Controversy about Neoadjuvant (pre-op) Chemotherapy Protocol

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PRO: Trial Results Report that M-VAC Before Surgery Increases Survival

Long awaited results from a 14 year long clinical trial conducted by the Soutwest Oncology Group [ref.#8710) were published in 2001. The study reported a 2.4 year survival advantage for people with locally advanced (stages T2-T4a, no metastases) who had been given 3 cycles of MVAC (methotrexate, vinblastine, adriamycin, doxorubicin, and cisplatin before having a radical cystectomy vs. radical cystectomy with no other treatment. The trial results were presented, discussed and debated between international oncologists at the ASCO meeting, May 15, 2001.

317 bladder cancer patients participated; median follow-up was 7.1 years. Median survival for patients having received the MVAC regimen was 6.2 years vs. 3.8 years for those patients undergoing cystectomy alone. Survival at 7 years was 57.2% in the MVAC/cystectomy arm and 42.1% in the cystectomy arm.

These results differ from seven previously conducted clinical trials which had shown that there was no benefit derived from receiving MVAC before surgery.

The study was based on the concept that such patients harbor microscopic cancer cells and that chemotherapy in the weeks before surgery, rather than after it, is more likely to prevent the spread of cancer cells. The phase III trial was conducted by Ronald B. Natale, MD, acting medical director, Cedars-Sinai Medical Center, Los Angeles. Dr. Natale claims that other potential advantages of MVAC as neoadjuvant (pre-surgery) chemotherapy regimen are;

*Tumor downsizing

*Chemotherapy is better tolerated before undergoing surgery rather than later

*The study hinted that chemotherapy alone might be effective in some patients with bladder cancer. In 38 percent of patients in the study, a pathologist could find no evidence of cancer in bladders removed from people who had chemotherapy.

Dr. Natale said, doctors can address the question of whether they can forgo bladder removal, or at least delay removal, for many patients. Such a step would require further study. "The results of a single trial shouldn't change the standard of care, he added, but "the striking results of this study require that patients at least be informed that preoperative chemotherapy might significantly change their survival."

CON: Too many flaws in the trial design, results are not convincing enough

Dr. Cora N. Sternberg, one of the pioneers of the original MVAC regimen which was first developed at Memorial Sloane Kettering Cancer Center, NYC, questioned many of the assumptions put forth by Dr. Natale, such as:

*SWOG data accounted for just 10% of all the data in the literature

*Many preceding trials have not shown any benefit using neoadjuvant chemo

* MVAC is a very toxic regimen

*Gemcitabine and cisplatin might be a better combination

*Adjuvant chemotherapy was superior to neoadjuvant chemotherapy

*Study design was methodologically and statistically flawed (slow patient accrual, large discrepcancy between stages/tumor load of people in the trial, etc).

Dr. Sternberg questioned whether the study actually proved a survival benefit, and said that a larger group was needed for statistical analysis, thus making the findings misleading.

Despite the controversy, Memorial Sloane Kettering Cancer Center in NYC, which treats more cases of bladder cancer than any other US institution, cites the studie's findings, and announced that it is beginning a new clinical trial using adjuvant (as opposed to neo-adjuvant) chemotherapy for locally advanced bladder cancer, but with less toxic drugs than MVAC. Dr. Bajorin, who is heading the trial, said, "Chemotherapy regimens with fewer toxic side effects than M-VAC will be given to patients immediately after surgery. We don't think it's important whether patients are given chemotherapy immediately before or after their surgery. "This has been tested extensively for breast cancer and was found not to make a difference in long-term outcome. What is important is that patients get chemotherapy right away, instead of waiting for disease to recur, at which point it is often too late to treat successfully." source: the MSKCC site http://www.mskcc.org

Update: December 2002 - Concern about interpretations of trial results

It is this same clinical trial (SWOG 8710) that provided the data for expert surgical-uro/oncologist Dr. Harry Herr's presentation at the State of the Science Meeting sponsored by the National Cancer Institute and the Society for Urologic Oncology, December 2002. Dr. Herr's presentation was titled, Surgical Variables Impact Bladder Cancer Outcomes.

Abstract: Surgical variables impact bladder cancer outcomes: A cooperative group report. H. Herr, J. R. Faulkner, H. B. Grossman, E. D. Crawford, for the Southwest Oncology Group; Memorial Sloan-Kettering, New York, NY; SWOG Statistical Center, Seattle, WA; MD Anderson Cancer Center, Houston, TX; U. of Colorado, Denver, CO Proc Am Soc Clin Oncol 22: page 383, 2003 (abstr 1540) Meeting slides at the ASCO site;

The National Cancer Institute and the Society for Urologic Oncology published a transcript
along with same slides of Dr. Harry Herr's presentation to fellow professionals at the 'State of the Science' lecture. He discusses some of the issues around the SWOG8710 trial. Some excerpts:

