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ANALYSIS

Cancer drugs, survival, and ethics

Despite considerable investment and innovation, chemotherapy drugs have had little effect on survival in adults with metastatic cancer. **Peter Wise** explores the ethical issues relating to research, regulation, and practice

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Cancer survival has improved in recent decades. Trends in the US show that five year relative survival in adults with solid cancer has increased from 49% to 68% over 40 years.[1] There have been important advances in chemotherapy in recent years, including for melanoma, medullary thyroid cancer, and prostate cancer. Immunotherapy, together with targeted and precision (personalised) approaches guided by patient and tumour biomarkers, also produces benefit in subgroups of the more common cancers.[2] But how much of the improvement in cancer survival can we attribute to drugs?

Survival

A meta-analysis published in 2004 explored the contribution of cytotoxic chemotherapy to five year survival in 250 000 adults with solid cancers from Australian and US randomised trials.[3] An important effect was shown on five year survival only in testicular cancer (40%), Hodgkin's disease (37%), cancer of the cervix (12%), lymphoma (10.5%), and ovarian cancer (8.8%). Together, these represented less than 10% of all cases. In the remaining 90% of patients—including those with the commonest tumours of the lung, prostate, colorectum, and breast—drug therapy increased five year survival by less than 2.5%—an overall survival benefit of around three months.[3] Similarly, 14 consecutive new drug regimens for adult solid cancers approved by the European Medicines Agency provided a median 1.2 months overall survival benefit against comparator regimens.[4] Newer drugs did no better: 48 new regimens approved by the US Food and Drug Administration between 2002 and 2014 conferred a median 2.1 month overall survival benefit.[5] Drug treatment can therefore only partly explain the 20% improvement in five year survival mentioned above. Developments in early diagnosis and treatment may have contributed much more.[6]

The approval of drugs with such small survival benefits raises ethical questions, including whether recipients are aware of the drugs' limited benefits, whether the high cost:benefit ratios are justified, and whether trials are providing the right information.

Cancer trial concerns

At most 3% of adult cancer patients participate in trials,[7] and given the many new drugs and regimens, greater enrolment is a constant aim. Since they are mostly financed by the drug industry, trials can significantly reduce national expenditure on cancer drugs at a time of escalating global costs (around $110bn (£85bn; $95bn) was spent on cancer drugs in 2015).[8] Trials also allow patients the opportunity of having otherwise unavailable or unaffordable treatment under close supervision of a trial centre, although most studies show that patients do not realise that participating in a trial will primarily benefit others.[9] An unethical pressure to enrol is reflected by several studies showing that up to half of patients in cancer drug trials were led to believe that such participation was their only option.[9]

Furthermore, we cannot infer that the benefits seen in the small number of trial participants will be replicated in the 97% or more outside trial centres, where staffing, procedure, and facilities might be different. Although there are a few reports of similar outcomes in patients inside and outside trials, the uncontrolled nature of those studies and non-homogeneous patient characteristics do not allow a wider scale assumption of similarity.[10]

Bypassing previous university based trial procedures, pharma now outsources many trials to commercial contract research organisations (CROs), responsible only to the company that hires them. A recent WHO supported Dutch study concluded that many such trials "place patients at ethical risk."[11]

The agreed primary response marker of overall survival—the time from drug assignment to death from any cause—is meaningful and, most importantly, understandable by patients. However, to shorten trial duration, minimise the number of trial participants, and enable rapid access of drugs to the market, many trials use surrogate endpoints. These include overall response rate, early tumour shrinkage, and, most commonly, progression-free survival (time from assignment to progressive disease or death from any cause). These endpoints are imaging

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based and more rapidly available but, with some exceptions, have been shown to correlate poorly with overall survival.[12 13]

Many drugs approved on the basis of better progression-free survival have been subsequently found not to produce better overall survival than the comparator drug.[14] Some of these drugs are logically withdrawn but others remain inexplicably on the market.[15]

Surrogate endpoints are also used by the FDA and EMA for accelerated and conditional approval, respectively, of what are judged to be urgently needed new drugs. A 2010 FDA review revealed that 45% of cancer drugs given accelerated approvals were not granted full approval, either because subsequent trials failed to confirm effectiveness or because the results of trials were not submitted.[16] One reason may be the industry's reluctance to communicate negative results[17] (heavy penalties for delayed or absent submission of confirmatory trial results have only recently been introduced). Bearing in mind the usually marginal survival benefits, any haste for approval is only occasionally justified.

The FDA's decision to introduce a "breakthrough" category in 2012 compounds the risks of premature approval on limited evidence.[18] The pressure for early approval is enhanced by lobbying from patient advocacy groups, prompted by industry and with often premature media announcements of drugs that are "game changing," "groundbreaking," "revolutionary," "miracle," or other unjustifiable superlatives. The risky practice of approval before proof gains even more momentum.

