IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

The silent minority – unpublished data on cancer care

Daniel F. Hayes

From 1989 to 2003, 709 phase III trials evaluating systemic cancer treatment were presented at ASCO meetings. Tam and collaborators have now reported that 9% of these trials were never published, and 13% were published after a five-year delay. More than half of these studies would have had clinical impact if published promptly.

This article was first published in ***Nature Reviews Clinical Oncology*** vol.8 no.11, and is published with permission.
 doi:10.1038/nrclinonc.2011.148, www.nature.com/nrclinonc

Two key elements of the scientific method are methodology transparency and reproducibility of results by others. Traditionally, these elements have been facilitated by the well-entrenched system of peer-review publication. This concept has had almost universal acceptance among the scientific community, although in the past few years there have been calls for open publication of all scientific results without the peer-review process. Some experts have advocated the creation of a type of 'free-for-all' post-publication peer review, with the view that classic, pre-publication peer review is usually selective (based on whom the editor knows and on who actually agrees to referee the article) and arbitrary (based on the respective biases of the reviewers).[1] A search in PubMed with the search terms "journal: Nature" and "all fields: peer review" yielded more than 300 articles, commentaries, and letters extolling the virtues and weaknesses of the system.

Regardless of the outcomes of this debate, at present, the peer-reviewed manuscript remains the gold standard for establishing whether a scientific concept is worthy of further pursuit, and whether there should be a change in the accepted paradigm in the respective field. Although this dictum is accepted in all areas of science, perhaps it is of most relevance in the field of medicine, as acceptance of a new scientific concept leads to a change in clinical practice, thereby affecting the lives of patients afflicted with, or at risk of, a particular disease.

A recent article by Tam et al.[2] in the *Journal of Clinical Oncology* documents a worrisome failure to publish results of phase III randomised trials that were previously reported in abstracts and presentations at the annual meeting of ASCO. They report that, of the 709 abstracts of phase III studies presented at ASCO meetings from 1989 to 2003, nearly a quarter (162 trials including almost 24,000 enrolled patients) were not published in peer-reviewed journals within five years after the meeting in which they were presented. Even after 10 years of follow up, 9% of the presentations remained unpublished. To determine what the relative impact of these studies might have been on clinical practice if they had been published, the researchers queried experts in several of the major cancer types (such as breast,

lung, gastrointestinal and haematologic), who estimated that 38 of 54 (70%) of the unpublished studies "addressed important clinical questions." Although none of the 38 studies was judged to have "critical impact," 32 of them "may have had some impact on clinical practice if the results had been published shortly after presentation."[2]

What can practising physicians learn from these data? Are there any unpublished results that are also unknown to the average physician, and is peer-review publication actually necessary to guide clinical practice? In the days before rapid internet access and widespread attendance at major medical meetings, clinical practice was mostly driven by four factors: publication of data in peer-reviewed journals; expert opinion expressed in published reviews and/or continuing medical education (CME) meetings; pharmaceutical representatives providing drug information; and personal or colleagues' experience. Today, any report presented at a major meeting, without having been published in a peer-reviewed publication, can have a substantial impact on practice. Attendance at meetings has risen dramatically. Nearly 30,000 people attended the ASCO annual meeting in 2010, compared with 3000 in 1980. Furthermore, results from ASCO and other major meetings are now made widely available, occasionally in real time, as webcasts or other media presentations for those not able to attend in person. The effects of these changes on practice are exemplified by the rapid acceptance of adjuvant trastuzumab for patients with HER2-positive breast cancer following the reporting of dramatic reductions in recurrence from four prospective randomised clinical trials at the May 2005 ASCO meeting.[3,4,5] In a survey of practising oncologists conducted in February 2005, fewer than 10% reported that they would recommend adjuvant trastuzumab for a patient with node-positive, HER2-positive breast cancer.[6] In August of that same year, just three months after the ASCO presentation, more than 95% of oncologists said they would recommend adjuvant trastuzumab, preceding the peer-reviewed publications by several months. This sea change in practice was a result of physicians attending the ASCO meeting (36%), attending other meetings in which the ASCO results were provided (56%), and/or hearing about the data in either CME-like publications, audio series or in the lay press.[7]

