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Correcting Warfarin-Induced Coagulopathy: Low-Dose Oral Vitamin K is Not Only Sufficient— Its Better!

ABSTRACT & COMMENTARY

Synopsis: Warfarin is an effective anticoagulant used in a variety of clinical situations. Hematologist/oncologists frequently find themselves managing warfarin therapy and adjusting doses according to the international normalized ratio (INR). However, if excessive anticoagulation is observed, there is currently no standard approach to management. In this report, Crowther and colleagues demonstrate that oral vitamin K normalized the INR faster than the subcutaneous route.

Source: Crowther MA, et al. *Ann Intern Med.* 2002;137:251-254.

It is not uncommon in clinical practice to observe anticoagulation beyond the therapeutic range when treating with warfarin. When the international normalized ratio (INR) is in excess of 6, major hemorrhage may occur spontaneously,[1] yet there is no established standard of management to prevent such untoward consequence. Crowther and colleagues from Canada and Italy report a randomized controlled trial in which low doses (1 mg) of vitamin K, administered either orally or by subcutaneous injection to patients with INRs of 4.5-10, with the primary measure being those who returned to therapeutic range the following day. The study took place at 2 teaching hospitals, one in Hamilton, Ontario and the other in Varese, Italy. Randomization resulted in comparable groups.

Based upon their own preliminary experience,[2,3] Crowther et al's hypothesis was that vitamin K would be more effective administered orally than subcutaneously. This proved to be the case. Of the 26 patients receiving oral vitamin K, 15 had therapeutic INRs on the day following treatment. In contrast, of the 25 receiving subcutaneous injections, 6 reached therapeutic INRs (P = 0.015; odds ratio, 4.32; 95% CI, 1.13-17.44). In fact, 3 patients who received oral vitamin K, but no patients who received subcutaneous vitamin K, had an INR of less than 1.8 on the day after study

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drug administration. Crowther et al conclude that vitamin K is an effective antidote to warfarin-induced coagulopathy, and that oral administration is more effective than subcutaneous.

■ COMMENT BY WILLIAM B. ERSHLER, MD

This brief report provides useful information for practicing hematologist/oncologists, particularly those who find themselves managing warfarin therapy. Although there clearly are regional variations, it is not uncommon practice to simply withhold warfarin when a patient unexpectedly is found to have an INR between 4.5 and 10. Yet, this complacency may not be wise in light of the recent report in which 5 of 114 patients with INRs of greater than 6 went on to have major hemorrhage.[1] With this in mind, clinicians should consider vitamin K for those patients with INRs significantly above the therapeutic range, particularly those at increased risk of hemorrhage. The current well-constructed trial indicates that oral vitamin K is not only effective, it is more effective than an equal dose administered subcutaneously. Although a "no treatment" arm (other than withdrawal of warfarin) was not included, it is very unlikely that just withholding the warfarin would be as successful as either of the vitamin K approaches (oral or subcutaneous) with regard to promptly returning the patient to the therapeutic range. Clinicians should be aware that oral vitamin K is superior to subcutaneous injection of the vitamin with regard to prompt resolution of warfarin-induced coagulopathy. ■

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Radiotherapy Alone for Distal Rectal Cancer

ABSTRACT & COMMENTARY

Synopsis: Standard therapy for invasive distal rectal cancers is radical surgery. Sphincter-sparing may be attempted and can often be facilitated by the use of neoadjuvant therapy. However, when a tumor is found to be too close to, or traverses, the internal sphincter at the time of surgery, a colostomy is unavoidable. This study found that, in patients who were borderline candidates for sphincter-sparing, and in patients deemed inoperable, dose escalation with primary combined radiotherapy achieved acceptable local control with moderate toxicity. They concluded that abdominoperineal resection should rarely be performed for T2 lesions, even when there is invasion of the anal canal.

Source: Gerard J, et al. *Int J Radiat Oncol Biol Phys.* 2002;54:142-149.

