Phase 1 Trial of High-Dose Intravenous Vitamin C Treatment for Patients With Cancer

To the Editor:
For more than 30 years, the medical profession has had lingering questions about the efficacy of vitamin C in cancer therapy. Initial clinical reports1 and early preclinical studies2 indicated that vitamin C administered intravenously may have potential抗癌 benefits. Yet, few definitive clinical reports supporting this finding have been published. Thus, in October 2006, Cancer Treatment Centers of America (CTCA) initiated a US Food and Drug Administration–approved phase 1 study of intravenous vitamin C for patients with solid tumors who have exhausted all other available treatments. The investigators include an osteopathic internist (C.M.S.), a medical oncologist (R.D.L.), and a clinical epidemiologist (C.G.L.).

High doses (30 g/m² to 130 g/m²) of vitamin C are used to achieve blood levels greater than the 20 mM that have been reported to be cytotoxic to tumor cells grown in hollow fibers.3 Neil H. Riordan, PA-C, and colleagues,4 reported that vitamin C infusions of 60 g resulted in brief blood level elevations to 24 mM. Blood levels are only elevated 0.2 mM when vitamin C is given orally. In the CTCA study, the first cohort of 3 patients is being treated with 30 g/m²—approximately 50 g for an average-sized individual—vitamin C infusions on 4 consecutive days per week for a period of 4 weeks.

Doses of vitamin C will be increased incrementally in future cohorts until the maximum tolerated dose is reached. Our goal is to have six dose escalations involving 18 patients. We are attempting to determine the safety, tolerability, optimum therapeutic dose, and pharmacokinetic profile of intravenous vitamin C, in addition to evaluating patient quality of life during treatment. We will also assess patients’ tumor burden for preliminary indications of intravenous vitamin C anticancer activity. Information from this study may provide the basis for a phase 2 trial of intravenous vitamin C.

The phase 1 clinical trial is open for accrual. As of February, 3 patients in the first cohort had completed their 4-week series of vitamin C infusions. One of these patients, whose disease was in stable condition, wanted to continue the vitamin C infusions and is currently on a continuation protocol. We are actively recruiting the second cohort of 6 patients. The current study should resolve some critical unanswered questions about the efficacy of vitamin C in cancer care.

We will keep the osteopathic medical community informed as the study progresses during the next year. We also welcome readers’ comments and insights.

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Letters

References


Is Estimating USMLE Performance Useful?

To the Editor:

Should I take the USMLE?

With a large proportion of graduates from colleges of osteopathic medicine (COMs) continuing to apply for residency programs accredited by the Accreditation Council for Graduate Medical Education (ACGME),1 this question is being asked of COM educators more than ever. In the September 2006 issue of JAOA—The Journal of the American Osteopathic Association, Philip C. Slocum, DO, and Janet S. Louder2 proposed a mathematical method to estimate performance on the United States Medical Licensing Examination (USMLE) based on Comprehensive Osteopathic Medical Licensing Examination (COMLEX-USA) scores. The authors note that the impetus of their analysis was to reduce potential selection bias against COM graduates seeking ACGME-accredited residency training.

Although the method used by the authors is sound, the equation generated is valid only for evaluating graduates of the A.T. Still University-Kirkville College of Osteopathic Medicine in Mo—because these graduates were the only members of the cohort. The various COMs use an array of curriculum models and assessment methods.1 It is possible that each COM, when surveyed separately, will have variation in its regression analysis. Thus, the authors’ proposed method may be validated only if the study is completed in aggregate, with all COMs sharing their data.

Should we undertake such a profession-wide study? An accurate tool for estimating USMLE performance might be useful for program directors at residency programs accredited by the ACGME, but it would have a debatable effect on removing selection bias against COM graduates. The tacit reality behind the study by Slocum and Louder2 is that the medical profession has been enabled by the ACGME graduate surplus to expand at a hurried pace. The sanctioned increase in allopathic medical school size3 is placing the academic leadership of COMs on alert. The method that allopathic medical schools will use to provide postdoctoral training for their increasing number of graduates was clearly stated by Michael E. Whitcomb, MD,4 of the Association of American Medical Colleges:

...some IMGs [international medical graduates] and DOs who might otherwise have been accepted into allopathic GME [graduate medical education] programs will not be accepted in the future.

Residency programs approved by the American Osteopathic Association are faced with increasing pressures to remain competitive in an ever-tightening match with ACGME-accredited programs. In the 2004-2005 academic year, the COMs had only roughly half of their participating graduates accept positions through the American Osteopathic Association’s Intern/Resident Registration Program.5 If the ACGME starts shutting its doors on our graduates, will this “translation” methods help?

Walk a mile in our students’ shoes and ask yourself, “Would I take the USMLE?”

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Response

I thank Isaac J. Kirstein, DO, for his thoughtful comments about the September 2006 JAOA article I cowrote with Mrs Louder.1 Dr Kirstein is correct to point out that the cohort was composed entirely of students enrolled at A.T. Still University-Kirkville College of Osteopathic Medicine in Mo. I briefly reviewed the medical literature on the effects of curriculum on standardized testing and could find little support for arguing that curriculum plays a significant role in outcomes.2 Though I suppose a different curricular approach might have resulted in different outcomes, I doubt that theory. I encourage an ambitious reader to seek an answer to the question Dr Kirstein’s letter suggests.