Quality of life assessments increasingly form part of cancer drug trials. However, many evaluations are invalidated by selective use of questionnaire items and time points to demonstrate drug benefit,[19] together with frequent "drop out" of patients, inability or refusal to answer questionnaires, and other causes of missing data. Few studies show anything more than small and transient improvements in quality of life from chemotherapy, mostly reflecting temporary tumour shrinkage.

Drug approval

The low threshold of approval (efficacy bar) for these expensive drugs ignores the ethical principle of fairness and equity.[20] By promoting treatment of poorly responsive cancers it denies valuable resources to early diagnosis approaches and other health needs. Generous approval may benefit some patients, but it also helps pharma and government to profit. Corporate taxation of 30-35% on cancer industry's average 22% profit margins on $50bn national drug sales[21] yielded the US government alone an estimated $3.8bn in 2015.

In a further doubtfully ethical practice of regulatory capture[22] industry attracts former staff from regulatory agencies to help perfect new applications and so smooth their transit.[23] Thus the regulator risks being regulated by the industry that it has been appointed to regulate. This so called revolving door phenomenon has proved difficult to eliminate, as is the case with other industry-government interactions.

In England, the National Institute of Health and Care Excellence (NICE) has now taken control of the Cancer Drugs Fund, which enables individual patients to receive funding for drugs not routinely paid for by the NHS.[24] The fund had been criticised for poor monitoring of performance, spiralling annual costs (over £300m), and inappropriate approvals. NICE is highly cost aware, and it is to be hoped that a less permissive approval principle will evolve. Evaluations using the European Society of Medical Oncology's clinical benefit scale should also help to clarify ethically important cost-benefit relations[25] in order to achieve the same aim.

More post-approval "real world" evaluation of cancer drugs would be an important step forward. Together with industry, the integration of the Cancer Drugs Fund into NICE could facilitate a systematic and highly relevant national assessment of the community's benefit from cancer drugs.

In low and middle income countries, funding drugs for a rapidly increasing incidence of cancer is even more difficult. With cost:benefit ratios probably even higher, it remains to be seen how valuable the cancer drugs from the World Health Organization's recently published essential medicines list prove to be.[26]

Inadequate consent

In the US, cancer treatment now represents a major cause of personal bankruptcy.[27] Cancer drugs have a greater imbalance of risks and benefits than many surgical procedures and therefore warrant a consent document. However, this is often not issued or signed.[28] Furthermore, consent is valid only if it relates to the individual information discussed with that patient[20]—which is usually even less well documented.

There are few data on patients' awareness of cancer drug effectiveness or the incidence and potential severity of their side effects. Many are likely to be unaware of the 80% risk of diverse side effects, of which up to 64% are serious (grades 3-4).[29] There is also a drug and disease dependent risk of death from treatment itself, especially in the first month of therapy.[30] Nor are patients likely to be informed of the increased risk of dying in hospital compared with patients receiving only supportive care.[31] This is important, since studies show that most patients prefer to end their lives in their own homes or hospices rather than in hospital.[32] Unawareness of poor treatment outcomes leads patients to only rarely question a physician's proposal for chemotherapy.[33]

Patients overestimate potential drug benefits. In an important multicentre study, almost 75% of 1200 patients with metastatic colorectal and lung cancers considered it likely that their cancers would be cured by chemotherapy.[34] Yet a cure in these situations is virtually unknown. In another study of decision making discussions about chemotherapy between doctors and patients, survival issues were considered to have been properly covered in only 30%.[35] Dutch and Australian studies have found that the option of supportive care is raised in only one quarter of oncologist consultations,[33 36] probably because of patient and family expectations of active treatment. Physicians also have competing interests; known to influence the choice of drug and even a decision on whether to treat.[37] Yet supportive care can extend life and enhance its quality, especially if introduced early.[38]

Informed consent is clearly a complex process extending far beyond the signed consent form.[39] It should follow discussions based on balanced and fully documented verbal and written information, which perhaps would be more ethically provided by independent trained counsellors less exposed to competing interests.[20] Patients should be fully empowered by discussion and subsequent triage to receive cancer drugs, to enrol in a clinical trial, or to accept best supportive care—realising that a decision not to have drug treatment (often referred to pejoratively as refusal) is ethically and morally appropriate.[20] In one study of 128 people with lung cancer, around a third of patients wished to share decision making, yet were poorly catered for.[40]

In search of ethics

Many irregularities and competing interests—in pharma, in trials, in government approval, and in the clinical use of cancer drugs—impact ethically on the care and costs of patients with cancer. Non-representative clinical trials with imprecise endpoints and misinformed patients with unrealistic expectations compel interventions that are mostly not in their best interests. Spending a six figure sum to prolong life by a few weeks or months is already unaffordable, and inappropriate for many of the 20% of the (Western) population who will almost inevitably die from solid tumour metastases.

