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Percutaneous Intra-Tumoral Oral Injection of Cisplatin Gel Can Achieve Local Control of Lesions in the Liver

ABSTRACT & COMMENTARY

Synopsis: The most common life-threatening manifestation of cancer is disease involving the liver. Barring surgery, there is no single predominant technique that offers durable local control in patients with unresectable malignant lesions in the liver. This study from Europe has reported the results of a Phase II trial evaluating CT-guided intralesional injections of chemotherapy. They found that achieving local control is possible in both cohorts studied, including primary hepatocellular carcinoma patients and metastatic colorectal carcinoma patients.

Source: Vogl TJ, et al. *Br J Cancer.* 2002;86:524-529.

Vogl and colleagues at the university of frankfurt reported on results of their Phase II trial of percutaneous injections of cisplatin gel into primary hepatocellular carcinomas (HCC) and metastases from colorectal cancer (CRC). Seventeen patients participated in the study, all of whom had biopsy-proven progression of their liver disease following other treatment, including systemic chemotherapy, chemoembolization, and liver resection. No patient had evidence of extrahepatic disease, and no patient had > 3 liver lesions. There were 9 patients with 13 unresectable lesions from primary hepatocellular carcinoma, and 8 patients with 17 unresectable colorectal metastases. The average age was 67 years (range, 39-79), and there were 13 males and 4 females.

The injected agent consisted of cisplatin in a biodegradable bovine collagen carrier gel matrix, along with epinephrine used as a vasoconstrictor to keep the cisplatin from dispersing away from the injection site through local blood vessels. Each patient was hydrated prior to being injected. The number of injections per patient depended on the size of the lesions and the patient's overall condition. Up to 4 weekly administrations were used per injection cycle, with a maximum of 40 mg of cisplatin in 10 cc of gel per session. The HCC patients aver-

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INSIDE

aged 3.1 injections (range, 1-4) and the CRC patients averaged 5.1 injections per patient (range, 1-8). A 19.5 gauge CT-guided needle with 6 side holes was used for injecting, and the various localizations per lesion were manipulated through a CT guidance system. Either 1 or 2 injection cycles were carried out, at the discretion of the physician. Responses were assessed by CT imaging at 2 weeks, 8 weeks, and 6 months, and by examination or phone interview every 3 months thereafter.

Initial median tumor volume in the HCC patients was 16 cc (range, 1-113 cc), and 107 cc in the CRC patients (range, 2-125 cc). Tumor volumes were further broken down into viable and necrotic components by CT volumetric evaluation.

Local control, defined as complete inactivity of the treated lesion at 3 and 6 months, was established in 70% of HCC lesions treated, and 38% of CRC lesions. Despite this, the volume of viable tumor in the liver did not drop significantly in either group. There were no reported cisplatin toxicities, and the treatment was well tolerated. Some patients exhibited transient subclinical elevations in their liver enzymes. Median survival for the entire group was 10.1 months. All except 2 patients died of overall disease progression by the conclusion of the study.

COMMENT BY EDWARD J. KAPLAN, MD

Available modalities for palliation of malignant disease in the liver include systemic chemotherapy, chemoembolization, ethanol injections, radiofrequency ablation, and laser thermotherapy. Cryotherapy has also been used, as has intrahepatic arterial and intralesional administration of radioactive microspheres. Vogl et al took an approach previously reported by them for palliation of head and neck lesions,[1] and applied it to palliation of liver tumors. The advantages of this type of local chemotherapy administration are: 20-30 times higher cisplatin concentrations than that achievable with systemic administration, direct injection of every segment of a lesion regardless of its perfusion by vessels, and slow dispersion of cisplatin from the injection site. The latter is due to reduced blood flow as a result of the epinephrine in the gel, as well as tumor vessel compression by the gel bolus, and tumor vessel occlusion by the gel itself.

Vogl et al reported that this therapy was safe and effective, without major toxicity. Suggestions for future improvements are the establishment of optimum tumor size criteria, and better visualization of the gel. There were too few patients in the study to draw meaningful conclusions other than to say that this technique warrants additional investigation.