Gerard and colleagues at the centre Hospitlier Lyon Sud in Lyon, France, performed a retrospective analysis of 63 patients who were treated in a pilot study of primary radiotherapy for middle or lower rectal adenocarcinomas from 1986-1998. There were 26 patients who were medically inoperable, 22 who refused APR, and 15 who wished to attempt sphincter preservation for borderline operable lesions. All tumors were ultrasound stage T2-3N0-1 lesions, including 18 patients with perirectal adenopathy. Forty-one patients had T2 tumors, and 22 had T3 tumors. Forty-three percent of patients had tumors involving the anal canal. Patients were excluded from the study for

technical reasons if their tumors involved more than two thirds rectal circumference, mainly because of the difficulty treating circumferential lesions with contact x-ray therapy. All patients had a negative metastatic work-up.

Treatment consisted of contact x-ray therapy, external beam radiotherapy, and brachytherapy, which Gerard et al called "combined radiotherapy." Contact x-ray therapy was administered on days 1, 7, and 21 with a 50-kilovoltage photon unit through 1 or 2 fields to a median surface dose of 80 Gy (r, 35-140). The number of fields varied by tumor size and response. Contact between the radiotherapy device and the tumor was achieved via a proctoscope for a median of 2 sessions (r, 1-3). External beam radiotherapy was initiated on Day 14 using 18 MV photons administered via a 3 or 4 field technique encompassing the primary tumor and perirectal lymph nodes up to S1-2 or S2-3. Three centimeter distal and lateral margins were used. The external and common iliac lymph nodes were not included, and neither was the anal canal. Treatment was given at 3 Gy per fraction for 13 fractions over 17 days with 2:1 weighting favoring the posterior over the lateral fields. A 4-fraction concomitant boost to gross tumor at 1 Gy per fraction using an AP/PA approach was given, as well. The dose of external beam RT was felt to be comparable to 50-54 Gy at conventional 2 Gy fractions. Finally, an interstitial iridium-192 boost was undertaken 4-6 weeks following completion of the external beam RT, for a median brachytherapy dose of 20 Gy to the 85% isodose line (r, 10-25) in 22 hours. This was done with either a 5-wire perineal template (n = 38) for the lower lesions, or a 2-wire "rectal fork" (n = 17) applied with a rigid proctoscope with the patient in the knee-chest position without general anesthesia. Seven frail patients who had complete responses of their T2 lesions did not receive a brachytherapy boost. The median dose rate for the template was 1.13 Gy per hour, and for the rectal fork, it was 1.72 Gy per hour.

Median follow-up for the entire group was 54 months, and for surviving patients it was 78 months. Among the 63 patients treated, 58 (92%) exhibited a complete clinical response at 2 months posttherapy. Thirty-three patients had supple rectal walls, 24 had a small area of fibrosis, and 5 had small residual biopsy-proven tumors. Two of the 3 attempts at salvage APR were successful. The 58 complete responders had a 28% local recurrence rate (n = 18), with a median time to failure of 16 months (r, 7-49). Five of the local failures were salvaged with APR or a second course of contact therapy. Only 2 of the persistent failures required a palliative colostomy. Forty patients (63%) achieved local control with primary therapy, and 6 more were salvaged for an overall local control rate of 73%. Overall survival at 5 and 10 years was 64% and 45%. Overall survival and local control at 5 years was 82% and 83% for T2 tumors. Overall survival at 5 years was 35% for T3 tumors. Twelve patients died of cancer. There were no Grade 3-4 acute toxicities. Twenty-four patients developed intermittent rectal bleeding 6 months posttreatment that lasted 2-3 years, but only one required transfusions. No patient required a colostomy because of radiation toxicity. Anorectal function was assessed using the MSKCC Scale, and was good or better in 92% of patients. Statistical analysis of results was not provided, although Gerard et al stated that T-stage was "a strong prognostic factor."

Gerard et al concluded that combined radiotherapy alone is a suitable treatment for inoperable patients with < 5 cm T2-3 lesions. For patients that manifest a poor response by Day 21, the option to pursue surgery may be reassessed. For T3 lesions, RT dose escalation or concurrent chemotherapy should be explored. While surgery remains the mainstay for rectal cancer, APR should rarely be performed for T2 lesions, even if they invade the anal canal.