Ethical cancer care demands empowerment of patients with accurate, impartial information followed by genuinely informed consent in both the clinical trial and therapeutic settings. Intensified prevention, earlier detection, more prompt and radical treatment of localised and regional disease, together with highly skilled, earlier, supportive care are the important yet underfinanced priorities in cancer control. Ethical impediments to sound practice need to be addressed and corrected. Above all, the efficacy bar for approval needs to be raised for both new and existing cancer drugs[41] —by using more meaningful statistical and disease specific criteria of risk-benefit and cost-benefit.[25] Finally, aggressively targeting the less than ethical actions of stakeholders in the heavily veiled medical-industrial complex may be the only way forward: current market driven rather than health driven priorities and practices do not benefit cancer patients.

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1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29. doi:10.3322/caac.21254 pmid:25559415.
2 Masters GA, Krilov L, Bailey HH et al. Clinical cancer advances 2015: annual report on progress against cancer from the American Society of Clinical Oncology. JCO, 2014.
3 Morgan G, Ward R, Barton M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. *Clin Oncol (R Coll Radiol)* 2004;16:549-60. doi:10.1016/j.clon.2004.06.007 pmid:15630849.
4 Apolone G, Joppi R, Bertele V, et al. Ten years of marketing approvals of cancer drugs in Europe. *Br J Cancer* 2005;93:504-9. doi:10.1038/sj.bjc.6602750 pmid:16136026.
5 Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014;140:1225-36. doi:10.1001/jamaoto.2014.1570 pmid:25068501.
6 Hiom SC. Diagnosing cancer earlier: reviewing the evidence for improving cancer survival. *Br J Cancer* 2015;112(Suppl 1):S1-5. doi:10.1038/bjc.2015.23 pmid:25734391.
7 Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* 2004;291:2720-6. doi:10.1001/jama.291.22.2720 pmid:15187053.
8 Constantino T. Global market for cancer treatments grows to $107 billion in 2015. 2 Jun 2016. https//www.imshealth.com/en/about-us/news/ims-health-study-global-market-for-cancer-treatments-grows-to-107bn-in-2015-led-by-record-level-of-innovation
9 Nurgat ZA, Craig W, Campbell NC, Bissett JD, Cassidy J, Nicolson MC. Patient motivations surrounding participation in phase I and phase II clinical trials of cancer chemotherapy. *Br J Cancer* 2005;92:1001-5. doi:10.1038/sj.bjc.6602423 pmid:15770219.
10 Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 2004;363:263-70. doi:10.1016/S0140-6736(03)15383-4 pmid:14751698.
11 Van Huijstee M, Schipper I. Ethical concerns. In: *Putting contract research organisations on the radar.* Social Sciences Research Network, 2011: 55-72.
12 Prasad V, Kim C, Burotto M, et al. The strength of association between surrogate endpoints and survival in oncology. *JAMA Intern Med* 2015;175:1389-98. doi:10.1001/jamainternmed.2015.2829 pmid:26098871.
13 Wilson MK, Collyar D, Chingos DT, et al. Outcomes and endpoints in cancer trials: bridging the divide. *Lancet Oncol* 2015;16:e43-52. doi:10.1016/S1470-2045(14)70380-8 pmid:25638556.
14 Kim C, Prasad V. Strength of validation for surrogate end points used in the US Food and Drug Administration's approval of oncology drugs. *Mayo Clin Proc* 2016;91:713-25. doi:10.1016/j.mayocp.2016.02.012.
15 Nabors LB. The role of bevacizumab in glioblastoma. *J Natl Compr Canc Netw* 2014;12:1201-2.pmid:25190689.
16 Johnson JR, Ning Y-M, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. *J Natl Cancer Inst* 2011;103:636-44. doi:10.1093/jnci/djr062 pmid:21422403.
17 Wise P, Drury M. Pharmaceutical trials in general practice: the first 100 protocols. An audit by the clinical research ethics committee of the Royal College of General Practitioners. *BMJ* 1996;313:1245-8. doi:10.1136/bmj.313.7067.1245 pmid:8939118.
18 Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category--implications for patients. *N Engl J Med* 2014;370:1252-8. doi:10.1056/NEJMhle1311493 pmid:24670173.
