



Uptake of novel medical therapies in the general population

C.M. Booth MD and B. Rapoport MD MMed†*

KEY WORDS

Outcomes research, health services, breast cancer, chemotherapy, supportive care

~

The randomized controlled trial (RCT) remains the “gold standard” for establishing the efficacy of new medical therapies. Its place in the hierarchy of medical evidence is largely based on the excellent internal validity it offers¹.

Clinicians are accustomed to critically appraising the internal validity of a RCT, but understanding how trial results may relate to patient care and outcomes in the general population often remains less certain. In this issue of *Current Oncology*, Madarnas *et al.* report a retrospective cohort study evaluating the rate of febrile neutropenia associated with FEC-D chemotherapy (5-fluorouracil–epirubicin–cyclophosphamide and then docetaxel) in the general population². The study cohort was assembled from patients treated at 4 regional cancer centres in Ontario, Canada. The impetus for the study was the clinical impression of the investigators that FEC-D was associated with substantial rates of febrile neutropenia beyond those reported in the pivotal clinical trial³. The authors are to be congratulated for formally addressing their clinical hypothesis in the context of a population-based study.

POPULATION-BASED OUTCOME STUDIES

The classic *Users' Guide to the Medical Literature* series introduces clinicians to 3 fundamental questions to ask when considering whether the results of a clinical trial should be adopted in practice^{1,4}:

- “Are the results of this study valid?” relates to fundamental methodologic principles, including randomization, follow-up, blinding, and intention-to-treat analyses.

- “What were the results?” explores issues of effect size and the degree of precision associated with the study findings.
- “Will the results help me in caring for my patients?” relates to the concept of external validity and the degree to which the results may be generalizable to “usual” patient care.

Because patients, physicians, and current care in the general population may be very different from the controlled context of a clinical trial⁵, it is essential to avoid the assumption that outcomes and toxicities in the general population will be comparable to those observed in the controlled context of a clinical trial. Recently, innovative study designs and access to large electronic databases have allowed investigators to evaluate the effects of new medical therapies in the “real world”^{6,7}. These population-based outcome studies can offer insight into the uptake of new therapies and the effects of a change in practice or policy on outcomes. Investigators can also learn about toxicities and outcomes associated with therapies given to patient groups that are often under-represented in RCTs (that is, elderly patients, or those with other medical conditions). Population-based studies also provide a mechanism for identifying gaps in care after publication of a pivotal RCT and can facilitate targeted efforts in knowledge translation.

Important design limitations in such studies include the possibility that changes in outcome at the population level may reflect confounding by other changes in treatment or by case mix. One potential strength of population-based outcome studies is their inclusion of the entire population of interest; for that reason, the referral bias that plagues traditional institution-based observational studies can be minimized. A well-defined temporal (or geographic) difference in practice allows investigators to use a before-and-after approach to minimize error by confounding^{8,9}. Finally, the large sample size in population-based studies provides ample statistical power to identify even small absolute differences

in outcome and toxicity. Population-based outcome studies are increasingly being recognized for their importance in the generation and dissemination of medical evidence^{7,10-12}.

USE OF GRANULOCYTE-STIMULATING FACTORS IN CLINICAL PRACTICE

Neutropenia is the primary dose-limiting toxicity in patients treated with myelosuppressive chemotherapy, leading in some cases to substantial morbidity and early mortality and disrupting treatment with potentially curative regimens. The use of granulocyte colony-stimulating factors (G-CSFs) such as filgrastim and pegfilgrastim as primary prophylaxis starting in the first cycle of chemotherapy has been shown to reduce the rates of febrile neutropenia (FN) and FN-related hospitalization, and the use of intravenous antibiotics¹³. Chemotherapy-induced neutropenia and FN have been documented in breast cancer patients undergoing treatment with anthracycline- and docetaxel-based treatment. Most of the relevant trials reported FN rates of approximately 15%–20%¹⁴.

Filgrastim and pegfilgrastim were originally approved on the basis of their effectiveness in patients treated with chemotherapy regimens that are associated with a 40% or greater risk of FN¹⁵. Current guidelines recommend that G-CSF be used in patients receiving chemotherapy regimens that are associated with a 20% or greater risk of FN¹⁴. Pegfilgrastim, which is given once per cycle, has been shown to reduce the risk of FN by 94% in breast cancer patients treated with docetaxel. The randomized phase III study reporting that statistic was conducted in 928 patients, among whom 465 received placebo and 463 received pegfilgrastim¹⁶. Compared with patients receiving placebo, patients receiving pegfilgrastim had a lower incidence of FN (1% vs. 17%, $p < 0.001$), of FN-related hospitalization (1% vs. 14%, $p < 0.001$), and of use of intravenous antibiotics (2% vs. 10%, $p < 0.001$). However, it is important to emphasize that this prospective phase III study failed to show a reduction of mortality in its patient population.