To my knowledge, there is only one similar chemotherapy product which has been FDA approved for implantation into tumors, and that is the Gliadelâ wafer used for applying carmustine directly onto the resection bed of recurrent high-grade gliomas. There is a small body of literature exploring the integration of external beam radiotherapy used in conjunction with implanted chemotherapy, and this remains an intriguing, albeit esoteric, area of investigation. Attawia et al described an in vitro system of Ewing's sarcoma cells cultured with taxol-loaded microspheres, and demonstrated that taxol can be effectively released from a biodegradable system to serve as a radiosensitizer with much larger reductions in tumor cell counts than in control cultures.[2] Similarly, Yapp and colleagues have shown synergistic effects between implanted cisplatin-impregnated polymer and radiation administered in mouse tumor models.[3]

Implantable chemotherapy is a relatively new area of oncology that holds interesting prospects for the future. The paper by Vogl et al is likely to be one of the first of many in this young field. ❖

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VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
MANAGING EDITOR: Robin Mason.
ASSOCIATE MANAGING EDITOR: Neill Larmore
SENIOR COPY EDITOR: Robert Kimball.

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Customer Service E-Mail Address:
customerservice@ahcpub.com

Editorial E-Mail Address:
robert.kimball@ahcpub.com

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Subsite-Specific Incidence Rate And Stage Of Disease in Colorectal Cancer by Race, Gender, and Age Group in the United States

ABSTRACT & COMMENTARY

Synopsis: To better understand the influence of screening strategies, this study examined stage of colorectal cancer at different anatomic subsites. The relation between stage and site-specific data from 344,775 patients diagnosed between 1992-1997 was analyzed by race, gender, and age group. Overall, the percentage of localized disease increased from 31.9% in the proximal colon to 41.5% in the distal colorectum, implying that screening strategies have had a strong preventive influence on distal disease. Black patients were more likely than white to receive a diagnosis of advanced disease for every subsite and more likely to receive a diagnosis of proximal colon than distal colorectal cancer. Male-to-female rate ratios monotonically increased from the proximal colon to the distal colorectum. With increasing age, ratios of proximal-to-distal disease increased.

Source: Wu XC, et al. *Cancer.* 2001;92:2547-2554.

Variation in subsite-specific incidence rates of colorectal cancer has been demonstrated between genders, among different age groups, and among racial groups.[1-3] In this population-based study, Wu and colleagues analyzed variations in stage of colorectal cancer at different anatomic subsites, stratified by race, gender, and age group, in order to explore the inherent screening implications.

Data were derived from 28 central cancer registries representing 40% of the US population. Population estimates from 1992-1997 were based on 1999 US Bureau of Census estimates, as reported by the Surveillance, Epidemiology, and End Results program. Age adjustment rates were based on the 1970 US population. Specific racial and ethnic information was only adequate to determine black-white differences.

For staging, 11 registries used the SEER program's Extent of Disease system, which converts to a Summary Stage. The remaining 17 registries use the Summary Stage directly. Internal analysis by Wu et al revealed 95% agreement between the 2 systems, which justified combining stage data for all registries. Staging collapsed into 4 major stage categories: localized (confined to the colon or rectum), regional (extension to adjacent tissues or regional lymph nodes), distant (metastastic to other organs or distant areas of the body), and unknown.

The colon was divided into 4 major subsites: proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure), descending colon, distal colorectum (sigmoid, rectosigmoid, rectum), and others (appendix and NOS).

Among the 344,775 colorectal cancer patients older than age 50 whose data were available for analysis, 88.3% were white, 8.3% were black, 2.8% were other races, and 0.6% were unknown. Consistent with other epidemiologic studies, 41.2% of tumors were located in the proximal colon, 4.7% in the distal colon, and 49.3% in the distal colorectum. Stage information was available for 93.1% of tumors overall.

For all race, gender, and age groups, localized cancer rates increased from 31% in the proximal colon to 37% in the descending colon to 41.5% in the distal colorectum. Conversely, percentages of regional disease were much higher proximally and decreased more distally in the colorectum. Percentages of distant disease remained similar throughout anatomic subsites. Taken together and given the relatively easy access to the distal colon and colorectum for polypectomy and early tumor identification, these data imply a beneficial effect of screening for the population overall.

