European Journal of Cancer 150 (2021) 95–98

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

The European Union and personalised cancer medicine

John A. Hickman [a,*], Ian F. Tannock [b], Lydie Meheus [c], Lisa Hutchinson [d]

[a] School of Biological Sciences, Manchester University, Dover Street, Manchester, M13 9PT, UK
[b] Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON, M5G 2M9, Canada
[c] Anticancer Fund, Boechoutlaan 221, 1853, Strombeek-Bever, Belgium
[d] 1 Stone House Gardens, Caterham, Surrey, CR3 6AW, UK

Received 5 March 2021; accepted 8 March 2021

KEYWORDS
Personalised cancer medicine;
European cancer policy;
Targeted therapies;
Tumour heterogeneity: drug resistance

Abstract Two recent policy documents by the European Union, 'Europe's Beating Cancer Plan' and its accompanying 'Conquering Cancer: Mission Possible' (CCMP), articulate broad policies aimed at reducing cancer mortality across Europe, for example, by promoting prevention and early detection. The focus for cancer treatment in these manifestos is the expansion of personalised cancer medicine (PCM). However, the CCMP document suggests that the uptake of PCM is "hampered by uncertainty about its outcomes". What are these outcomes and why this uncertainty? We address the limits of PCM in pathology-driven and pathology-agnostic PCM, briefly discussing the results of umbrella and basket trials. We suggest that the complexity, plasticity and genetic heterogeneity of advanced cancers will continue to thwart the impact of PCM, limiting it to specific pathologies, or rare subsets of them. Caution regarding the advancement of PCM is justified, and policymakers should be wary of the hype of lobbyists, who do not acknowledge the limits of PCM.

Two recent policy documents by the European Union, 'Europe's Beating Cancer Plan' (EBCP) [1] and its accompanying 'Conquering Cancer: Mission Possible' (CCMP) [2], articulate a welcome broadening of policy aimed at reducing cancer mortality across Europe. A prior consultative EBCP document stated that "Up until now, the response to cancer has primarily focussed on treatment" [3]. In these latest manifestos, prevention and early diagnosis are major pillars of future policy to reduce deaths from cancer.

* *Corresponding author*:
E-mail address: jhickman@hotmail.fr (J.A. Hickman).

https://doi.org/10.1016/j.ejca.2021.03.013
0959-8049/

For those unfortunate to be diagnosed with metastatic cancer, improving treatment should of course remain as one of the priorities. The focus on treatment in the EBCP document proposes to advance personalised cancer medicine (PCM), setting up a 'Partnership' on PCM [1], presumably with the pharmaceutical industry. The pursuit of PCM will be accompanied by advanced data analyses of the ongoing sequencing of cancer genomes, such as in the 'Genomics for Public Health' project, complementing the European 1+ Million Genomes Initiative [1]. By contrast, the CCMP document [2] recognises that the uptake of PCM is "hampered by uncertainty about its outcomes". What are these outcomes and why this uncertainty? We argue that the outcomes of PCM are inevitably going to be limited by the complex biology of advanced cancers and suggest caution in the allocation of resources to PCM.

First, there is PCM with a targeted therapy guided by a validated molecular biomarker [4] expressed in a specific pathology. The most successful example is the treatment of chronic myelogenous leukaemia (CML) with the ABL kinase inhibitor imatinib. Expression of the biomarker, the BCR–ABL fusion protein, allows potentially curative therapy, with >80% of imatinib-treated patients surviving at 10 years [5]. However, imatinib is an outlier: CML is a monoclonal pathology [6], whereas most cancers evolve to become polyclonal, with genetic heterogeneity, and will become resistant to therapy [7], as discussed further below. The wave of postimatinib optimism, "one can anticipate a postgenomic wave of sophisticated 'smart drugs' to fundamentally change the treatment of all cancers" [8], has instead resulted in more nuanced outcomes. Targeted treatments and PCM increase survival in specific pathologies, or rare subsets of them, rather than in 'all cancers'. Targeted therapies used for treatment of non–small-cell lung cancer (NSCLC) provide good examples: inhibition of the ALK kinase, expressed in 5% of patients with NSCLC inhibition of RET kinase, expressed in 1–2% of patients with NSCLC and inhibition of epidermal growth factor receptor (EGFR), expressed in 30% of patients with NSCLC provide prolongations of life in some patients, but are rarely curative (reviewed in [9]). In the recent and ambitious MATRIX 'umbrella' PCM trial in NSCLC [10], different drugs were appropriately matched with different genetic alterations found in 302 patients from the 5467 patients screened; only the light smokers or never-smokers, likely carrying reduced genomic damage [11], achieved better than a 10% response rate. The report of the MATRIX study highlighted in its discussion the high attrition rate (~94%) as patients were screened before being judged to be suitable for PCM, with its resulting modest outcomes. There are important resource implications here. Targeted treatments used in PCM cause both physical [12] and financial [13] toxicity, and many recently approved targeted drugs used for PCM provide marginal clinical benefit at best, as reviewed in 'Hans Christian Andersen and the value of new cancer treatments' [14].

