EDITORIAL

Liaisons Dangereuses? new drugs, physicians and the drug industry

Robert Peter Gale¹ · Hillard M. Lazarus²

Received: 10 April 2020 / Accepted: 23 June 2020 / Published online: 1 July 2020

© The Author(s), under exclusive licence to Springer Nature Limited 2020

US Food and Drug Administration (FDA) has approved record numbers of new cancer drugs in recent years. Many are relevant to readers of *BONE MARROW TRANSPLANTATION* who treat acute myeloid leukaemia (AML) including midostarin, gilteritinib, venetoclax, enasidenib, ivosidenib, glasdegib, acute lymphoblastic leukaemia

including inotuzumab ozogamicin, blinatumomab, dasatinib, ponatinib and tisagenlecleucel, chronic myeloid leukaemia including ponatinib and bosutinib, plasma cell myeloma including daratumumab, selinexor, elotuzumab, panobinostat and ixazomib, chronic lymphocytic leukaemia including ibrutinib, idelalisib and ofatumumab, lymphoma including vorinostat, mogamulizumab-kpkc, polatuzumab vedotin-piiq, acabrutinib, brentuximab vedotin, zanubrutinib, axicabtagene ciloleucel and tisagenlecleucel, myeloproliferative neoplasm (MPN)-associated myelofibrosis including fedratinib and acute and chronic graft-versus-host disease (GvHD) including ibrutinib and ruxolitinib.

This is extraordinarily good news but raises questions whether everyone receiving a haematopoietic cell transplant needs and/or benefits from these new drugs and whether physicians were complicit in promoting their approval and subsequent use. These questions are especially important in developing countries where many of these new drugs are not yet or may ever be approved, available and/or affordable.

First, do these new drugs really improve survival? For example, many approvals in AML relevant to haematopoietic cell transplantation were based on data from small, sometimes uncontrolled phase-2 studies. Also, many regular approvals were based on surrogate endpoints such as complete or overall response rate, response duration and/or progression-free survival (PFS) rather than survival. For example, between 2009 and 2014 the US FDA-approved 83 cancer drugs, 55 based on surrogate outcomes including 31 based on overall response rate and 24 based on PFS [1]. All accelerated approvals and one-half of conventional approvals were based on treatment effects with surrogate outcomes. In a recent review fewer than one-half of drugs approved based on a PFS endpoint were shown to improve survival or *quality-of-life* (QoL) [2]. Similarly, between 2009 and 2013 the European Medicines Agency (EMA) approved 48 cancer drugs only one-half of which were proved to increase survival or improve QoL [3]. Another problem with several new drug approvals is the choice of an

✉ Robert Peter Gale
robertpetergale@alumni.ucla.edu

¹ Centre for Haematology Research, Department of Immunology and Inflammation, Imperial College London, London, UK

² Department of Medicine, Division of Hematology and Oncology, Case Western Reserve University, Cleveland, OH, USA

inappropriate comparator therapy in randomized phase-2 or phase-3 trials. Finally, many of these approvals were based on analyses of hazard ratios rather than a preferred mean restricted survival time [4].

Another issue is the magnitude of benefit conferred by new drugs like midostaurin and how they should be used in persons with AML with a *FLT3* mutation. In the randomized study of midostaurin 57 percent of subjects received an allotransplant with an important imbalance between the midostaurin and placebo cohorts in subjects transplanted in 1st complete remission (28% versus 23%; $P = 0.10$) [5]. Elsewhere my colleagues and I explain this P value does not mean there is no difference in transplant rates between the arms [6, 7]. Rather, this P value means it is very likely transplant rates are different and that the *null hypothesis* is simply not a good statistical model of these (or more extreme) data. More importantly, although the trial reported a survival benefit of pretransplant midostaurin, many physicians fail to appreciate midostaurin was stopped at the time of transplant and that there are not data supporting giving midostaurin after a transplant regardless of whether it was given pretransplant. Our informal survey indicates most transplant physicians continue giving midostaurin despite this lack of supporting data. Their motto seems: *it can't hurt*. (Sounds like President Trump promoting chloroquine, hydroxychloroquine and bleach for COVID-19.) But who knows?