For both genders, age-adjusted incidence rates for proximal and descending colon cancers were higher in the black population than the white. However, as in previous reports,[1-3] cancer incidence rates in the distal colorectum were highest for white males. Also consistent with prior research, males had a higher incidence of cancer at all anatomic subsites than females. Moreover, male-to-female rate ratios increased with more distal progression throughout the colon. Some have suggested the gender difference in incidence rate may result from a protective estrogen effect; however, the mechanism of site-specific effects remains to be clarified.[4]

Examining subsite-specific stage, in contrast to incident disease, revealed that blacks were more likely than whites to have advanced disease and less likely to have localized disease at all anatomic subsites. For example, in the distal colorectum, blacks had 35.3% localized tumors, 41.4% regional tumors, and 23.2% distant (metastatic) tumors, while rates for whites were 41.9%, 40.7%, and 17.4%, respectively. The most pronounced black-white differential among anatomic subsites was that for localized (early) stage tumors in the distal colorectum. These data suggest both that black patients may benefit from more extensive screening regimens

(that include the right colon) and that black patients are not receiving any screening as frequently as white patients.

Lastly, among all races and genders, incidence rates increased with increasing age group and the rate of increase was steepest for proximal tumors. Considering that, as above, localized disease rates increased from proximal to distal sites (that is, proportionately more advanced stage disease was found more proximally), these data suggest that disease may be detected earlier or prevented more effectively in elderly patients who undergo full colonoscopy screening rather than flexible sigmoidoscopy.

In summary, Wu et al found that women, elderly patients, and black patients appear to comprise subpopulations at higher risk for proximal tumors. Furthermore, black patients are at higher risk for more advanced stage of colorectal cancer at presentation. They conclude that screening efforts specifically directed at proximal tumors for these patient groups may be more effective in identifying earlier stage, and therefore more curable, colorectal cancer.

COMMENT BY ARDEN MORRIS, MD

When different subpopulations present with dissimilar sites of incident disease, the potential implications range from differential disease behavior, to discrepancies in patient or provider behavior, to inequitable access to systems of care. Wu et al investigated these dissimilarities in colorectal cancer incidence further by examining the relationship between stage of disease and anatomic subsite, stratified by race, age, and gender. Because colorectal cancer screening and prevention are uniquely combined, such a study allows exploration of the etiologic influence of differential screening strategies. For example, previous work has documented higher prevalence of right-sided polyps in women.[2] Since polyp formation is an early step in malignant transformation, one might deduce that women are more susceptible to right-sided colon cancers. Furthermore, these cancers may be prevented by polypectomy if full colonoscopy screening were performed but wouldn't be identified by flexible sigmoidoscopy. Determining whether all women older than age 50 should undergo full colonoscopy screening every 10 years is a complex issue; risks and costs must also be considered. However, population-based outcome studies like this one add to our knowledge about which subpopulations may benefit from more extensive screening efforts.

Wu et al collapsed the colon into 4 anatomic subsites: proximal colon (cecum to splenic flexure), descending colon, distal colorectum (sigmoid to rectum), and other. The division was both anatomic, with mid-gut to hind-gut blood supply transition at the splenic flexure, and also relevant to screening strategies—a flexible sigmoidoscope typically extends 60 cm to the splenic flexure. Dissent in the literature regarding whether to include the splenic flexure in the right (proximal) colon vs. left (distal) colon was not discussed; however, given that this study sought to address screening issues, one might argue that the splenic flexure should have been grouped with distal tumors rather than proximal.

Staging was also collapsed into 4 major categories: localized (AJCC Stage I or II), regional (AJCC Stage II or III), distant (AJCC Stage IV), and unknown. For accurate data merging this was probably necessary, although using an AJCC or Dukes staging regimen might have greater resonance for clinicians.

For a cohort of this magnitude (n = 344,775), even tiny percentage variations carry statistical significance. Therefore, confidence intervals or *P* values were appropriately not reported and, instead, only clinically meaningful data were highlighted.

The study found an increasing percentage of localized disease with anatomic progression through the colon. This finding persisted for both genders, and among all racial groups and age groups. Within each anatomic subsite, men had increased incidence of disease but both genders appeared to have similar stages of disease. In contrast, blacks had an increased incidence rate of proximal disease and a more advanced stage of disease at every anatomic subsite than whites.