Prolonged survival after tumour-specific PCM, not only in lung cancer, has been thwarted by multiple mechanisms of drug resistance [15], thereby limiting the effectiveness of targeted agents. While Although modest extensions of life may occur, the impact on cancer mortality has been marginal [14]. Although recent immunotherapies are likely to make an impact and, for example, Programmed death-ligand 1 (PD-L1) expression can aid in guiding treatment of lung cancer [16], this and other potential biomarkers can be confounded by a complex biology, including tumour heterogeneity [17].

The second type of PCM is the 'pathology agnostic' use of targeted therapies evaluated in so-called 'basket' trials. Here, next-generation sequencing of a tumour after biopsy, irrespective of the pathology's site of origin, guides the choice of a targeted therapy. The outcomes of various 'basket' trials are not encouraging: in one survey of trials involving more than 20,000 patients, only 12% of patients whose cancer genomes were sequenced were able to receive a matched drug and fewer than 3% had a response [18].

Multiple mechanisms of resistance to targeted therapies were referred to above [15]. Primary resistance mechanisms revolve mainly around the target, its loss or mutation, and also refer to the target cell–driven resistance wherein biochemical plasticity and the 'rewiring' of cellular signalling pathways confounds drug action [15]. For advanced cancers, genetic intratumoural heterogeneity is the major obstacle to treatment [7,15]. Although a tumour may have had a dominant 'driver' genetic alteration to which it was 'addicted', as CML is 'addicted' to BCR-ABL signalling, genetic instability and clonal evolution [6,7] leads to the emergence of drug-insensitive subclones. This intratumoural heterogeneity is challenging to capture [19], and multiple biopsies are required to establish the spectrum of genetic changes that might be susceptible to therapy. The TRACERx project, which sampled 100 NSCLC cases, revealed more potentially actionable mutations because of multiregional sampling [11]. The authors commented that "without the use of multiregion whole-exome sequencing, 65% of branched subclone clusters could have erroneously appeared to be clonal". Single biopsy remains the standard sampling method in nearly all reported PCM studies, for practical and ethical reasons, raising questions regarding the optimal choice of targeted therapy. Liquid biopsy that identifies circulating tumour cells [20] or circulating tumour DNA [21] is an important alternative that may capture the spectrum of genetic changes expressed in a primary tumour and its metastases. But, when multiple potential 'drivers' of malignancy are revealed, complex decisions are needed about which single

targeted agent or a combination should be administered, the latter associated with risks of dose-limiting toxicity [22].

Multiple mechanisms of drug resistance [15], particularly the evolution of intratumoural genetic heterogeneity [7], have limited the ability of targeted therapies, and in consequence PCM, to deliver on their promise. Concerns regarding the uncertain outcomes of PCM [2] are therefore justified. Those driving the European initiatives [1,2] should be wary of the hype of lobbyists. For example, a report on PCM sponsored by the European Federation of Pharmaceutical Industries and Associations [23] failed to address the challenges of tumour heterogeneity or to cite key articles [22,24] that have questioned the limits or value of PCM.

The biological complexity of cancer, including genetic and epigenetic tumour heterogeneity that occurs in space and time, also has implications for how therapies might be used after early detection of tumours, early detection being a pillar policy of the two European Union (EU) manifestos [1,2]. Advances in imaging, surgery and radiation therapy will play important roles, but adjuvant targeted therapy may be appropriate as it might inhibit a 'truncal' clonal driver of malignancy before branching subclonal evolution [25]. Even here, there are some caveats: targeted therapies can impose selective evolutionary pressures on tumour cells; for example, inhibition of EGFR was shown to downregulate DNA repair, thereby promoting genetic instability [26] and hence tumour evolution. In a wide variety of tumour types, about 2–3% were found to undergo massive and catastrophic genomic rearrangements by chromothripsis [27] so that instead of a chronologically 'stepwise' evolution, permitting the drug targeting of an early 'truncal' genetic change, before subclonal branching occurs, a 'Big Bang' model of sudden tumour evolution has been proposed [28]. Here, genetic alterations occur over a very short period, for example, early in the development of colon cancer [28], rendering targeted therapy difficult.

The first recommendation of the EU's CCMP [2] policy document is an initiative to better understand the biology of cancer. This is sensible and will have an impact on its major pillars of prevention and early detection, by facilitating the use of molecular tools to better understand how cancers are initiated and how they progress [29]. Whether it will ameliorate PCM is a mute question, and the balance of effort and support for different themes in EU policy plans for cancer should recognise the many disappointing results and accommodate the continuing uncertainty surrounding PCM. To coin a phrase from James Carvelle, the political strategist ("it's the economy, stupid" [30]): "it's the biology, stupid".