Other studies with pegfilgrastim showed similar results. The U.S. Oncology Research Group conducted a trial in women undergoing doxorubicin and docetaxel treatment for breast cancer¹⁷. That study showed a reduction in the incidence of neutropenia. Similarly, an Italian study investigated the use of pegfilgrastim in women receiving CMF (cyclophosphamide–methotrexate–5-fluorouracil) chemotherapy. That trial demonstrated that the use of pegfilgrastim was well tolerated and that it provided effective protection against neutropenia in patients receiving intravenous CMF on days 1 and 8, allowing chemotherapy to be delivered on time and at the scheduled dose in most patients¹⁸. Despite the positive findings related to neutropenia, both of the foregoing studies failed to demonstrate a reduction

in mortality in the patients. The use of G-CSF support with an intensified regime has been reported by the Cancer and Leukemia Group B 9141 study in the adjuvant setting in women with breast cancer¹⁹. That study failed to show improvement in outcomes with the use of a maximally dose-intensified regimen of doxorubicin and cyclophosphamide in conjunction with G-CSF support.

To our knowledge, no prospective studies have demonstrated an improvement in quality of life for women with breast cancer treated with prophylactic G-CSF.

PAPER BY MADARNAS *et al.* AND PACS-01

The study by Madarnas *et al.*² serves as an example of how population-based data can augment knowledge of new medical therapies. In 2006, the results of PACS-01 were published, establishing the improved efficacy of FEC-D adjuvant chemotherapy compared with standard FEC-100³. The 1999 participating patients were randomized to receive 6 cycles of standard FEC-100 or 3 cycles of FEC-100 followed by 3 cycles of docetaxel. The primary endpoint was 5-year disease-free survival. Patients in the FEC-D arm experienced improved disease-free survival (78.4% vs. 73.2%, $p = 0.011$) and overall survival (90.7% vs. 86.7%, $p = 0.014$) at 5 years. Rates of FN were greater in the experimental arm (11.2% vs. 8.4%) and coincided with the introduction of docetaxel at cycle 4. Primary prophylaxis with G-CSF or antibiotics was prohibited.

Given the impressive magnitude of benefit reported in PACS-01, it is not surprising that FEC-D was adopted into clinical practice after publication of the pivotal trial. Madarnas and colleagues initiated their current study after noting a substantial rate of FN in their own clinical practices. Using patient data pooled from investigators at 4 regional cancer centres, Madarnas *et al.* identified 671 patients who were prescribed adjuvant FEC-D for early-stage breast cancer between June 2006 and December 2008. The occurrence of FN in 22.7% of all cases largely coincided with the introduction of docetaxel at cycle 4. In a departure from the clinical trial protocol, some clinicians adopted primary prophylaxis with G-CSF. Febrile neutropenia was observed in 6.4% of patients who received primary growth factor support and in 31.4% of patients who did not receive such support. The rate of FN among patients in the general population that did not receive G-CSF support was 3 times that seen in the clinical trial (31% vs. 11%).

The data presented by Madarnas *et al.* suggest a substantial reduction in the incidence of FN with the use of growth factor support. However, this retrospective study did not show a statistically significant reduction in mortality. In addition, given the reliance on retrospective data from 4 centres, the study lacked detailed information about comorbidity or performance status,

both of which are well-established risk factors for FN²⁰. Furthermore, a determination of whether the care delivered to patients in PACS-01 differed in a substantial way from the care provided at the 4 regional cancer centres in Ontario is impossible. As highlighted by Madarnas *et al.*, recent work has demonstrated that clinical trial reports often lack essential therapeutic details necessary for appropriate adoption of the therapy in a general population²¹.

Madarnas and colleagues concluded that patients should be considered for prophylactic treatment with G-CSF in the setting of adjuvant treatment for breast cancer. However, the use of G-CSF cannot be routinely recommended based on a retrospective analysis; furthermore, this treatment has not been shown to be associated with a reduction in mortality or an improvement in quality of life. Prospective studies with a higher level of evidence failed to show a lower mortality rate in breast cancer patients prophylactically treated with G-CSF. Advanced age is one of the conditions for which prophylactic use of G-CSF may be indicated, regardless of the threshold risk of neutropenia. However, aside from data in patients with lymphoma, evidence to support the use of prophylactic G-CSF based solely on the age of the patient is insufficient¹⁴. Finally, it is important to recognize that most of the commonly used chemotherapy regimens have a FN risk of less than 20%. In determining whether to use prophylactic G-CSF in the adjuvant setting, clinicians should consider the optimal chemotherapy regimen for the individual patient, the risk factors for the individual patient, and treatment intent.