Wu et al did not clarify whether there was any racial variation in patients whose cancers had available stage information. For example, 8% of the cohort was black and 7% had missing stage information. Were black patients disproportionately represented in the missing category? Such a scenario may have a misleading affect on the ultimate conclusions, although this may be mitigated by special biostatistical techniques such as multiple imputations.

In conclusion, population differences in subsite-specific stages lend support to Wu et al's argument for targeted screening of susceptible subgroups. However, further evaluation of risks, costs, and other possible etiologies for advanced stage of disease (e.g., differential tumor biology or exposure variables) is warranted before broad scale implementation of full colonoscopy as the most effective screening strategy. ❖

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Neoadjuvant Chemotherapy Does Not Preclude the Need for Postmastectomy Radiation

ABSTRACT & COMMENTARY

Synopsis: Currently available data that correlate pathologic features identified at the time of mastectomy with increased risk of locoregional recurrence of breast cancer are derived from chemotherapy-naïve patients. This study retrospectively assessed whether such features remain important in patients who received neoadjuvant chemotherapy, and they determined that, regardless of pathologic response, patients with locally advanced breast cancer might benefit from postmastectomy irradiation.

Source: Buchholz TA, et al. *J Clin Oncol*. 2002;20: 17-23.

Neoadjuvant chemotherapy preceding mastectomy has been explored in various clinical trials over the past several years. Two of the potential advantages to this approach are early treatment of micrometastatic disease, and facilitation of breast conservation in patients with large breast tumors. Given that recommendations regarding adjuvant breast radiotherapy are derived from chemotherapy-naïve patients status postmastectomy, Buchholz and colleagues sought to evaluate whether up-front chemotherapy might alter the indications for radiotherapy or perhaps eliminate the need for it altogether. Their retrospective review of data accumulated from consecutive neoadjuvant chemotherapy trials conducted from 1974-1998 at the M.D. Anderson Cancer Center (MDACC) involved the 150 patients who opted out of postmastectomy radiotherapy among 970 participants.

There were no cases of inflammatory carcinoma among the 150 patients. Twenty percent of participants were younger than 40 years old, 59% were 40-60 years old, and 21% were older than 60 years. Forty-eight percent of patients were estrogen-receptor positive. The breakdown by stage was: 1% stage I, 43% stage II, 23% stage III, and 7% stage IV. The median number of lymph node samples per patient was 15. There were 121 patients (81%) who received adriamycin-based chemotherapy (FAC or VACP), and 29 (19%) received paclitaxel as a single agent. Ninety-two percent of patients received adjuvant chemotherapy, and one third received adjuvant tamoxifen. Median follow-up was measured from the time of diagnosis, and was 4.1 years (r, 1.5-17.7).

Fifteen patients (10%) manifested a complete pathologic response to neoadjuvant chemotherapy. Sixty-two patients (41%) had negative lymph nodes at the time of mastectomy, 28% had 1-3 + lymph nodes (LNs), 20% had 4-9 + LNs, and 7% had > 10 +LNs. Forty-seven percent of patients (n = 70) developed a recurrence, including 23% (n = 35) with locoregional recurrences (LR) and 42% (n = 63) with distant metastases (DM). Among the former, 23 of 35 had isolated locoregional recurrences, and the rest had both LR and DM. Actuarial overall survival was 57% at 5 years, and 40% at 10 years. Actuarial LR was 27% at 5 and 10 years. For patients who presented with clinically negative axillary nodes that were confirmed to be pathologically negative, the LR rate was 3%. In patients with clinically negative but pathologically positive axillary nodes, the LR rate was 14%. For clinically positive, pathologically negative nodes, the LR rate was 63%, and for clinically/pathologically positive nodes, the LR rate was 32%. There was no statistical difference in locoregional recurrence rates for patients with pathologic complete responses in comparison to the rest of the group.

In multivariate analysis, there were 3 factors that correlated with LR. Those were: clinical stage IIIB or higher presentations; > 4 involved LNs at the time of axillary dissection; and use of tamoxifen. Higher stage patients had higher LR rates ($P < .001$) as did patients with > 4 involved LNs ($P = .008$). Patients taking tamoxifen had lower LR rates ($P = .001$).

Buchholz et al concluded that a complete pathologic response to neoadjuvant chemotherapy does not preclude the need for postmastectomy radiation. Both clinical and pathologic findings must be considered when deciding whether there is a role for postmastectomy radiotherapy. Downstaged patients still have a significant risk of locoregional recurrence absent adjuvant radiotherapy.

