarian Cancer Remission

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *There is emerging evidence that maintenance chemotherapy is of value for ovarian cancer patients after surgery and remission-induction chemotherapy. Paclitaxel remains effective in this capacity but has cumulative toxicity. In this report, experience with long-term pegylated doxorubicin (Doxil®) administered monthly for up to 5 years is reported in 16 patients. In general, treatment was well tolerated, without cumulative myelotoxicity or cardiotoxicity (with one exception). Thus, Doxil® may prove a useful agent for maintaining ovarian cancer remission.*

Source: Andrepoulou E, et al. Pegylated liposomal doxorubicin HCL (PLD; Caelyx/Doxil®): Experience with long-term maintenance in responding patients with recurrent epithelial ovarian cancer. *Ann Oncology.* 2007;18:716-721.

Pegylated liposomal doxorubicin (Doxil) has significant antitumor activity when administered to ovarian cancer patients.[1,2] In the current report, a retrospective review, Andreopoulou and colleagues from New York University examined the role for this drug in long-term maintenance after initial treatment with a platinum-based regimen. Their experience with 16 patients who received Doxil for greater than one year for either ovarian (n = 14) or fallopian tube (n = 2) cancer is described. All 16 patients had either stable disease or objective tumor regression with prior doublet treatment either as initial or secondary therapy. Doxil (30 to 40 mg/m2) was administered every four to eight weeks, indefinitely. This analysis was primarily to assess the safety and tolerance of such an approach.

In this regard, the investigators noted a lack of evidence for cumulative myelosuppression and, with one exception, cardiac toxicity. One patient required hospital-

ization for cardiogenic shock, which occurred during a period of neutropenic sepsis associated with topotecan treatment 10 months after the Doxil maintenance had been discontinued. The other 15 patients did not have any evidence of acquired cardiac dysfunction. Seven of the 16 patients continued to receive Doxil maintenance therapy with a median cumulative dose of 1680 mg/m2 (range 1180 to 2460 mg/m2). Of the seven, four had tumor relapse after three to six years of maintenance therapy, but this occurred during a time when the interval had been stretched typically because of cutaneous toxicity. In these patients, maintenance Doxil was reinstituted after "reinduction" with a platinum-based regimen.

Some level of skin toxicity was evident in all treated patients. However, rarely did it exceed a low level (grade 1). Most commonly observed was the well-described palmar-plantar erythrodysesthesia. In addition, some patients experienced rash elsewhere while others developed increased pigmentation. If skin toxicity exceeded grade 1, dosing interval was increased by one week. The analysis revealed that during the second year and in subsequent years, the dosing intervals were adjusted, primarily on the basis of patients' convenience but did not exceed eight-weeks.

It is notable that patients did not require antiemetic or steroid premedication during treatment. Thus, during the maintenance phase, Doxil monotherapy was well tolerated with no grade 4 toxicity, two grade 3 neutropenias, one grade 3 mucositis, and one grade 3 diarrhea. As noted, there was no observable change in cardiac function in 15 of the 16 patients.

COMMENTARY

Induction chemotherapy with platinum-based regimens results in a high response rate, but unfortunately, the majority of patients relapse within two years. Impetus for sustained treatment in patients with ovarian cancer has recently been gained by the Southwest Oncology Group/Gynecologic Oncology Group (SWOG-GOG) study demonstrating 12 cycles of intravenous paclitaxel administered every 28 days after achieving a clinical remission resulted in a seven-month improvement in median progression-free survival compared with those received only three cycles of paclitaxel.[3] In fact, further analysis reveals that those who achieve the lowest CA125 level after induction chemotherapy may be precisely the ones who benefit most from sustained treatment.[4] Paclitaxel, however, over the long term is associated with a cumulative toxicity, most notably neurotoxicity. Doxil, on the other hand, may be particularly suitable for long-term maintenance therapy inasmuch as it may be administered at longer intervals and is less likely to be associated with cumulative myelosuppression or other toxicities. Cardiac safety of course is of concern for any anthracycline. However, preclinical and clinical investigations have indicated the safety of the pegylated formulation. For example, data from a series of patients with AIDS-related Kaposi's sarcoma indicated some patients may tolerate cumulative Doxil doses up to 2360 mg/m2 over a five-year period with no decrement in cardiac function.[5] When compared to doxorubicin, Doxil was found to be less cardiotoxic when treating breast cancer.[6]

In this study, long-term monthly doses of Doxil proved well tolerated and safe. Although this was an observational study and not a clinical trial, the data is encouraging in that years (rather than months) of therapy were described. Certainly, there would seem enough here to warrant a clinical trial in which pegylated liposomal doxorubicin, administered indefinitely, is compared to a limited paclitaxel maintenance schedule for patients in complete remission after induction chemotherapy for ovarian cancer.