COMMENT BY EDWARD J. KAPLAN, MD

This paper from the Lyon group is fascinating from many different perspectives, and represents an ongoing effort reflected in serial publications of their experience. Although brachytherapy boosts are not uncommon, very seldom do we see regimens that incorporate 3 radiotherapy delivery systems in a single protocol. Despite the fact that radiotherapy alone has been shown to confer good results with smaller low-lying rectal tumors since the 1980s,[1] this approach has never gained popularity. In a situation where there seems to be no alternative to an APR, an attempt to control the disease with primary radiotherapy makes sense.

Though the combined radiotherapy approach used by Gerard et al seems logical, widespread adoption of their technique in the United States seems unlikely. The 2 major problems I see are the fact that Philips Medical no longer manufactures RT-50 contact x-ray units,[2] and most radiation oncologists in the United States have never performed brachytherapy for rectal cancer. Looking back on a recent paper by Wallner,[3] from Seattle, perhaps at least some radiation oncologists here could adapt to the French group's style. Wallner et al performed template guided permanent interstitial brachytherapy on awake Veterans Administration prostate cancer patients using local anesthesia, and reported no problems.

Aumock et al from Washington University published

their experience with 207 patients treated with primary radiotherapy from 1981-1995.[4] In contrast to the Gerard study, tumors involving the anal canal were excluded because it was felt that endocavitary treatment entails the risk of severe pain due to ulceration in the anus. Patients were treated with a mean external beam dose of 45 Gy at 1.6-1.8 Gy per fraction, which preceded contact x-ray therapy with the Philips 50 kV unit. The latter was used to administer two 30 Gy mucosal surface doses 2 weeks apart. Dose penetration at the center of the contact x-ray field was 54% at 0.5 cm and 33% at 1 cm. Local control with RT alone was 71%, and this rose to 81% with surgical salvage. All T1 lesions were controlled, as were 85% of mobile T2 lesions, and 56% of T3 lesions and tethered T2 tumors. No patient received chemotherapy. No patient underwent a brachytherapy boost. Multivariate analysis indicated that N1 disease and absence of gross total endoscopic debulking were negative prognostic factors.

Gerard et al achieved their goal of preserving good anal function in a group of compromised patients by escalating the radiotherapy dose. Their regimen was vastly different from what is considered conventional radiotherapy in the United States, and it was aggressive even by European standards. For example, while large doses per fraction are accepted in Europe, concomitant boosts go a step further. The dose rate for the interstitial boost was also high in comparison to the 0.5-0.6 Gy per hour that we typically use. One way the French group was able to succeed with this aggressive format was by limiting the treatment volume. Had they included the external and common iliac lymph nodes, their patients probably would not have tolerated the therapy as well as they did.

The concept that primary radiotherapy can be successful in patients who would otherwise have little hope of avoiding a colostomy is important, and should not be brushed aside. What we need to focus on is devising a modern protocol that can achieve similar or better results using equipment that is widely available, such as the high dose rate afterloader with an endorectal applicator. As the Gerard group suggested, chemotherapy would probably improve results for the larger T2 lesions, and T3 tumors. Just as the University of Washington group reported, giving the endorectal therapy after the tumor has been downstaged with external beam RT is attractive. This would eliminate the problem that the French had handling circumferential lesions. The beauty of endorectal HDR as a boost therapy is that the entire circumference of the rectum can be treated easily. ■

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Anemia Predicts Poor Response to Lung Cancer Treatment

ABSTRACT & COMMENTARY

Synopsis: In a retrospective series of non-small cell lung cancer patients with locally advanced disease who were treated at the University of Pennsylvania with neoadjuvant chemoradiation therapy and surgery, an association of pretreatment anemia with poor response to chemoradiation was discovered. The finding raises the question of whether efforts to treat anemia early in patients receiving cancer therapy will be associated with more favorable outcomes in addition to the improved quality of life which has already been established.

Source: Robnett TJ, et al. *Cancer J*. 2002;8:263-267.