19 Joly F, Vardy J, Pintilie M, Tannock IF. Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer. *Ann Oncol* 2007;18:1935-42. doi:10.1093/annonc/mdm121 pmid:17698837.
20 English V, Sommerville A, Brannan S. Medical ethics today. Blackwell, 2012.
21 QuintilesIMS Institute. Global oncology trend report. 2016. http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-oncology-trend-report-a-review-of-2015-and-outlook-to-2020
22 Abraham J. The pharmaceutical industry as a political player. *Lancet* 2002;360:1498-502. doi:10.1016/S0140-6736(02)11477-2 pmid:12433532.
23 Bien J, Prasad V. Future jobs of FDA's haematology-oncology reviewers. *BMJ* 2016;354:i5055. doi:10.1136/bmj.i5055 pmid:27677772.
24 NICE/NHS. Proposals for a new Cancer Drugs Fund (CDF) operating model. 2015. https://www.engage.england.nhs.uk/consultation/cdf-consultation
25 Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 2015;26:1547-73. doi:10.1093/annonc/mdv249 pmid:26026162.
26 Shulman LN, Wagner CM, Barr R, et al. Proposing essential medicines to treat cancer: methodologies, processes and outcomes. *J Clin Oncol* 2016;34:69-75. doi:10.1200/JCO.2015.61.8736 pmid:26578613.
27 Zafar SY, Peppercorn JM, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist* 2013;18:381-90. doi:10.1634/theoncologist.2012-0279 pmid:23442307.
28 Weingart SN, Flug J, Brouillard D, et al. Oral chemotherapy safety practices at US cancer centres: questionnaire survey. *BMJ* 2007;334:407. doi:10.1136/bmj.39069.489757.55 pmid:17223629.
29 Chan JK, Kiet TK, Monk BJ, et al. Applications for oncologic drugs: a descriptive analysis of the oncologic drugs advisory committee reviews. *Oncologist* 2014;19:299-304. doi:10.1634/theoncologist.2013-0276 pmid:24599479.
30 Wallington M, Saxon EB, Bomb M, et al. 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based, observational study. *Lancet Oncol* 2016;17:1203-16. doi:10.1016/S1470-2045(16)30383-7 pmid:27599138.
31 Wright AA, Zhang B, Keating NL, Weeks JC, Prigerson HG. Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study. *BMJ* 2014;348:g1219. doi:10.1136/bmj.g1219 pmid:24594868.
32 Higginson IJ, Sen-Gupta GJ. Place of care in advanced cancer: a qualitative systematic literature review of patient preferences. *J Palliat Med* 2000;3:287-300. doi:10.1089/jpm.2000.3.287 pmid:15859670.
33 Gattellari M, Voigt KJ, Butow PN, Tattersall MH. When the treatment goal is not cure: are cancer patients equipped to make informed decisions? *J Clin Oncol* 2002;20:503-13. doi:10.1200/JCO.20.2.503 pmid:11786580.
34 Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med* 2012;367:1616-25. doi:10.1056/NEJMoa1204410 pmid:23094723.
35 Audrey S, Abel J, Blazeby JM, Falk S, Campbell R. What oncologists tell patients about survival benefits of palliative chemotherapy and implications for informed consent: qualitative study. *BMJ* 2008;337:a752. doi:10.1136/bmj.a752 pmid:18669570.
36 Koedoot CG, Oort FJ, de Haan RJ, Bakker PJ, de Graeff A, de Haes JC. The content and amount of information given by medical oncologists when telling patients with advanced cancer what their treatment options are. palliative chemotherapy and watchful-waiting. *Eur J Cancer* 2004;40:225-35. doi:10.1016/j.ejca.2003.10.008 pmid:14728937.
37 Malin JL, Weeks JC, Potosky AL, Hornbrook MC, Keating NL. Medical oncologists' perceptions of financial incentives in cancer care. *J Clin Oncol* 2013;31:530-5. doi:10.1200/JCO.2012.43.6063 pmid:23269996.
38 Bauman JR, Temel JS. The integration of early palliative care with oncology care: the time has come for a new tradition. *J Natl Compr Canc Netw* 2014;12:1763-71, quiz 1771.pmid:25505216.
39 Hall DE, Prochazka AV, Fink AS. Informed consent for clinical treatment. *CMAJ* 2012;184:533-40. doi:10.1503/cmaj.112120 pmid:22392947.
40 Pardon K, Deschepper R, Vander Stichele R, et al. Are patients' preferences for information and participation in medical decision-making being met? Interview study with lung cancer patients. *Palliat Med* 2011;25:62-70. doi:10.1177/0269216310373169 pmid:20621948.
41 Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277-80. doi:10.1200/JCO.2013.53.8009 pmid:24638016.

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