Author statements

All authors contributed to writing and editing.

Funding

None declared.

Conflict of interest statement

J.A.H., L.M., I.F.T. and L.H. declare no conflict of interest.

References

[1] https://ec.europa.eu/commission/presscorner/detail/en/ip_21_342.
[2] https://ec.europa.eu/info/publications/conquering-cancer-mission-possible_en.
[3] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12154-Europe-s-Beating-Cancer-Plan.
[4] Hey SP, et al. The evidence landscape in precision medicine. Sci Transl Med 2020;12. https://doi.org/10.1126/scitranslmed.aaw7745.
[5] Hochhaus A, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376:917–27. https://doi.org/10.1056/NEJMoa1609324.
[6] Greaves M, Maley CC. Clonal evolution in cancer. Nature 2012;481:306–13. https://doi.org/10.1038/nature10762.
[7] McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. Cell 2017;168:613–28. https://doi.org/10.1016/j.cell.2017.01.018.
[8] Shawver LK, Slamon D, Ullrich A. Smart drugs: tyrosine kinase inhibitors in cancer therapy. Canc Cell 2002;1:117–23. https://doi.org/10.1016/S1535-6108(02)00039-9.
[9] Chan, Bryan A, Hughes Brett GM. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Canc Res 2015;4(1):36–54. https://doi.org/10.3978/-j.issn.2218-6751.2014.05.01.
[10] Middleton G, et al. The National Lung Matrix Trial of personalized therapy in lung cancer. Nature 2020;583:807–12. https://doi.org/10.1038/s41586-020-2481-8.
[11] Jamal-Hanjani M, et al. Tracking the Evolution of non–small-cell lung cancer. N Engl J Med 2017;376:2109–21. https://doi.org/10.1056/NEJMoa1616288.
[12] Niraula S, Seruga B, Ocana A, Shao T, Goldstein R, Tannock IF, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol 2012;30:3012–9. https://doi.org/10.1200/JCO.2011.40.3824.
[13] Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. Nat Rev Clin Oncol 2017;14:381–90. https://doi.org/10.1038/nrclinonc.2017.31.
[14] Schilsky RL, Schnipper LE. Hans Christian Andersen and the value of new cancer treatments. J. Natl. Cancer Inst. 2018;110:441–2. https://doi.org/10.1093/jnci/djx261.
[15] Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 2018;15:81–94. https://doi.org/10.1038/nrclinonc.2017.166.
[16] Mok TSK. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819–30. https://doi.org/10.1016/S0140-6736(18)32409-7.
[17] Hegde PS, Chen DS. Top 10 challenges in cancer immunotherapy. Immunity 2020;52:17–35. https://doi.org/10.1016/j.immuni.2019.12.011.
[18] Chan KK-W, Tannock IF. Basket trials as pathways to drug registration for biomarker-defined subgroups of advanced cancers? J Clin Oncol 2021 (in press).
[19] Gerlinger M, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883–92. https://doi.org/10.1056/NEJMoa1113205.

[20] Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease — latest advances and implications for cure. Nat Rev Clin Oncol 2019;16:409–24. https://doi.org/10.1038/s41571-019-0187-3.
[21] Wan JCM, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Canc 2017;17:223–38. https://doi.org/10.1038/nrc.2017.7.
[22] Tannock IF, Hickman JA. Limits to personalized cancer medicine. N Engl J Med 2016;375:1289–94. https://doi.org/10.1056/NEJMsb1607705.
[23] https://www.efpia.eu/news-events/the-efpia-view/blog-articles/unlocking-the-value-of-personalised-cancer-care/.
[24] Prasad V. Perspective: the precision-oncology illusion. Nature 2016;537. https://doi.org/10.1038/537S63a. S63–S63.
[25] Amirouchene-Angelozzi N, Swanton C, Bardelli A. Tumor evolution as a therapeutic target. Canc Discov 2017;7:805–17. https://doi.org/10.1158/2159-8290.CD-17-0343.
[26] Russo M, et al. Adaptive mutability of colorectal cancers in response to targeted therapies. Science 2019;366:1473–80. https://doi.org/10.1126/science.aav4474.
[27] Stephens PJ, et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 2011;144:27–40. https://doi.org/10.1016/j.cell.2010.11.055.
[28] Sottoriva A, et al. A Big Bang model of human colorectal tumor growth. Nat Genet 2015;47:209–16. https://doi.org/10.1038/ng.3214.
[29] Ginsburg O, Ashton-Prolla P, Cantor A, Mariosa D, Brennan P. The role of genomics in global cancer prevention. Nat Rev Clin Oncol 2021;18:116–28. https://doi.org/10.1038/s41571-020-0428-5.
[30] https://en.wikipedia.org/wiki/It%27s_the_economy,_stupid.