Anemia is common in patients with cancer and there is mounting clinical evidence that its presence is a negative prognostic factor. For example, in patients with head and neck or uterine cervical cancer, the presence of anemia has been shown to correlate with negative treatment outcomes.[1,2] In this recently reported series, the success of neoadjuvant chemo-irradiation for non-small cell lung cancer was examined in the context of pretreatment hemoglobin. This was a retrospective analysis from the University of Pennsylvania in which 41 consecutive patients with clinical stage IIIA (N2 documented by mediastinoscopy or other invasive procedure) NSLC were treated preoperatively with chemotherapy (either cisplatin or paclitaxel based regimens) and radiation (median dose, 48.6 Gy). Responses were graded on a 4-point scale: 1) progressive disease before surgery (or excluded from surgery for technical reasons; 2) stable disease with resection performed, but specimen containing > 50% viable tumor; 3) partial response with specimen containing < 50% tumor; and, 4) complete response or near-complete response: R0 resection with no residual carcinoma or pT1N0 with only microscopic residual foci. Pretreatment hemoglobin levels were correlated with pathological outcomes

using ANOVA and the nonparametric test for trend across ordered groups.

The mean hemoglobin level found for each of the 4 response groups noted above was: 1) 11.8 g/dL; 2) 12.1 g/dL; 3) 12.5 g/dL; and 4) 13.2 g/dL. This association was statistically significant. Thus, it was apparent that response to chemoradiation of NSLC improves with increasing hemoglobin levels.

■ COMMENT BY WILLIAM B. ERSHLER, MD

The goal of this work was to assess the relationship between anemia and pathological tumor response in a neoadjuvant setting for locally advanced NSLC and the data clearly indicate a significant association. For a number of reasons this seems like a likely conclusion, but outside of the clinical trial setting, supportive data would be unlikely available. Indeed, this retrospective analysis proved fortuitous in this regard, inasmuch as pathological specimens were available posttreatment on a relatively homogenous group of patients with a common variable being hemoglobin concentration. That stated, it is important to emphasize that this was a retrospective analysis and the sample size was relatively small. There is, without a doubt, some element of selection bias because patients included were only those who were deemed as candidates for trimodality therapy, including a likely aggressive surgical intervention. Thus, an untold number of patients with similarly advanced NSLC who were not eligible for neoadjuvant chemoradiation followed by surgery could not be included. Nonetheless, this may well be the first series to show that anemia is associated with a poorer response documented pathologically to neoadjuvant therapy for NSLC.

Like many clinical studies, the results bring more questions. In this case was the pretreatment anemia, a coincidental finding indicative of some other comorbidity that might itself be associated with reduced response? In this highly selected series, this seems unlikely. However, and obviously of great importance, would correction of the anemia prior to or during the neoadjuvant therapy improve the response rate? Some answers to this may be gleaned from a current Radiation Therapy and Oncology Group (RTOG) trial (RTOG 99-03) which randomly assigns anemic patients to receive XRT with or without recombinant human erythropoietin. Outcome measures for this study include both local control and quality of life. It would seem likely in these days of aggressive attention to supportive issues, such as quality of life and availability of effective growth factors, that such data would also eventually be available for NSLC. ■

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CODOX-M and CODOX-M Alternating with IVAC in Adult Burkitt's Lymphoma

ABSTRACT & COMMENTARY

Synopsis: Burkitt's lymphoma is a rapidly progressive form of B-cell non-Hodgkin's lymphoma. Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) is a highly effective alternating non-cross-resistant regimen developed by Magrath and colleagues at the National Cancer Institute.[1] The aim of this paper was to confirm these results in a larger, international, multi-center study using International Prognostic Index-based criteria to assign prognostic groups, while slightly simplifying the protocol. This study confirms high cure rates with this CODOX-M/IVAC approach and the benefit of stratifying patients into low and high-risk groups.

Source: Mead G, et al. *Ann Oncol.* 2002;13:1264-1274.