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An Analysis of Primary Hormonal Therapy without Surgery for Elderly Patients with Operable Breast Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *A meta-analysis of existing data on the primary management of operable breast cancer in elderly women demonstrates that when the approach is hormonal (tamoxifen) rather than surgery, local recurrence is higher. Overall survival, however, was not different.*

Source: Hind D, et al. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. *Br J Cancer.* 2007;96:1025-1029.

THE STANDARD OF CARE FOR EARLY-STAGE BREAST CANcer in women of all ages has been well established to include surgery with or without adjuvant radiation, chemotherapy, or hormonal therapy. In this country, primary endocrine therapy is not typically considered an option.

However, in the UK there is a growing trend towards treating women over 70 years of age with primary endocrine therapy. Over 40 percent of women over the age of 70 in the UK, with breast cancer, are being treated with primary endocrine therapy. The justification advanced is that surgery for breast cancer, especially when it includes axillary node dissection, is associated with a high morbidity and negative impact on overall quality of life, whereas the natural history of breast cancer in older women is often indolent.[1] However, the duration of local disease control has been demonstrated to be shorter than with surgery, and it is not unusual that surgical intervention is ultimately required.[2]

This study was designed to compare the overall survival (OS) and progression free survival (PFS) of surgery with or without endocrine therapy to endocrine therapy alone. The Cochrane Breast Cancer Group Specialized Register served as the database for seven eligible randomized controlled trials included in this meta-analysis. Six of these trials had published outcome data. Three of the trials were surgery vs primary endocrine therapy, and three were surgery plus endocrine therapy vs primary endocrine therapy; only one of these studies reported estrogen receptor status of the tumors. Tamoxifen was used as the endocrine therapy in all of the trials. When surgery alone was compared to primary endocrine therapy, there was no significant difference in the OS (HR 0.98, 95% CI 0.74-1.30, $P = 0.9$), but there was a significant difference in the PFS (HR 0.55, 95%CI 0.39-0.77, $P = 0.0006$). Similar results were seen in the surgery with endocrine therapy group vs primary endocrine therapy, with no significant difference in OS (HR 0.86. 95%CI 0.73-1.00, $P = 0.06$), but a significant difference in the PFS (HR 0.65, 95% CI 0.5300.81, $P = 0.0001$). This study demonstrates that although surgery (with or without endocrine therapy) may have comparable overall survival to primary endocrine therapy, primary endocrine therapy does not provide the same level of local control of breast cancer. Further trials addressing the hormone receptor status and using other forms of endocrine therapy such as aromatase inhibitors are needed to evaluate the appropriateness of primary endocrine therapy in older women.

COMMENTARY

The results of this meta-analysis will come as a surprise to few U.S. oncologists. It makes sense that primary endocrine therapy would be less effective at local control than surgery and also that overall survival may be no different. When it comes to patient management, U. S. surgeons and oncologists are often very conservative. One needs only to remember how long it took (nearly a century) to adopt the modified rather than radical mastectomy as the primary surgical approach for resectable breast cancer. Once again, it is a matter of local control, and this time, the meta-analysis would seem to favor the more aggressive, surgical approach.

Yet, optimal therapy for elderly patients with small, hormone receptor positive cancers remains to be defined. Like so many issues in geriatric medicine, patient heterogeneity presents problems when it comes to generalizing "standard" approaches. Women at the age of 70 may be very healthy, and for them optimal primary breast cancer therapy should probably be no different than younger patients. However, for those with substantial comorbidity, survival may be more a function of other factors and minor differences in the success of primary breast cancer management of lesser importance. For these patients, the risks of surgery, albeit typically minimal, may be exaggerated and the local control provided by tamoxifen or other hormonal approach may be an excellent choice. One thing that geriatricians emphasize in examining issues relevant to older patients is that patients should be examined in the context of functional status and not chronological age. The study that needs to be done (not included in the current meta-analysis) would be an assessment of primary hormonal therapy vs surgery in those post menopausal patients with 2 or more comorbidities associated with limitation in one or more of the activities of daily living. My guess is that hormonal therapy might come out on top in that trial. ■

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CML Blast Crisis: Imatinib Plus Chemotherapy Effective for Some

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a series of 16 patients with CML blast crisis, treatment mitoxantrone, etoposide, and imatinib on four different schedules was studied in a phase I/II trial. The regimens were well tolerated and although median survival was only 6.4 months, all those on the more intensive schedule met criteria for hematological response and six patients ultimately received allogeneic stem cell transplant and four of these remain alive at the time of publication.*

Source: Fruehauf S, et al. *Cancer.* 2007;109:1543-1549.