" ... Chemotherapy effects are eclipsed, unless good surgery is done...when all of these surgical variables are taken into account, the group, that is whether they received MVAC versus surgery alone, tends to become less signigicant. High quality surgery is important. To conclude,.... surgical variables impact bladder cancer outcomes after cystectomy. This appears to be independent of those patients who received chemotherapy. This translates into an experienced surgeon, negative surgical margin, a standard pelvic lymph node dissection, retrieval of at least 10 or more nodes, and a density ratio of less than 20 percent. ..this means the surgical standards need to be factored proscpectively into clinical trials where multiple treatments, especially chemotherapy, are used in order to interpret their results favorably." [see lymph node
density]

New England Journal of Medicine - SWOG 8710, Trial update, Sept. 2003

The September New England Journal of Medicine published an update about the progress of the ongoing randomized phase III clinical trial SWOG 8710, studying the use neo-adjuvant chemo with MVAC followed by cystectomy. The article made headlines in print and on internet medical news sites stating that the pre-op chemo regimen considerably improves the survival rates for invasive bladder cancer. The article gives the strong impression that a survival advantage of +/- 33 months was extended to the chemotherapy arm:

"The median survival among patients assigned to surgery alone was 46 months, as compared with 77 months among patients assigned to combination therapy [MVAC+radical cystectomy]. In both groups, improved survival was associated with the absence of residual cancer in the cystectomy specimen. Significantly more patients in the combination-therapy group had no residual disease than patients in the cystectomy group (38 percent vs. 15 percent). CONCLUSIONS: As compared with radical cystectomy alone, the use of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy increases the likelihood of eliminating residual cancer in the cystectomy specimen and is associated with improved survival among patients with locally advanced bladder cancer."

Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED.M.D. Anderson Cancer Center, Houston, USA.N Engl J Med. 2003 Aug 28;349(9):859-66. Medline
abstract

The Lancet article: a difference of 5% survival at 5 years; a new standard of treatment?

As reported in The Lancet (Volume 361, Number 9373) in June, 2003, researchers from the Advanced Bladder Cancer Meta-analysis Collaboration, based in London, publushed combined results from 10 clinical trials to assess whether or not pre-op chemotherapy had an effect on outcome. Examining data from more than 2,600 patients, the researchers found that combination chemotherapy (using more than one drug as opposed to only one) improved

five-year survival by 5%.

Findings: Platinum-based combination chemotherapy showed a 5% survival benefit at 5 years; overall survival increased from 45% to 50%.

Interpretation This improvement in survival encourages the use of platinum-based combination chemotherapy for patients with invasive bladder cancer.

Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis Advanced Bladder Cancer (ABC) Meta-analysis Collaboration Correspondence to: C Vale, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
Medline
abstract

Editorial Commentary in The Lancet

Expert uro/oncologists Walter M Stadler and Seth P Lerner comment on the Lancet article in the same issue:

Thus, after almost two decades of investigation, the conclusion is that neoadjuvant chemotherapy for patients with locally advanced bladder cancer is a standard of care. A declaration of victory would, however, be out of place. The relative benefit of potentially toxic chemotherapy is extremely modest....with an absolute survival improvement at 5 years of 5%.

Walter M Stadler and Seth P Lerner Departments of Medicine and Surgery, Section of Hematology/Oncology and Urology, University of Chicago, IL 60637, USA (WMS); and Scott Department of Urology, Baylor College of Medicine, Houston, Texas, USA

Another European Opinion on the subject

In October, 2002, experts from Italy stated, " The data available from nonrandomized and randomized trials have not definitively established the exact role of neoadjuvant chemotherapy and its impact on survival. Even if neoadjuvant chemotherapy does not improve survival, preliminary data suggest that bladder preservation may be possible in selected patients and that such combined therapy will hopefully lead to better patient management. The trials of postoperative chemotherapy provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice as a result of small sample size, confusing analyses, and the reporting of questionable conclusions. New large-scale, multicenter trials are imperative to provide convincing results. A better understanding of the microbiology of bladder cancer will influence the search for new therapeutic modalities. Molecular-targeted small-molecule therapy and monoclonal antibodies have begun to dominate contemporary studies." Localized and locally advanced bladder cancer.Calabro F, Sternberg CN.Department of Medical Oncology, Vincenzo Pansadoro Foundation, Via Aurelia 559, Rome 00165, Italy.Curr Treat Options Oncol. 2002 Oct;3(5):413-28. PMID: 12194806 Medline
abstract

A survival advantage of 5% at 5 years must be balanced by clear explanations of risk vs benefit. Little attention seems to have been given regarding quality of life issues from the viewpoint of patient. Given the lack of alternatives at this point, any advantage is welcome in the world of invasive and metastatic bladder cancer.

Fortunately, there are many plans being made now, with experts collaborating on new trial designs. See National Cancer Institute - Priorities of the Kidney/Bladder Cancers Progress Review Group

back to chemos used for invasive bladder cancer