These considerations, however, do not obviate the need for peer-reviewed publications. Meeting abstracts usually consist of only two to three paragraphs in a proceedings booklet. Often, they do not even include results data, but rather a promise that they will be presented at the meeting. Abstracts cannot replace a complete report that details the design of the study, inclusion and exclusion criteria, dose and schedules used for the treatments and, most importantly, nuances of the benefits and toxic effects of the treatments. This desired level of detail is also not provided by a ten-minute presentation prepared solely by the author (sometimes with substantial influence by a supporting pharmaceutical company) with a five-minute question and answer period. Moreover, the media and public relations coverage at major meetings may amplify the true significance of the results, as they are often fuelled by companies or individuals with vested or biased interests in the drugs involved in the covered studies. So, although it is appropriate to consider an immediate application in practice of paradigm-changing results presented at a meeting, research ethics demand rapid publication of the full details in peer-reviewed publications to guide long-term clinical behaviour.

Furthermore, a single study alone may not change practice. Tam et al.[2] raise a second concern: that the lack of publication may prevent inclusion of important results in meta-analyses of published results, which often confirm or refute conclusions made from a single study. Some meta-analyses have attempted to identify trial reports included in abstracts from major meetings, and others have been able to include patient source data from trials regardless of publication status.[8,9] However, by definition, those meta-analyses that rely on the identification of studies through publicly accessible databases are hindered as a consequence of this lack of publication.

There is a difference in studies that are published compared with those that are not. It has been established that very positive studies are often published very quickly, whereas negative studies often languish on the investigators' desk or are not accepted by major journals and are relegated to journals with lesser impact. This publication bias, as a consequence of either authors' recalcitrance or editors' decisions, is a major concern in regards to making clinical decisions. Tam et al.[2] cite a number of previously recommended solutions for the problem of non-publication of clinical trial data: mandated publication as a condition of external funding or by ethics committee approval; medical journal acceptance of studies with negative results, perhaps in special sections of the journal; and/or

Practice points

- Practicing physicians need to keep up to date with data presented at major meetings as well as peer-reviewed publications
- Investigators need to accept the responsibility for publishing results that they present at meetings

insistence of inclusion of unpublished studies in meta-analyses and expert opinion reviews. They point out that the existence of transparent, publicly accessible trial registries is already in place, enabling interested parties to determine which studies have been opened and/or completed and whether they are published or not. A recently published article has called for such a registry in the field of clinical tumour marker studies, which suffers even more from publication bias than does that of prospective therapeutic trials.[10]

In summary, peer review is not perfect, and could certainly benefit from reform, but to paraphrase Winston Churchill's comment about democracy: "[it] is the worst form of government except all the others that have been tried." It is reassuring that unpublished results represent a small minority of clinical trial results in oncology, but their silence is disturbing. The stakes are high. Patients who participated in these trials did so out of a sense of altruism, and we betray that trust if we do not handle the precious data generated in these studies appropriately. Perhaps more important, future patients' well being and even their lives are at risk, and clinical decisions affecting these patients should not be left to the whims and vagaries of poorly reported evidence. I strongly concur with the reform recommendations and urge those with roles as funders, ethics reviewers, and editors to endorse and enforce them.

References

1. R Smith (2010) Classical peer review: an empty gun. *Breast Cancer Res* 12 (Suppl. 4):S13
2. VC Tam, IF Tannock, C Massey et al. (2011) Compendium of unpublished phase III trials in oncology: characteristics and impact on clinical practice. *JCO* 29:3133–39
3. EH Romond et al. (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *NEJM* 353:1673–84
4. MJ Piccart-Gebhart et al. (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *NEJM* 353:1659–72
5. H Joensuu et al. (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *NEJM* 354:809–820
6. N Love (ed.) (2005) *Patterns of care in medical oncology – Breast cancer edition*, vol. 1. Research to Practice, Miami
7. N Love (ed.) (2005) *Patterns of care in medical oncology – Breast cancer edition*, vol. 2. Research to Practice, Miami
8. C Lefebvre, E Manheimer and J Glanville. (2011) In: *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (JPT Higgins and S Green eds.), chap. 6. The Cochrane Collaboration, http://www.mrc-bsu.cam.ac.uk/cochrane/handbook/index.htm#chapter_6/6_7_chapter_information.htm
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365:1687–1717
10. F Andre et al. (2011) Biomarker studies: a call for a comprehensive biomarker study registry. *Nat Rev Clin Oncol* 8:171–176

Author affiliations
University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA

Competing interests
Daniel F. Hayes declares associations with the following organisations and companies: Biomarker Strategies, Chugai Pharmaceuticals, Novartis, Oncimmune, Pfizer, Veridex

Acknowledgements
Supported in part by a grant from the Fashion Footwear Charitable Foundation of New York/QVC Presents Shoes on Sale

Hodgkin lymphoma – absence of evidence not evidence of absence!