COMMENT BY EDWARD J. KAPLAN, MD

This retrospective analysis of patients treated with

neoadjuvant chemotherapy followed by mastectomy alone is the first time we have seen data regarding locoregional recurrences following omission of postmastectomy radiotherapy. The major thrust of the article addressed the question of whether postchemotherapy pathologic findings should change the way we make recommendations regarding postmastectomy radiotherapy. The typical factors which mitigate in favor of postmastectomy radiotherapy are: primary tumor size > 5 cm; > 4 positive LNs; inflammatory features; and positive surgical margins. These and similar factors were identified by these same researchers from MDACC in a previously published paper reporting their experience with local failures in a series of 1000 women treated with adjuvant chemotherapy after mastectomy without radiotherapy.[1] The Danish Breast Cancer Cooperative Groups and British Columbia trials published in 1997 said much the same thing. An updated analysis of the Danish DBCG 82b and c trials reiterated their conclusion that adjuvant systemic therapy does not prevent local recurrences.[2]

The multivariate analysis reported by Buchholz et al found that tamoxifen protected women against locoregional recurrences. This was the only treatment-related factor found to be important. Patients who used tamoxifen had a 7% rate of LR, while the others had a 36% rate of LR. In the Dutch DBCG 82c randomized trial where adjuvant tamoxifen alone was compared with tamoxifen plus postoperative radiotherapy, there was a 35% LR rate in the tamoxifen arm vs. an 8% LR rate in the combined arm (P < .001).[3] Therefore, while tamoxifen may play a role in prevention of LR, radiotherapy remains the mainstay in the postmastectomy population.

For now, while the optimal chemotherapy regimen and delivery sequence is being explored, the MDACC results offer us the first confirmation that our present standards for determining who receives postmastectomy radiotherapy are valid even after neoadjuvant chemotherapy. This is best appreciated by the fact that patients with a complete pathologic response had a statistically similar rate of LR as the other patients in the study.

I am not aware of any ongoing randomized trials that omit radiotherapy in mastectomy patients with locally advanced breast cancer, so studies like this one may be very important sources of data in terms of the decision-making process. ❖

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Risk of Lymph Node Metastasis in T1 Colorectal Carcinoma

ABSTRACT & COMMENTARY

Synopsis: This study involved a retrospective analysis of patients with T1 colorectal cancer. Using multivariate analysis, investigators found 3 variables that were statistically significant risk factors for associated lymph node metastasis in patients with sessile lesions. These factors were the presence of lymphovascular invasion, the depth of invasion into the submucosa, and tumor location in the lower third of the rectum.

Source: Nascimbeni R, et al. *Dis Colon Rectum*. 2002; 45:200-206.

Nascimbeni and colleagues from the mayo Clinic reviewed the records of more than 7000 patients in whom resection of a colorectal cancer was performed between 1979 and 1995. They identified 353 patients with sessile T1 adenocarcinomas after excluding cases with pedunculated tumors, synchronous tumors, hereditary predisposition, or inflammatory bowel disease. Patients treated with polypectomy or local excision alone were also excluded.

The 353 patients had a median age of 68 (range, 36-95). Eighty-seven patients had an attempt at local excision first, but a standard resection was subsequently performed because of unfavorable risk factors (57%), positive/uncertain margins (22%), or uncertain depth of invasion (13%).

Forty-six patients were found to have lymph node metastases (13%). A number of characteristics were studied as risk factors for lymph node metastasis. These included patient age, patient gender, size of the carcinoma, presence of mucinous carcinoma or grade (differentiation). Tumor grade was significant on univariate analysis (P = 0.004). However, only 3 factors were statistically significant on multivariate analysis: the presence of lymphovascular invasion (LVI), the location in the bowel, and the depth of invasion into the submucosa.

The location in the bowel yielded an interesting observation. Lesions of the lower third of the rectum had a higher risk of positive nodes (34%) than the middle (11%) or upper (8%) rectum (P = 0.007). However, no difference was seen when comparing tumors originating from the left colon vs. right colon vs. the rectum.