Clinicians may occasionally be faced with patients who might benefit from relatively non-myelosuppressive chemotherapy, but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary G-CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Clinical factors that predispose to increased complications from prolonged neutropenia include patient age greater than 65 years; poor performance status; extensive prior treatment, including large radiation ports; cytopenias because of bone marrow involvement by tumour; poor nutrition status; the presence of open wounds or active infections; and other serious comorbidities. In such situations, primary prophylaxis with CSF may be appropriate even with regimens having FN rates less than 20%¹⁴.

SUMMARY

In PACS-01, a clinically important improvement in patient outcomes demonstrated with adjuvant FEC-D led to early adoption of the regimen for patients

treated at 4 regional cancer centres in Ontario. The population-based retrospective data presented by Madarnas *et al.*² demonstrate an unexpectedly high rate of FN that raises important questions about how FEC-D should be used and whether primary growth factor support has a role to play. Further efforts are needed to better understand how novel therapies are used in the general population and whether they translate to outcomes that are comparable to those reported in the relevant clinical trials.

ACKNOWLEDGMENTS

Dr. Booth is supported as a Cancer Care Ontario Chair in Health Services Research.

CONFLICT OF INTEREST DISCLOSURES

The author has no conflicts of interest to declare.

REFERENCES

1. Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. *JAMA* 1998;279:545-9.
2. Madarnas Y, Dent SF, Husain SF, *et al.* Real-world experience with adjuvant FEC-D chemotherapy in four Ontario regional cancer centres. *Curr Oncol* 2011;18:119-25.
3. Roché H, Fumoleau P, Spielmann M, *et al.* Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. *J Clin Oncol* 2006;24:5664-71.
4. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1993;270:2598-601.
5. Meyer RM. Generalizing the results of cancer clinical trials. *J Clin Oncol* 2010;28:187-9.
6. Wen SW, Kramer MS. Uses of ecologic studies in the assessment of intended treatment effects. *J Clin Epidemiol* 1999;52:7-12.
7. Booth CM, Mackillop WJ. Translating new medical therapies into societal benefit: the role of population-based outcome studies. *JAMA* 2008;300:2177-9.
8. Groome PA, Mackillop WJ. Uses of ecologic studies in the assessment of intended treatment effects. *J Clin Epidemiol* 1999;52:903-4.
9. Earle CC, Tsai JS, Gelber RD, Weinstein MC, Neumann PJ, Weeks JC. Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. *J Clin Oncol* 2001;19:1064-70.
10. Vlahakes GJ. The value of phase 4 clinical testing. *N Engl J Med* 2006;354:413-15.
11. Avorn J. In defense of pharmacoepidemiology—embracing the yin and yang of drug research. *N Engl J Med* 2007;357:2219-21.
12. Juurlink DN. Rosiglitazone and the case for safety over certainty. *JAMA* 2010;304:469-71.

13. Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009;23:175–86.
14. Smith TJ, Khatcheressian J, Lyman GH, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–205.
15. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994;12:2471–508.
16. Vogel CL, Wojtukiewicz MZ, Carroll RR, *et al.* First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2005;23:1178–84.
17. Holmes FA, Jones SE, O'Shaughnessy J, *et al.* Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Ann Oncol* 2002;13:903–9.
18. Mattioli R, Gridelli C, Castellanos J, *et al.* Use of pegfilgrastim support on day 9 to maintain relative dose intensity of chemotherapy in breast cancer patients receiving a day 1 and 8 CMF regimen. *Clin Transl Oncol* 2009;11:842–8.
19. Liu MC, Demetri GD, Berry DA, *et al.* Dose-escalation of filgrastim does not improve efficacy: clinical tolerability and long-term follow-up on CALGB study 9141 adjuvant chemotherapy for node-positive breast cancer patients using dose-intensified doxorubicin plus cyclophosphamide followed by paclitaxel. *Cancer Treat Rev* 2008;34:223–30.
20. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 2004;100:228–37.
21. Duff JM, Leather H, Walden EO, LaPlant KD, George TJ Jr. Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application. *J Natl Cancer Inst* 2010;102:702–5.

Correspondence to: Christopher Booth, Queen's University Cancer Research Institute, 10 Stuart Street, Kingston, Ontario K7L 3N6.

E-mail: boothc@kgh.kari.net

* Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, ON.

† Medical Oncology Centre of Rosebank, Johannesburg, South Africa.