TREATMENT OF BLAST CRISIS REMAINS A MAJOR challenge. In the current report, Fruehauf and col-

leagues describe their experience in a phase I/II trial in which patients were treated with imatinib, mitoxantrone, and etoposide using four different treatment schedules. In each schedule, the mitoxantrone dose was 10 mg/m2 per day and the etoposide was 100 mg/m2 per day. The mitoxantrone and etoposide were administered on days one and two (schedule I) or days one, two, and three (schedule 2). Imatinib 600 mg per day was initiated on day 15. Schedules three and four were analogous with regard to mitoxantrone and etoposide, but the imatinib was administered from day one. After hematologic reconstitution (following the cytopenic phase) cytarabine was given at a dose of 10 mg/m2 per day in addition to the daily dose of imatinib.

There were 16 patients enrolled in this study. The majority had been treated with interferon or hydroxyurea during the chronic phase and only two had received prior imatinib. At the time of diagnosed blast crisis, the median age was 60 years (range 37 to 75 years) and the median time from diagnosis of CML diagnosis to enrollment was five months (range 1 to 23.6 months). Five patients had received prior treatment for blast crisis; each with a cytarabine-based regimen.

The treatment regimen was generally well tolerated by most patients. However, as expected, pancytopenia was commonly observed and platelet and red cell transfusions were required. The patients who received imatinib on day one (cohorts 3 and 4) had significantly longer duration of severe neutropenia. There were two treatment-related deaths; one secondary to pneumonia and the second due to intracranial hemorrhage.

The median survival was 6.4 months, comparable prior reports of imatinib used as a single agent alone for blast crisis.[1] Hematologic responses with normalization of the white blood count and reduction of the bone marrow blast percentage to less than 5% was observed in six of nine patients in cohorts 1 and 2 and in seven of seven patients in cohorts 3 and 4. Two of the nine patients in cohorts one and two and four of the seven patients in cohorts three and four went on to receive allogeneic stem cell transplant. Four of the transplanted patients remained alive and in complete remission at the time of this publication (range 16 to 31 months).

COMMENTARY

The combination of mitoxantrone, etoposide, and imatinib appeared to be well tolerated in patients with blast crisis CML. Although those who received imatinib starting on day one had more profound cytopenia, they also appeared to have higher hematologic response rates. Yet, the overall median survival of 6.4 months was disappointing although four of the six transplanted patients remain alive and in remission.

The trial was initiated at the time in which imatinib was not standard of care for chronic phase CML and for most, this was their first exposure to this agent. Perhaps the success at producing hematologic response will be less on the basis of developed imatinib resistance. In this regard, the newer tyrosine kinase inhibitors, such as nilotinib[2] and dasatinib[3] may be more suitable for the initial blast crisis combination with mitoxantrone/etoposide or other chemotherapy agents.

Although the role for allogeneic stem cell transplant for individuals with CML in chronic phase remains controversial for those in blast crisis, if patients are suitable candidates with regard to physiological status and limited comorbidities, this approach is likely to offer the best chance for long term survival. ■

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Dose Dense CHOP: Not for Everybody

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Dose-dense CHOP chemotherapy was compared with standard CHOP for patients with aggressive non-Hodgkin lymphoma. For young patients with low-intermediate risk disease there was improvement in response rate and survival. However, for other groups, no advantage was demonstrated. Toxicity was greater in the dose dense regimen, but treatment related mortality was comparable.*

Source: Verdonck LF, et al. *Blood.* 2007;2759-2766.

There had been sustained efforts over the past few decades to enhance overall response and cure rates for patients with non-Hodgkin's lymphoma (NHL) by modifying the standard CHOP chemotherapy approach. Verdonck and colleagues in the Dutch Belgian Hemato-Oncology Cooperative Group (HOVON) report the results of one such effort, a phase III trial of dose intensified cyclophosphamide and doxorubicin with added granulocyte colony stimulating fac-