It has been known for more than 2 decades that standard lymphoma therapy, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)[2] is inadequate for this highly aggressive lesion. The CODOX-M/IVAC regimen was developed at the National Cancer Institute and the results were published in 1996.[1] The regimen for high-risk patients consists of alternating cycles of regimen A (cyclophosphamide, adriamycin, vincristine and methotrexate [CODOX-M]) and B (ifosfamide, etoposide, high-dose cytarabine [IVAC]) for 4 cycles (ABAB). It showed a 92% 2-year event-free survival rate. The study was in children (median age, 12 yrs) and adults (median age, 25 yrs). This current study was to confirm these results in a large well-defined patient population.

Patients were accrued from 45 consultants at 39 centers. Fifty-two patients were reported whose pathology was confirmed by central pathologic review. The 2-year event-free survival (EFS) was 64.6% and 2 year overall survival was 72.8%. For low-risk patients, the 2-year EFS was 83.3% and overall survival 81.5%. For high-risk patients the 2-year EFS was 59.5% and overall sur-

vival was 69.9%. Toxicity was severe with World Health Organization (WHO) grade three quarters leucopenia and neutropenia in nearly all patients.

■ COMMENT BY STUART M. LICHTMAN, MD

Burkitt's lymphoma is a rare and highly aggressive and rapidly progressive form of B-cell non-Hodgkin's lymphoma. It can occur at any age but tends to present most commonly in males during childhood and young adult life and in patients with HIV infection. It has a distinct pathological appearance associated with an 8:14 translocation which results in overexpression of c-myc; these changes promote mitosis such that virtually 100% of cells are in cycle. There is occasional confusion regarding the classification of this disorder. Historically, Burkitt's lymphoma and Burkitt-like lymphoma have been treated together as diffuse noncleaved lymphoma according to the Working Formulation Classification. The current lymphoma classification, the WHO Classification of Neoplasms of the Lymphoid System, has Burkitt-like lymphoma a subtype of Burkitt's lymphoma and should be treated identically.

The literature relating to the treatment of adult Burkitt's lymphoma is scant and has developed over a long period of time with changing practice patterns and supportive care modalities. This has resulted in difficulty in interpretation of the data. Also, many studies have primarily involved children and young adults and are often not applicable to the patients seen by medical oncologists primarily treating adults. In addition, there has been a difficulty in diagnoses exacerbated by the changing lymphoma classification schemes. It is imperative that the diagnosis be considered in patients with clinically aggressive lymphomas, but it should also be kept in mind that a substantial number of patients will present with localized, low-risk disease. The diagnostic criteria should include 100% Ki-67 staining and studies to confirm either the 8;14 or 14;18 translocations. This can be performed with fresh tissue or paraffin blocks with fluorescence in situ hybridization (FISH). The study of Macgrath and associates emphasized the curability of this disease with an aggressive regimen. Other regimens have been reported in the literature.[3-5] The current study confirms Macrath et al's data, showing the high efficacy of this treatment with cure possible in this older population (median age, 35 yrs). It also confirmed the classification of low- and high-risk patients. Prognostic factor analysis was limited but there was a trend to a worsening EFS with increasing age and bone marrow involvement.

Clinicians now have a proven regimen that can cure this aggressive lesion. The long-term benefit of this therapy rests on the proper identification of patients with appropriate histologic and laboratory investigation of pathologic tissue. Supportive measures should be performed scrupulously and are imperative with this highly aggressive therapy. ■

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Recurrent Micropapillary Serous Ovarian Carcinoma: The Role of Secondary Cytoreductive Surgery

ABSTRACT & COMMENTARY

Synopsis: Optimal secondary cytoreductive surgery is feasible in the majority of patients with recurrent micropapillary serous carcinoma of the ovary and is an independent predictor of subsequent survival.

Source: Bristow RE, et al. *Cancer*. 2002;95:791-800.