Some data suggest one reason many new drugs gain favour with physicians and patients is because they are promoted by nationally or internationally by disease experts often referred to as key opinion leaders (KOLs) and by drug companies, often in media advertisements. *Une liaison dangerous?* This may be so in some instances [8]. However, there are several complex considerations here. KOLs are frequently principle investigators in the clinical trial(s) resulting in a new drug approval. Often, they believe, sometimes strongly or even too strongly, the new drug is an important advance. In psychology this process is known as *confirmation bias*. Having invested several years studying a new drug, often with considerable effort and problems working with ethical committees, clinical research organizations (<https://www.ashclinicalnews.org/viewpoints/editors-corner/contract-research-agonizations/>); sometimes known as clinical research aggravations), drug company study managers etc. people want to believe their effort worthwhile. Otherwise one would seem to have wasted their time, energy and perhaps destroyed your marriage, missed your children growing up, both or perhaps something even worse (a fling in Cancun?).

But we need to acknowledge other considerations such as the requirement to publish for *academic* promotion and advancement. It is far easier to publish a study claiming a new, typically more expensive drug is better than an old,

typically cheaper drug than the converse. And there are also some less altruistic considerations. Everyone likes to address a large, admiring audience, have your headshot (typically of you 20 years ago) projected on a huge screen, travel abroad, be feted at a reception and dine in Le Bernadine in New York, The Ivy in London or *La Tour d'Argent* in Paris. This behavior is human nature and we cannot unfairly fault them. Generic drug makers are likely to take you and the meeting organizers to Nathan's Famous Hot Dogs in Coney Island for dinner (excellent but expensive; currently \$7.99 USD; 2 for \$15.00), no fries or, for Europeans, traditional pie 'n' mash with eels at Cockney's at 314 Portobello Road, London W10 5RU (£ 7). Everyone likes to be liked.

In contrast, consider a world where drug companies do not develop new drugs for the diseases we need to treat. First, we would be left with methotrexate and corticosteroids to prevent or treat GvHD. Almost all new drugs we use in the past 30 years have come from drug companies, not academia. But there are other far-reaching implications. For example, annual educational meetings such as those of the recent Transplantation and Cellular Therapy (TCT) meeting in Orlando and the European Bone Marrow Transplant Group (EBMT) Meeting in Frankfurt would have 2000 rather than 3000 attendees. About one-third of the attendees are drug company employees or physicians sponsored to attend the meeting by drug companies. Much of the funding for these annual meetings comes from the drug industry, not registration fees. TCT and EBMT charge drug companies substantial monies for exhibition space and for the opportunity to present their new drugs in so-called *product theatres*. Imagine an exhibition space at one of these meetings without drug company booths. It would look like Grand Central Terminal devoid of people with only the central lonely information kiosk. A world without free cappuccino or frozen yogurt, video games, giveaways for which physicians earning >\$ 300,000 per year are willing to queue for 15 min. Amazing. *BLOOD AND MARROW TRANSPLANTATION* is filled with advertisements for new drugs. I doubt many journals would be able to achieve widespread distribution at a reasonable cost to society members without advertising income. Likewise, their websites are where you are bombarded by unsolicited advertisements for new transplant-related drugs. And think of the exhibit areas at the TCT and EBMT meetings. Our point is that although it is popular to disparage the drug industry for promoting new drugs with sometimes marginal benefits and high costs, the medical community benefits greatly from the investment of these drug companies. Much of our medical education in diverse areas is indirectly supported by the drug industry. Our lives would be entirely different if drug companies developing and promoting

new drugs ceased to exist. And we would be eating hot dogs at Nathan's rather than black cod in miso at Nobu. Remember, the estimated cost of bringing a new cancer drug to approval is about \$700 million USD [9]. These monies come from drug company research and development and need to be returned to stockholders with a profit.

Have we a solution to these potential *liaisons dangereuses* likely to work? No. It is unreasonable to expect drug companies not to promote drugs they have developed at great cost. Professional societies and publishers are addicted to drug company support. Individual investigators fight to participate in clinical trials of interesting drugs. Co-investigators fight for lead authorship on publications of successful drug trials which come with designation as a KOL and extensive travel on what are labeled *educational symposia*. Regulatory agencies such as US FDA and EMA have helped curb inappropriate drug labeling and promotional activities but have limited jurisdiction and are subject to political influences.