Although not part of the TNM staging system, the risk

of lymph node metastasis was analyzed by the degree of invasion into the submucosa. Positive nodes were significantly more common if the cancer penetrated the lower third of the submucosa (23%) compared with the middle third (8%) or upper third (3%) ($P = 0.001$).

COMMENT BY KENNETH W. KOTZ, MD

In their retrospective analysis, Nascimbeni et al make several interesting observations regarding the risk of lymph node metastasis in T1 colorectal cancer with sessile lesions. On a multivariate model, only the presence of LVI, the depth of invasion into the submucosa, and tumor location in the lower third of the rectum retained statistical significance. A poorly differentiated cancer was also statistically significant ($P = 0.004$), but only in the univariate model due to the association of these higher-grade tumors with deeper invasion into the submucosa ($P = 0.001$).

Lymphovascular invasion and tumor differentiation are well-recognized risk factors for lymph node metastasis in colorectal cancer. Less frequently discussed but previously reported[1] is the depth of submucosal invasion. Compared with the study by Nascimbeni et al, remarkably similar rates of positive nodes were reported for each segment of submucosal invasion (25%, 10%, and 0% for the lower, middle and upper third, respectively).[1] Although the depth of invasion makes biologic sense, it has not been shown to be reproducible.

In the multivariate analysis, a T1 tumor in the lower third of the rectum had a higher rate of lymph node involvement than tumors in the upper two thirds of the rectum or the colon. The reasons for this are unclear although one could hypothesize inherent biologic differences similar to the right-sided tendency of colon cancer in HNPCC. Nevertheless, the clinical significance of this is unclear because it is not reported how many of these node-positive, lower-third rectal cancers were well differentiated and without LVI.

Because patients treated with polypectomy were excluded, this study provides no information regarding the indications for resection after a polypectomy. Nascimbeni et al also point out that positive margins should be considered inadequate treatment rather than a risk factor. Their interesting study confirms the importance of tumor grade and LVI in early rectal cancer, and raises awareness of the potential importance of depth of submucosal invasion. Their results also suggest that there may be variations in the biologic behavior of rectal cancer depending on the site of origin within the rectum. ❖

Reference

1. Kikuchi R, et al. *Dis Colon Rectum*. 1995;38: 1286-1295.

CME Questions

16. Which of the following statements best describes the pathologic findings noted in the neoadjuvant chemotherapy breast cancer study?

a. A majority of patients were found to have complete pathologic responses.
b. Patients with inflammatory carcinoma had a high number of involved LNs at the time of surgery.
c. Most patients had 0-3 involved LNs at the time of surgery.
d. Most patients had > 4 involved LNs at the time of surgery.

17. Which of the following statements is *false* regarding the neoadjuvant chemotherapy breast cancer trial?

a. Patients with clinically/pathologically negative axillary nodes had a LR rate that was about the same as patients with clinically positive/pathologically negative axillary nodes.
b. Inexplicably, patients with clinically positive/pathologically negative axillary nodes had the highest LR rate of any patients.
c. Patients treated with adjuvant hormones did better than those who were not treated with adjuvant hormones.
d. Patients treated with neoadjuvant adriamycin did the same as those treated with neoadjuvant taxol.

18. The black-white differential in percentage of localized disease stage was most pronounced for:

a. proximal colon cancer.
b. descending colon cancer.
c. distal colorectal cancer.
d. women.

19. In the study by Nascimbeni et al, which of the following was *not* associated with an increased risk of lymph node metastases?

a. Lymphovascular invasion
b. Tumor penetration into the deepest third of the submucosa.
c. Tumor location in the lower third of the rectum.
d. Size of the carcinoma.

20. Which of the following statements regarding the cisplatin gel study is true?

a. As many as 3 tumors in the liver could be injected at any one session.
b. Patients in both the hepatocellular and metastatic colorectal carcinoma groups achieved local control of their lesions.
c. Intralesional concentrations of cisplatin potentially reached 20-30 times the levels that could be expected with systemic administration of drug.
d. All of the above

21. In the cisplatin gel study:

a. cisplatin was introduced with epinephrine to achieve a vasodilatory effect.
b. cisplatin was introduced with epinephrine to achieve a vasoconstrictive effect.
c. cisplatin was introduced with ephedrine to achieve a vasodilatory effect.
d. cisplatin was introduced with ephedrine to achieve a vasoconstrictive effect.