➜ Peter Borchmann, Andreas Engert and Volker Diehl

The optimal treatment for patients with advanced-stage Hodgkin lymphoma is an ongoing controversy. A recent trial seemed to answer some of the important open questions in the field; however, closer examination of the data indicates that the answers are not as clear as they might initially seem.

This article was first published in ***Nature Reviews Clinical Oncology*** vol.8 no.11, and is published with permission.
 doi:10.1038/nrclinonc.2011.149, www.nature.com/nrclinonc

The majority of patients (85–95%) with advanced-stage Hodgkin lymphoma can be cured; however, it is currently unclear which treatment strategy offers the best balance between toxicity and efficacy. This key question has been discussed extensively since the introduction of the dose-intense therapy BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) a decade ago. The efficacy and toxicity of BEACOPP in patients with advanced-stage Hodgkin lymphoma was initially evaluated in the GHSG-HD9 trial that compared it with COPP–ABVD (an alternating regimen of cyclophosphamide, vincristine, procarbazine and prednisone [COPP], and doxorubicin, bleomycin, vincristine and dacarbazine [ABVD]).[1] With 10 years of follow up, the escalated regimen of BEACOPP was clearly superior to COPP–ABVD in terms of tumour control – the difference in freedom from treatment failure was 18% and the difference in overall survival was 11%.[2] However, despite the efficacy superiority of BEACOPP over COPP–ABVD, ABVD alone followed by consolidation radiotherapy

for residual disease (required by approximately 65% of patients) is still commonly being used to treat patients with advanced-stage Hodgkin lymphoma. This lack of change in the treatment paradigm has arisen because COPP–ABVD was not regarded as standard of care by some opinion leaders owing to its similar efficacy but increased toxicity compared with ABVD alone.[3,4]

With regard to the lower efficacy of ABVD as compared with BEACOPP (five-year progression-free survival difference 14%; overall survival difference 8%),[5] those advocating ABVD as first-line treatment refer to the 'second-shot' hypothesis that includes high-dose chemotherapy as late intensification in patients who have progressive disease or who relapse after first-line ABVD. These patients can be rescued with high-dose chemotherapy – the 'second shot'. This strategy results in an overall survival rate of 80–85% for the whole group, including those patients (estimated 25–35%) who require high-dose chemotherapy rescue.

By contrast, an early intensification approach (the 'Kairos Principle') using the more-effective (but also more-toxic) BEACOPP regimen aims to cure as many patients as possible with a 'first shot'. After treatment with BEACOPP, only 12% of patients need consolidation radiotherapy and only 10–15% of patients will relapse,[6] which results in an overall survival rate of 90–95% at five years (A Engert et al., unpublished data). First-line treatment with BEACOPP has been adopted by most European study groups as standard-of-care for advanced-stage Hodgkin lymphoma.

When one considers particularly the survival difference between treatment with ABVD and BEACOPP one might wonder why one should treat young and otherwise fit patients with Hodgkin lymphoma using ABVD. The reason for the persistent use of ABVD in this patient population is the lack of evidence from randomised trials. Only one trial has directly compared BEACOPP with ABVD, and this trial was too small to obtain significance for survival rates.[5] Therefore, there has been a debate on the question of whether ABVD results in preventable death for one in ten patients or if BEACOPP is an unnecessarily aggressive overtreatment for three quarters of patients.[6]

Against the background of this controversial discussion, a recent publication in the *New England Journal of Medicine* has come as a surprise. Viviani et al.[7] report a direct comparison of a modified BEACOPP regimen with ABVD; both regimens were followed by salvage high-dose chemotherapy for relapsing or progressing patients. The aim of this study was to analyse long-term disease control and treatment-induced morbidity.