In the US, FDA is required by law to approve any drug determined *safe and effective* whether or not the new drug is safer or better than a current drug. Price is dictated by the drug company, not the FDA. Cost control (if any) lies with the Centers for Medicare and Medicaid Services (CMS), payor for Americans without medical insurance and for persons >65 years and with pharmacy benefit managers who affect discounts, not price. Moreover, US physicians can prescribe any FDA-approved drug in settings different from those for which the drug was approved, a practice termed *off-label* use. Again, the only control of off-label use are payors.

Controls of drug use and pricing are different in some other countries such as the UK where approval based on a determination of safety and efficacy is done by one Health Authority (Medicines and Health care Products Regulatory Agency) and appropriateness of use and price are determined by another agency (National Institute for Health and Care Excellence (NICE)).

Can we correct the threat of *liaisons dangereuses*? There are some rays of hope. In the US CMS and the State Children's Insurance Program are required to enforce the Physicians Payments Sunshine Act which requires drug companies to collect and track all financial relationships with physicians and teaching hospitals. The goal is to increase transparency of financial relationships between health care providers and drug companies and uncover potential conflicts of interest. The bill also allows states to enact additional requirements which several states have done. Another step is that some universities have limited or completely restricted participation of their faculty in promotional activities. However, data on effectiveness of this ban is far from promising [10]. For example, in a cohort of academic oncologists at US public medical schools

two-thirds received payments from the drug industry in 2017 accounting for >20% of their annual salary. Recently, there has been considerable controversy over participation in China's Thousand Talents Plan under which US academic physicians have established relationships with Chinese universities and, in some instances, drug companies receiving substantial research and personal monies. The FBI is currently investigating these relationships which have led to the firing of several prominent physician scientists.

None of these developments is surprising. For example, US medical schools have been selling themselves for a price. For a mere \$200 million David Geffen was able to have the UCLA School of Medicine, a state institution, named for him. And UCLA Medical Center is named for ex-President Ronald Reagan after his friends donated \$150 million. (Full disclosure: RPG's wife is in the Case family of Case Western Reserve University.) It would seem the California Board of Regents would be on shaky moral ground trying to control physicians' drug prescribing activities. The truth is physicians and the drug industry have a symbiotic relationship. Physicians like to complain but nobody really wants change. But there is hope because what ultimately saves us from these *liaisons dangereuses* is the moral compass of most physicians who want to do what's best for their patients.

Our bottom line is some of these new drugs are important advances such as cyclosporine, mycophenolate mofetil and several new antibiotics and anti-fungal drugs. However, the impact of many new approved drugs on transplant outcomes is mostly modest and not everyone needs them. Health care resources need to be used to reduce infant mortality, increase childhood vaccination rates, eradicate malaria etc. and most recently to combat the SARS-CoV-2 pandemic and treat COVID-19; these new drugs are unlikely to be the most effective investment of health care resources, especially in developing countries.

Despite the above comments, criticisms and admonitions we are standing by to renounce all of these potential *liaisons dangereuses* if a drug company offers to sponsor us to lecture on a new drug for transplant recipients in Milano with dinner at Cracco thrown in *buon appetito*.

Acknowledgements RPG acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Med.* 2017;15:134.
2. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival. An analysis of 5 years of US Food and Drug Administration approvals. *JAMA.* 2015;175:1992–4.
3. Davis C. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. *BMJ.* 2017;359:j4530.
4. Kloecker DE, Davies MJ, Khunti K, Zaccardi F. Uses and limitations of the restricted mean survival time: illustrative examples from cardiovascular outcomes and mortality trials in type 2 diabetes. *Ann Intern Med.* 2020. <https://doi.org/10.7326/M19-3286>. Online ahead of print. PMID: 32203984.
5. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med.* 2017;377:454–64.
6. Gale RP, Zhang MJ. What is the *P*-value anyway? *Bone Marrow Transpl.* 2016;51:1439–40.
7. Gale RP, Hochaus A, Zhang MJ. What is the (p-) value of the p-value? *Leukemia.* 2016;30:1965–7.
8. Fugh-Berman A, Ahari S. Following the script: how drug reps make friends and influence doctors. *PLoS Med.* 2007;4:e150.
9. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med.* 2017;177:1569–75.
10. Gill J, Haslam A, Crain T, Herrera-Perez D, Prasad V. Comparison of industry payments in 2017 with annual salary in a cohort of academic oncologists. *JAMA Intern Med.* 2020. <https://doi.org/10.1001/jamainternmed.2020.0090>.