tor (G-CSF) in young patients with intermediate risk aggressive NHL. For this, previously untreated patients between 16 and 65 years of age ($N = 513$) with untreated aggressive NHL according to the intermediate or high-grade Working Formulation (groups D, E, F, G, and H) and an intermediate risk profile according to the HOVON criteria, were included in the study. The intermediate risk profile was defined as either stage II disease with serum lactate dehydrogenase (LDH) levels greater than 1.5 times the upper limit of normal, or as stage III or IV disease with LDH levels less than 1.5 times the upper limit of normal. The patients were randomized to receive either standard CHOP (CHOP 21) or the intensified CHOP regimen (I-CHOP). The standard regimen included cyclophosphamide (750 mg/m2), doxorubicin (50 mg/m2), and vincristine (2 mg) on day one and prednisone (100 mg orally) given on days one to five. The patients were treated every three weeks for a total of eight cycles. The experimental intensive approach included cyclophosphamide (1000 mg/m2), doxorubicin (70 mg/m2), and vincristine (2 mg) on day one and prednisone (100 mg orally) given on days one to five. G-CSF at a dose of 5 mcg/kg was given subcutaneously from days two to 11 in the intensive arm only. The patients were treated every two weeks for six cycles. The treatment was designed to offer the same total amount of cyclophosphamide and doxorubicin in 12 weeks in the intensive regimen compared with 24 weeks in the standard regimen, thus doubling dose intensity without increasing cumulative dose. A standardized dose modification scheme was implemented as well. Although there was a tendency in favor of the intensive regimen for better overall, disease-free and event-free survival, the differences did not reach a level of statistical significance. However, when the intermediate risk group was divided into low-intermediate and high-intermediate risk according to the International Prognostic Index (IPI), low intermediate risk patients had improved six-year overall survival (67% vs 52%; $P = 0.05$), disease free survival (58% vs 45%; $P = 0.06$), and event-free survival (41% vs 30%; $P = 0.21$) when they were treated with intensive regimen compared with standard. In contrast, those in the high intermediate risk received no benefit from the intensive regimen. The toxicity was greater in the intensive regimen; however, treatment-related mortality was similar.

COMMENTARY

CHOP chemotherapy has been the standard approach for aggressive NHL for close to three decades, but over this period there have been efforts to improve upon the regimen to gain better response rates and cures. These efforts, however, have not met with much success, with the exception of the addition of anti-CD20 (rituximab) to CHOP, which has been demonstrated to enhance response rates and overall survival in elderly patients.[1] The current trial, which recruited patients before rituximab became standard, examined the popular notion that shortening the overall treatment time by making cycles more frequent and at higher dose (ie, increasing dose density) would be associated with more favorable outcomes. These data suggest that I-CHOP might be preferable to standard CHOP for a subset of patients with aggressive NHL (ie, younger patients with low-intermediate-risk[2]). This is similar to the study conducted in Germany and reported by Pfreundschuh et al[3] in which dose density was achieved by comparing shortened CHOP interval (21 day vs 14 day) but using standard drug doses. As with the current study, a survival advantage was demonstrated for young patients with low-intermediate risk NHL when treated on the more intensive schedule.

Thus, it appears that the more intensive (dose dense) CHOP regimen may be the optimal choice for this particular subset of patients. However, it remains to be demonstrated whether dose density favorably influences rituximab-CHOP (R-CHOP) to the same extent. Trials currently underway will soon provide the answer. In the meantime, standard R-CHOP remains the standard. It's been difficult to improve responses beyond what this regimen achieves. ■

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CME Questions

17. In this study of dasatinib for imatinib intolerant and resistant blast crises CML, what did the authors find?

a. dasatinib leads to hematologic responses and cytogenetic responses in some patients
b. BCR/ABL mutations at T315I showed excellent response to dasatinib
c. allogeneic transplant was superior to dasatinib
d. no patients achieved a complete cytogenetic remission

18. The use of pegylated doxorubicin (Doxil®) for ovarian cancer remission maintenance was shown to be limited by:

a. cumulative cardiotoxicity

b. cumulative myelotoxicity
c. progressive cutaneous toxicity
d. none of the above

19. For the primary management of breast cancer in women over the age of 70 years, meta-analysis of existing data suggests that tamoxifen alone (without surgery) resulted in:
a. better local control
b. comparable local control
c. comparable overall survival
d. worse overall survival

20. The combination of imatinib, etoposide and mitoxantrone, used in combination for blast crisis CML was shown by Fruehauf and colleagues to be:
a. ineffective
b. effective in producing hematological responses in the majority of patients.
c. effective in producing molecular remissions in 50% of patients
d. effective in producing hematological responses in the majority of patients but treatment-related mortality precludes its widespread use

21. Dose-dense CHOP was demonstrated by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) to provide survival advantage to which group of NHL patients:
a. elderly (over the age of 70 years)
b. young patients with low-intermediate risk (IPI)
c. young patients with high-intermediate risk (IPI)
d. all of the above

Answers: 17 (a); 18 (d); 19 (c); 20 (b); 21 (b)

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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:

Lung Cancer Screening

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.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■