Although the comparison of these treatment strategies had been eagerly awaited, unfortunately the trial design is inadequate to answer this 'main' objective. The trial was designed and powered only for the primary endpoint (freedom from first progression), and testing hypotheses for secondary endpoints such as overall survival is specifically excluded by the authors (see statistical analysis plan, page 14, section 14.3 in the online appendix).[7] Nonetheless, *P* values for secondary endpoints are presented throughout the manuscript. The 5% overall survival difference in favour of BEACOPP is interpreted by the authors as 'nonsignificant' ($P=0.39$) and an overall benefit for the less-toxic ABVD treatment is concluded; actually, the lack of significance is a limitation of the study, not a result. In fact, the results of this trial are in sharp contrast to the authors' conclusion because there was a survival difference in favour of BEACOPP in line with the significantly superior freedom from first progression, which was the primary endpoint ($P=0.004$).[7] In addition, the conclusions are in contrast to published data showing an overall survival benefit of 8–11% associated with treatment with BEACOPP.[2,5] Thus, if one considers overall survival to be the most relevant endpoint for young patients with cancer, the data presented by Viviani et al.[7] rather support the early intensification approach provided by first-line treatment with BEACOPP.

When making the assessment of which therapy to use in the first-line setting, one should carefully weigh potential risks and benefits and should have a closer look at the data reported. This closer look at the data is, unfortunately, disappointing; not only the design but also the reporting quality of the Viviani et al.[7] study is surprisingly deficient. The manuscript contains numerous mistakes and discrepancies, both within the publication itself and when compared with a previously reported interim analysis of the same trial, as we have outlined in a letter to the authors that has been accepted for publication in the *New England Journal of Medicine*.[8] Furthermore, regarding the important comparison of the toxic effects associated with the two treatments, Viviani et al.[7] emphasise the problem of late toxicities induced by BEACOPP, but they observed three secondary malignancies in the BEACOPP group, and four in the ABVD group. To underline the good tolerability of ABVD, they cite the results from a clinical trial in which only six cycles of ABVD were applied to each patient;[9] however, eight ABVD cycles were administered in their own study. In fact, little is known about the long-term sequelae (for example, infertility, therapy-induced cardiac dysfunction, bleomycin-induced pulmonary toxicity, and quality of life) associated with eight cycles of ABVD. Unfortunately, the authors have missed the opportunity to add important and missing information to the field.

Even though the publication of the data from the trial seems to have some serious limitations, the reported statistic

that 73% of patients might be cured using ABVD as first-line treatment should be accepted and interpreted. The important question then is how to safely discriminate at diagnosis those patients who will respond to ABVD from those who will progress or relapse after ABVD therapy, which unfortunately is still impossible. As long as we cannot detect these patients, who have a difficult-to-treat and life-threatening disease, patients and physicians should be aware of the overall survival difference in favour of BEACOPP for patients with advanced-stage Hodgkin lymphoma. The conclusion that a 5–11% survival difference is not relevant might sound strange or even cynical to some patients.

Needless to say, we should be carefully looking for evidence to provide the best treatment for our patients. Therefore, we rely on properly designed, conducted and reported clinical studies. Fortunately, medicine is more than just politics. With this in mind, we look forward to the upcoming publication of the EORTC 20012 trial comparing ABVD with a modified regimen of BEACOPP in patients with advanced-stage Hodgkin lymphoma.[10] Even more so, we need to enrol patients into worldwide ongoing clinical trials investigating new strategies such as PET-guided response-adapted treatment to restrict more-aggressive treatment to the subset of patients who really need it.

References

1. V Diehl et al. (2003) Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *NEJM* 348:2386–95
2. A Engert et al. (2009) Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *JCO* 27:4548–54
3. GP Canellos et al. (1992) Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *NEJM* 327:1478–84
4. DB Duggan et al. (2003) Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *JCO* 21:607–614
5. M Federico et al. (2009) ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *JCO* 27:805–811
6. P Borchmann and A Engert. (2010) The past: what we have learned in the last decade. *Hematology Am Soc Hematol Educ Program* pp 101–107
7. S Viviani et al. (2011) ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *NEJM* 365:203–212
8. V Diehl et al. (in press) Should the treatment of advanced Hodgkin lymphoma patients be a question of faith or a question of medical science? *NEJM*
9. A Santoro et al. (1987) Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *JCO*. 5:27–37
10. US National Library of Medicine. (2010) ClinicalTrials.gov

Author affiliations

German Hodgkin Study Group, University Hospital of Cologne, Cologne, Germany (Peter Borchmann, Andreas Engert and Volker Diehl)