European Journal of Cancer 52 (2016) 197–200

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Editorial Comment

Translation failure and medical reversal: Two sides to the same coin

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Received 20 August 2015; accepted 22 August 2015
Available online 12 December 2015

KEYWORDS
Oncology drugs;
Translation failure;
Medical reversal;
FDA approval;
Regulatory bar;
End-points;
Randomised trials;
Hard-wired bias

Abstract Translation failure occurs when the results of preclinical, observational and/or early phase studies fail to predict the results of well done (i.e. appropriately controlled, adequately powered, and properly conducted) phase III or randomised clinical trials.

Some failures occur when promising basic science findings fail to replicate in human studies, while others happen when promising uncontrolled trial data show an exaggerated effect that vanishes in the setting of a randomised trial.

Medical reversals occur when the results of preclinical, observational and/or early phase studies fail to predict the results of subsequent randomized clinical trials, but the practice has already gained widespread acceptance. Oncologic examples include bevacizumab and the use of autologous stem cell transplant in metastatic breast cancer.

In a well-intentioned effort to reduce the rate of translation failure, oncologists must be careful that changes to regulatory processes and clinical trial design do not actually work to increase the approval of ineffective compounds. By trying to cure translation failure, we should be careful to avoid medical reversal. The rise of surrogate end-points and role of hard-wired bias in oncology trials suggest that we may be currently ignoring the simple fact that translation failure and medical reversal are two sides to the same coin.
Published by Elsevier Ltd.

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http://dx.doi.org/10.1016/j.ejca.2015.08.024
0959-8049/Published by Elsevier Ltd.

1. Translation Failure and Medical Reversal: Two Sides to the Same Coin?

Translation failure occurs when the results of preclinical, observational and/or early phase studies fail to predict the results of well done (i.e. appropriately controlled, adequately powered, and properly conducted) phase III or randomised clinical trials. Recently, the mammalian target of rapamycin inhibitor everolimus was tested in a phase III trial, called EVOLVE-1, against best supportive care among patients with advanced or metastatic hepatocellular carcinoma whose disease had progressed on the only Food and Drug Administration (FDA) approved therapy, sorafenib [1]. That trial, included over 500 patients, and employed 2:1 randomisation, but failed to show either an overall survival (OS) or progression free survival (PFS) benefit from everolimus. EVOLVE-1 is emblematic of translation failure in oncology: a costly phase III trial fails to show a benefit for a promising compound and drug development is halted. Indeed, everolimus was a promising drug for this indication. In their publication, the authors of EVOLVE-1 cite 12 distinct references, reflecting well done basic science studies, all supporting their hypothesis. Yet, despite this abundant preclinical data, the phase III trial failed.

Based upon studies like EVOLVE-1 investigators have sought to improve the success rate of phase III trials, but by doing so, the field has increasingly embraced surrogate end-points of dubious clinical significance. As such, it is likely that in pursuing our goal of reducing translation failure, we may inadvertently be adopting therapies that will be contradicted down the road, a phenomenon called medical reversal.

2. How prevalent is translation failure in oncology?

Empirical analyses reveal that translation failure is common for drugs in the cancer drug pipeline, and may exceed the failure rate for other fields, such as cardiology or infectious disease [3]. Hay and colleagues recently reported on the experience of over 4000 drug products, which sought approval for 7000 indications from over 750 pharmaceutical and biotechnology companies between the years 2003–2011 [3]. These results represent the largest empirical analysis of translation successes and failures to date.

Among all compounds examined, which had at least entered phase I testing, future follow up found that just 10.4% of marketing indications pursued led to FDA approval [3]. Oncology drug products did worse than other fields with a 6.7% likelihood of progressing from phase I to FDA approval [3].

Some writers have blamed the epidemic of drug failures on poor reproducibility of preclinical research [4]. Yet, translation failure cannot be blamed solely on failures of basic science to yield clinical results, as failure occurs at all stages of drug development, including the phase II to phase III transition—where promising historically controlled data fail when tested in a randomised fashion [3]. In a seminal example of phase II to III failure, Fisher and colleagues report, on behalf of the Eastern Cooperative Group, that the multi drug regimen ProMACE-cytaBOM did not improve time to treatment failure (TTF) or OS compared against the prior generation combination chemotherapy, CHOP [5]. At the time, many found the results shocking as ProMACE-cytaBOM had demonstrated impressive TTF and OS in uncontrolled phase II trials [6]. Although the dose intensity of ProMACE-cytaBOM was the same in the single centre and multi centre study [5], response rate was 30 percentage points lower [5,6]— a surprising, but common finding. Zia and colleagues have empirically examined discrepant response rates in phase II and phase III testing, noting that 85% [CONFIRM] official the time the response rate (RR) in phase II trials exceeds the response rate in subsequent phase III testing, suggesting a consistent trend to spurious and exaggerated results in uncontrolled trials [7]. The lesson here is two fold: first, that basic science irreproducibility does not account for all translation failure, and second, that the field of oncology is prone to a well-recognised bias in evidence based medicine—the unreliability of historically controlled data [8].

3. The vexing problem of medical reversal

Translation failure occurs when preclinical or early trial evidence fails to predict success in subsequent well done randomized controlled trial (RCTs), while medical reversal occurs when the same preliminary evidence similarly fails to predict subsequent success, but the practice has already been widely adopted [2]. The case of autologous transplantation for breast cancer captures many of the hallmarks of reversal.

In the 1980s and 90s, uncontrolled experiences found that intensive chemotherapy with an autologous stem cell salvage could induce remission among some patients with metastatic breast cancer, and this was thought to confer long term survival in a subset of women [9–11]. At a minimum, autologous stem cell transplant, was considered superior to conventional chemotherapy, and became widely adopted though it lacked randomised controlled trial evidence of benefit. Some estimate that 30 to 40,000 women underwent this treatment outside of any clinical protocol [9,12]. However, when multiple randomised trials had been conducted on this clinical question—a clear consensus emerged: auto-transplantation carried significantly greater toxicity, but no improvement in survival [13].

Another medical reversal in oncology is the use of bevacizumab in combination with chemotherapy in