Dr Kirstein also argues that the formula Mrs Louder and I created has little “effect on removing selection bias against COM [college of osteopathic medicine] graduates.” I agree. That was not the intended goal of our study. What the study does provide, however, is a gauge that program directors at residency programs accredited by the Accreditation Council for Graduate Medical Education can use to make reasonable comparisons if they are other-

References


wise impressed with an osteopathically trained candidate. Our study was not intended to answer any of the larger questions Dr Kirstein rightly poses.

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References

Limitations of Survey-Based Assessments on Duty-Hour Work Standards

To the Editor:
Aspects of the July 2005 JAOA—The Journal of the American Osteopathic Association medical education article on resident duty-hour limits demonstrate that attitudes or perceptions, though useful to some extent, are not necessarily accurate reflections of reality (ie, statistically significant but not clinically important). The authors report that—consistent with previous findings—general surgery residents were more likely to feel that duty-hour standards “will have a serious, negative effect on training future physicians.” My contention is that a “feeling” based on a quantitative assessment (ie, the total number of procedures performed during residency training) is not equivalent to assessment reached through qualitative measurements (ie, the total number of procedures performed during residency training when one is fully alert). Studies of resident duty hours should then focus on assessing qualitative issues rather than quantitative ones. Why?

In the same issue of the JAOA, Brian H. Foresman, DO, cites ample evidence to show that prolonged work hours at any job are hazardous. Similarly, a 2004 study showed that mistakes tripled when nurses work more than 12 hours. In addition, not one study has demonstrated that workers can build tolerance for long work hours. Clearly, working long hours can lead to problems, and the duty-hour mandate, from my point of view, is headed in the right direction—regardless of some residents’ feelings based on quantitative assessments.

Duty-hour limits for residents were initially sparked by the accidental death of a journalist’s daughter in 1984, forcing the state of New York to institute regulations that eventually lead to nationwide reform.

As Zonia and coauthors note, some trainees argued that the duty-hour limits will result in a lower level of resident exposure to medical procedures and patient cases, compromising the quality of physician training. Indeed, as Zonia and her coinvestigators report, some survey respondents believed that the “standards will prolong residency training,” similar to what others have suggested. I disagree.

In fact, the perceived negative impact of the 80-hour work week on medical education has no real basis—except perhaps in terms of a decline in patient numbers. I believe that this loss is counterbalanced by the gains made in terms of an increase in the quality of patient care and safety, as well as the strengthening of acquired knowledge because residents will be more alert, make fewer mistakes, and have increased productivity. This viewpoint is not new, and is supported by numerous studies. For example, duration of work hours compared with the duration and quality of sleep, are viewed as factors that influence healthcare quality. Similarly, Howard and colleagues reported that resident skill level was negatively affected, and “post-call conditions were near or below levels associated with clinical sleep disorders,” justifying reforms for residents’ work and duty hours. In two studies of intensive care units, the Harvard Work Hours and Health Study Group concluded that attention failures decreased with significant increase in sleep during night work hours and there were “substantially more” serious medical errors with frequent 24-hour shifts. Similar results were found in a smaller scale study. Additional studies, all on simulations of laparoscopic surgeries, showed that more errors (ie, limited dexterity, impaired speed, accuracy, economy of motion) occurred as sleep loss increased and after multiple nights on call. One of these studies showed that performance decreased after 17 hours, consistent with results reported elsewhere for nurses. In addition, some evidence exists that problems related to sleep-deprivation extend for 2 days beyond a sleepless night.

It is my contention that residents with healthier sleep patterns will establish better habits of alertness and mental focus for their individual medical readings and projects, as well as their journal clubs, seminars, and conferences. All of this will benefit residents as future physicians—ultimately benefiting patients.

How does one convince residents that a limit of 80 duty-hours per week is better than no duty-hour restrictions?

A follow-up study might take the following form:

Please answer the following questions for the resident in your program, regardless of the year in training.
1. How many residents do you have in your medical residency program?
2. Of this number, how many residents do you trust to perform a surgical procedure on you or on one of your family members?

These two questions would establish a baseline for the survey’s remaining questions:

3. Of the number of residents you would trust to perform a surgical procedure on you or on one of your family members, how many residents would you trust after they had been working for 10 hours straight?
4. Of this number, how many residents would you still trust after they had been working for 15 hours straight?
5. Of this number, how many residents would you still trust after they had been working for 22 hours straight?

If answered honestly, such survey questions could help researchers begin to address issues about the underlying quality of medical education within the context of the duty-hour restrictions. Would the survey or its results change the attitude of residents whose primary focus is on quantity rather than quality in their medical training? Probably not, but again, this information is worth finding out.

As the husband of a DO who recently completed her fourth year of residency training in an obstetrics/gynecology program approved by the American Osteopathic Association—and as someone involved in biomedical research and development and associated legal issues in my own career—I think quality in residency programs outweighs quantity any day. And again, how does one measure quality?

Is one a better surgeon, for example, because one performed 60 procedures in a 24-hour period, 40 of which were performed after hour 16 at work? Or is one a better surgeon because one performed 35 procedures in a 24-hour period, all of which were performed between hours 5 and 8 at work? Is doing 30 personal histories and physical examinations in 1 hour by one resident better for the resident, patients, or the hospital than doing 15 in the same 60-minute period? What are our expectations, and are they realistic? My guess would be that the answer depends on whom you ask.

I can tell you one thing for certain: our society should not tolerate allowing the legal system to determine our answers for us.

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References

Letters