Introduction

Provocative Optimism in the Treatment of Early Stage Disease

NORMAN WOLMARK

National Surgical Adjuvant Breast and Bowel Project, and Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

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This supplement includes reports from a satellite symposium held in association with the 2005 annual meeting of the American Society of Clinical Oncology (ASCO). The focus of the meeting was the early treatment of carcinomas and the move from palliative to curative treatment. Terry Mamounas, associate professor of surgery of the Northeastern Ohio Universities College of Medicine and medical director of the Aultman Cancer Center, discussed the possibility of achieving zero relapse in breast cancer [1]. Mark Kris, from the Memorial Sloan-Kettering Cancer Center, addressed the effect of current treatment in non-small cell lung cancer (NSCLC) on the future standard of care in this patient population [2]. William Oh, from Harvard Medical School, provided an overview of chemotherapy in high-risk localized prostate cancer [3]. Aimery de Gramont, from Hôpital Saint Antoine, reviewed the evolution of the treatment of colorectal cancer (CRC) and discussed future developments [4]. Marc van de Vijver, of the Netherlands Cancer Institute, delivered an overview on gene-expression profiling and the future of adjuvant chemotherapy [5].

On first impression, we have heard similar claims before; talk of breakthroughs, thresholds, and paradigm shifts in therapy have been commonplace. Is this anything different? In my view, it is. The past 2 years have seen unprecedented advances sufficient to justify what I term “provocative optimism.” In part, this is a result of the coming of age of molecularly targeted agents. But it is also a result of our increasing ability to use genomics to identify subsets of patients who are at particularly high risk, or who stand to gain particular benefit even from relatively mundane therapies, such as cyclophosphamide/methotrexate/5-fluorouracil (5-FU) (CMF) chemotherapy in node-negative, receptor-positive breast cancer patients.

As is appropriate, this supplement contains reference in Terry Mamounas’ presentation [1] to the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B-14 gene panel, and a contribution from Mark van de Vijver [5], in which he describes the evolution of his technique for genetic profiling. In light of recent developments in breast cancer, it is not unreasonable to talk about our approaching an era of zero relapse, albeit only in selected populations of patients.

Almost 100 years ago, in 1908, Sir Charles Ball, Regius professor of surgery at the University in Dublin, wrote a passage that eloquently expressed the distant hope of his generation [6]. It seems possible that that hope may be realized in our own.

In Prof. Ball’s words: “We can as yet only look forward to the time when that earnest band of men who are devoting their lives to cancer research will solve the problem of the cause of this terrible disease, and show us how its cure may be effected.

“Then possibly the hypodermic needle may be enabled to claim a greater success than can today be achieved by the most extensive surgical procedures, conducted with scrupulous attention to elaborate technique.”

Correspondence: Norman Wolmark, M.D., National Surgical Adjuvant Breast and Bowel Project, 4 Allegheny Center, Pittsburgh, Pennsylvania 15212, USA. Telephone: 412-359-3336; Fax: 412-359-3096; e-mail: nwolmark@whs.org Received September 7, 2005; accepted for publication September 7, 2005. ©AlphaMed Press 1083-7159/2005/$12.00/0

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CRC offers an example of extraordinary progress. One important illustration is the finding from a study that showed that oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us) in the adjuvant setting can extend disease-free survival [7]. This finding confirmed that an agent valuable in the palliation of advanced disease could also have benefit in a potentially curative context. It is fitting that Aimery de Gramont, who has played such an important role in the evolving story of oxaliplatin and irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com), should be part of this symposium.

Another important development in CRC treatment was the demonstration that the monoclonal antibody bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com) and prolonged survival [8–11]. The question now (further addressed below) is whether this benefit can be translated into the adjuvant setting. CRC treatment is playing catch-up with breast cancer, for which we now know that trastuzumab (Herceptin®; Genentech, Inc., New York, http://www.gene.com) and prolonged survival [8–11].

The outcomes of these studies have implications for three adjuvant trials that have recently been opened. In the N0147 Intergroup study, stage III patients are randomized in a 3 × 2 factorial design to receive FOLFOX, FOLFIRI, or FOLFOX followed by FOLFIRI, with or without cetuximab (Erbitux®; ImClone Systems, Inc., New York, http://www.imclone.com). If the PETACC-3 trial is judged not to show a robust benefit for FOLFIRI, the current Intergroup trial could be collapsed into a study of FOLFOX with or without cetuximab.

There is also interest in the outcome of the NSABP C-07 trial, in which 2,407 stage II and III patients accrued between February 2000 and November 2002 were randomized to weekly LV-modulated bolus 5-FU (FULV) with or without the addition of oxaliplatin (FLOX) at weeks 1, 3, and 5. As in the MOSAIC and other current studies (and as approved by the U.S. Food and Drug Administration), the end point was DFS at 3 years. As results turned out, patients randomized to FLOX did have a significantly better outcome on this primary end point (3-year DFS, 76.5% versus 71.6%; p < .004) [17].

That finding confirmed and extended the MOSAIC data. It suggests that the benefits of oxaliplatin are reproducible and independent of whether the 5-FU schedule is bolus or infusional. It also shows oxaliplatin to be versatile in the settings in which it produces benefit.

The immediately pressing question is whether the benefits of targeting vascular endothelial growth factor with bevacizumab in the advanced setting can also be realized in the adjuvant treatment of CRC. To this end, study NSABP C-08 is randomizing Dukes’ B and C patients receiving FOLFOX6 to receive either bevacizumab or no additional treatment. That trial opened in September 2004. The 520 patients entered so far represent an outstanding rate of accrual, which is continuing steadily toward the target of 2,632.

There is also a global dimension to the effort being made to assess the adjuvant potential of bevacizumab. The AVANT trial B017920 is randomizing stage II and III patients to FOLFOX4, FOLFOX plus bevacizumab, or capecitabine/oxaliplatin (XELOX) plus bevacizumab. Since that trial began in January 2005, 120 of the target number of 3,450 patients have been accrued.

The progress being made in CRC treatment is in many ways emblematic of Sir Charles Ball’s dream. Similar appreciable advances are also being made in NSCLC and in carcinoma of the prostate.

Disclosure of Potential Conflicts of Interest

The author indicates no potential conflicts of interest.


REFERENCES