Bristow and colleagues present a retrospective report of 26 patients with recurrent micropapillary serous ovarian carcinoma (MPSC) from the Johns Hopkins Hospital. The major purpose of this study was to characterize the clinical outcome of patients with recurrent MPSC and to evaluate the effect of secondary cytoreductive surgery on survival. The median age of the patients at recurrence was 46 years. The mean progression-free interval was 32 months, and 92% of patients had advanced stage disease at the time of the initial diagnosis. Twenty-one patients underwent secondary cytoreductive surgery; tumor debulking was performed in 91% of cases and 52% of patients required intestinal resection. Optimal resection (residual disease < 1 cm) was achieved in 15 patients (71%). Patients undergoing optimal secondary cytoreduction had a median survival time of 61 months from date of disease relapse compared with 26 months for those patients in whom suboptimal residual disease remained ($P < .02$) and 30 months for nonsurgical patients ($P < .01$). On multivariate analysis, optimal secondary cytoreduction was found to be the only independent predictor of survival. Salvage chemotherapy produced an objective response in 25% of patients with mea-

surable disease. Bristow et al concluded that optimal secondary cytoreductive surgery is feasible in the majority of patients with recurrent MPSC and is an independent predictor of subsequent survival.

■ COMMENT BY DAVID M. GERSHENSON, MD

Within the past few years, Kurman and associates[1] from Johns Hopkins have published extensively on so-called micropapillary serous ovarian carcinoma (MPSC). The MPSC pattern is proliferative microscopically and is considered by most gynecologic pathologists to be a subset of serous borderline tumor. However, the pattern is distinct from the typical serous borderline pattern and, in general, is associated with more aggressive behavior—principally, a higher frequency of associated invasive peritoneal implants and a greater risk of relapse. Kurman's group has suggested that the typical serous borderline pattern is essentially almost always associated with a benign course and should be reclassified as "atypical proliferating tumors." They believe that the micropapillary pattern should actually be an entirely separate category—one almost always associated with a more aggressive course in the advanced stages. The ultimate goal of this group appears to be abandonment of the serous borderline category altogether. However, the vast majority of both gynecologic pathologists and gynecologic oncologists have not embraced this concept; they believe that the biologic behavior of MPSC, while more aggressive than the typical serous borderline tumor pattern, is much closer to it than to invasive ovarian cancer. In fact, extensive data from our group and that of others suggest that the typical pattern in the advanced stages is not infrequently associated with an aggressive clinical course and that not infrequently the 2 patterns are admixed in the same primary tumor. While Bristow et al have split out their series of patients with recurrent MPSC, we would consider these relapsed patients to have invasive low-grade serous carcinoma, as described in a series from our institution that is not dissimilar from Bristow's series.[2] Thus, the controversy continues regarding the optimal classification of serous borderline tumor. By focusing just on the so-called MPSC, Bristow et al promote their philosophy, which, in my opinion, is not supported by fact. However, I do agree entirely with the clinical observations detailed in this nice study; the controversy is focused on nomenclature and classification. ■

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CME Questions

15. In a patient receiving warfarin for deep vein thrombosis, a pro-time reveals an INR of 7.0. Which of the following would be considered optimal therapy?

a. Hold warfarin, no other intervention.
b. Hold warfarin, and administer vitamin K, 1 mg orally.
c. Hold warfarin, administer 1 mg vitamin K subcutaneously.
d. Insert inferior vena caval filter and forget about future warfarin.

16. Which of the following regarding the French sphincter sparing paper is *false*?

a. Few patients receiving combined radiotherapy were able to retain useful sphincter function.
b. Ultrasound T-stage was related to tumor response.
c. During their concomitant boost, patients received 4 Gy daily.
d. None of the above

17. Regarding the Gerard paper, which statement is correct?

a. Patients with involvement of their anal canal by rectal cancer did just as well as those without involvement of the anal canal.
b. Patients with involved lymph nodes on ultrasound staging did just as well as those without adenopathy.
c. Patients treated with the perineal template boost did just as well as those treated with the rectal fork approach.
d. All of the above

18. The presence of anemia in patients with locally advanced NSLC has been shown to:

a. correlate with a less satisfactory pathological response to neoadjuvant chemoradiation therapy.
b. correlate with a lower response rate when evaluated clinically after chemoradiation therapy.
c. correlate with reduced survival after chemoradiation therapy and surgery.
d. have no association with pathological or clinical responses, or survival after chemoradiation therapy.

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