Attention Readers . . .

The editorial staff at *Clinical Oncology Alert* is pleased to announce the introduction of *Pharmacology Watch.* This monthly supplement is a current update on the pharmaceutical industry and its effects on your daily practice. Written by William T. Elliott, MD, FACP, *Pharmacology Watch* is your source to the current events and announcements of the major pharmaceutical companies, as well as standings of ongoing trials, vaccines, and more. The staff at *Clinical Oncology Alert* looks forward to offering this supplement as an added bonus to our subscribers. Look for it every month!

In Future Issues:

Adjuvant Chemotherapy for Older Colon Cancer Patients

PHARMACOLOGY WATCH

GlaxoSmithKline Withdrawals Lymerix: Company 'Cuts Losses' on Controversial Lyme Disease Vaccine

Citing poor sales, GlaxoSmithKline has announced that it is withdrawing Lymerix, the Lyme disease vaccine, from the market. The vaccine was the first, and only, Lyme disease vaccine on the market. Lymerix generated $40 million in sales in 1999, its first year on the market, but sales have fallen steadily since. The vaccine has also been plagued by controversy regarding side effects claimed by patients—side effects that seem to mimic Lyme disease and include arthralgias, fatigue, and neurocognitive symptoms. The FDA reviewed a study of 10,000 patients (5000 active vaccine, 5000 placebo) and found no increase in side effects with the vaccine. But because of continued complaints by consumers, the Centers for Disease Control (CDC) independently reviewed more than 900 reported side effects. In a report issued in January, the CDC declared that the vaccine was not associated with unexpected events. Despite the report and statistics that show Lyme disease cases reaching record highs, Glaxo has decided to cut their losses and is pulling the vaccine from the market.

Measles Vaccine Weathers Storm in Europe

An outbreak of more than 600 cases of measles in Germany has been reported in the last few weeks. Most cases have occurred in Bavaria, an area that is known as a hotbed of opposition to the MMR vaccine. The German pediatricians report that only 80% of infants in Bavaria received the first dose of MMR and only 60% of children received the second dose in 2000. European opposition MMR has centered in England and Germany after early research linked the vaccine to autism. A soon-to-be-published English study also suggests that the measles virus is present in children with ileocolonic lymphodular hyperplasia, a variant of inflammatory bowel disease, and speculates that the source of the virus may be MMR. News of the data, which will be published in the April issue of *Molecular Pathology*, was broadcast on the BBC. The lay press in England and other European countries has run many related stories, which have fed the fears of parents that the vaccine causes more harm than benefit. This is complicated by the fact that hundreds of lawsuits are currently pending in England—lawsuits filed by parents who feel that their children have been harmed by the vaccine. Vaccine-phobia exists in the United States but is less pervasive, in part due to the work of the National Network for Immunization Information (NNII), which has helped disseminate useful information to parents and physicians regarding childhood immunizations. The organization has set up a new web site to provide an on-line clearinghouse for vaccine information. The web site, which is sponsored by several medical professional societies and has an impressive advisory board, can be found at www.immunizationinfo.org. The Network is a non-profit and receives no financial support from the pharmaceutical industry. The web site has just added the recommended 2002 schedule for childhood immunizations. Changes for this year include recommendations for routine use of hepatitis B vaccine for all infants before hospital discharge, a schedule for catch-up vac-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com.

cinations for children who are behind on routine immunizations, and recommendations for preadolescent assessment of the vaccine status. The site also offers a color-coded, easy-to-use schedule for all childhood immunizations.

Too Many Injections for Children?

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Once Yearly Osteoporosis Treatments a Possibility

Women may soon be able to make a once yearly appointment to treat their osteoporosis. A recent study shows that an annual infusion of the bisphosphonate zoledronic acid is as effective as more frequent dosing for the treatment of osteoporosis. A yearly infusion of zoledronic acid also appears to be as effective as daily dosing of other bisphosphonates, such as alendronate or etidronate. The study, which was performed in Europe, New Zealand, and Canada, followed more than 350 postmenopausal women with low bone density. The women were randomized to placebo or intravenous zoledronic acid given in several dose regimens at 3-month intervals, 2 mg given every 6 months, or a single 4 mg dose administered once a year. At the end of 1 year, bone mineral density was assessed in the spine and the femoral neck. Increases in bone mineral density at both sites were found in all active medication groups and the increase was similar in all dosing schedules including the 4 mg once yearly group. The effect was also similar to published results with other oral bisphosphonates. The authors suggest that a once yearly infusion of zoledronic acid may eventually be a realistic alternative to oral bisphosphonates (and all their attendant side effects including esophagitis). This study is a phase II trial. (*N Engl J Med*. 2002;346:653-661). An FDA advisory board on oncologic drugs also recently recommended the approval of zoledronic acid for the treatment of bony metastases associated with a broad range of tumors including breast cancer in lung cancer. Novartis plans to market zoledronic acid under the trade name "Zometa."

Niacin and Statin Use Found to Raise HDL Cholesterol

Even low doses of niacin can effectively RAISE HDL cholesterol when used in conjunction with a statin, according to a recent study. Fifty patients who are stabilized on a statin were randomized to receive niacin 50 mg twice a day or placebo. The primary end points were change in HDL cholesterol and side effects such as flushing. The niacin patients had an increase in HDL cholesterol of 2.1 mg/dL, an increase that was statistically significant. Only 5 patients taking niacin noted flushing vs. 2 patients in the placebo group. There were no other significant side effects noted (*Am Heart J.* 2002;143:514-518). This study is important because traditional niacin therapy uses doses of 2000-3000 mg, doses that frequently result in intolerable side effects for many patients. Using low doses of niacin in conjunction with a statin safe and well-tolerated way to increase HDL cholesterol. ■

PHARMACOLOGY WATCH

GlaxoSmithKline Withdrawals Lymerix: Company 'Cuts Losses' on Controversial Lyme Disease Vaccine

Citing poor sales, GlaxoSmithKline has announced that it is withdrawing Lymerix, the Lyme disease vaccine, from the market. The vaccine was the first, and only, Lyme disease vaccine on the market. Lymerix generated $40 million in sales in 1999, its first year on the market, but sales have fallen steadily since. The vaccine has also been plagued by controversy regarding side effects claimed by patients—side effects that seem to mimic Lyme disease and include arthralgias, fatigue, and neurocognitive symptoms. The FDA reviewed a study of 10,000 patients (5000 active vaccine, 5000 placebo) and found no increase in side effects with the vaccine. But because of continued complaints by consumers, the Centers for Disease Control (CDC) independently reviewed more than 900 reported side effects. In a report issued in January, the CDC declared that the vaccine was not associated with unexpected events. Despite the report and statistics that show Lyme disease cases reaching record highs, Glaxo has decided to cut their losses and is pulling the vaccine from the market.

Measles Vaccine Weathers Storm in Europe

An outbreak of more than 600 cases of measles in Germany has been reported in the last few weeks. Most cases have occurred in Bavaria, an area that is known as a hotbed of opposition to the MMR vaccine. The German pediatricians report that only 80% of infants in Bavaria received the first dose of MMR and only 60% of children received the second dose in 2000. European opposition MMR has centered in England and Germany after early research linked the vaccine to autism. A soon-to-be-published English study also suggests that the measles virus is present in children with ileocolonic lymphodular hyperplasia, a variant of inflammatory bowel disease, and speculates that the source of the virus may be MMR. News of the data, which will be published in the April issue of *Molecular Pathology*, was broadcast on the BBC. The lay press in England and other European countries has run many related stories, which have fed the fears of parents that the vaccine causes more harm than benefit. This is complicated by the fact that hundreds of lawsuits are currently pending in England—lawsuits filed by parents who feel that their children have been harmed by the vaccine. Vaccine-phobia exists in the United States but is less pervasive, in part due to the work of the National Network for Immunization Information (NNII), which has helped disseminate useful information to parents and physicians regarding childhood immunizations. The organization has set up a new web site to provide an on-line clearinghouse for vaccine information. The web site, which is sponsored by several medical professional societies and has an impressive advisory board, can be found at www.immunizationinfo.org. The Network is a non-profit and receives no financial support from the pharmaceutical industry. The web site has just added the recommended 2002 schedule for childhood immunizations. Changes for this year include recommendations for routine use of hepatitis B vaccine for all infants before hospital discharge, a schedule for catch-up vac-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com.

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