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Starting and stopping cancer drugs: The need for randomized trials

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ABSTRACT

Precision oncology has gained widespread popularity over the past decade, and increasingly oncologists strive to provide the right treatment to the right patient. To date, precision efforts have focused on the specific mutational target(s), food/ drug interactions, functional oncology, or dose of drug given. Moreover, the tumor and blood samples of hundreds of thousands of patients with cancer have been sequenced in the United States alone with the goal of identifying and prescribing the most precise treatment. Despite this broad consideration of precision oncology, one neglected aspect of precision oncology is identifying the optimal start time and stopping point for cancer therapies. Is it possible to improve overall survival (OS) or quality of life for patients with more precise initiation and discontinuation of therapy? In this commentary, we review the historical basis to initiate, discontinue or switch therapies. We emphasize that largely these time points were selected arbitrarily, and subsequently constrained by historical accident. We highlight randomized efforts to better elucidate the time points in starting or stopping therapy. Finally, we provide suggestions for a research agenda on precision timing of anti-cancer drugs.

1. Introduction

Precision oncology has gained widespread popularity over the past decade, and increasingly oncologists strive to provide the right treatment to the right patient. To date, precision efforts have focused on the specific mutational target(s), food/ drug interactions [1], drug/ drug interactions [2], avatar construction [3], functional oncology [4], or dose of drug given. In fact, the Food and Drug Administration (FDA) launched Project Optimus to specifically reform drug dosing and selection in oncology. Moreover, the tumor and blood samples of hundreds of thousands of patients with cancer have been sequenced in the United States alone with the goal of identifying and prescribing the most precise treatment.

Despite this broad consideration of precision oncology, one neglected aspect of precision oncology is identifying the optimal start time and stopping point for cancer therapies. Is it possible to improve overall survival (OS) or quality of life for patients with more precise initiation and discontinuation of therapy? In this commentary, we review the historical basis to initiate, discontinue or switch therapies. We emphasize that largely these time points were selected arbitrarily, and subsequently constrained by historical accident. We highlight randomized efforts to better elucidate the time points in starting or stopping therapy. Finally, we provide suggestions for a research agenda on precision timing of anti-cancer drugs.

2. When to start therapy

Historically, a cancer-directed therapy is started immediately if the intent of treatment is curative. Similarly, if a treatment merely extends survival, there are varying opinions on when to initiate treatment. For instance, most oncologists would observe asymptomatic myeloma precursor states, but few would observe asymptomatic, early-stage pancreatic cancer. The literature exploring the question on when to start treatment is scarce.

Across cancer medicine, there are limited randomized controlled trials testing when to initiate systemic therapy. For instance, in low volume prostate cancer, studies suggest similar survival outcomes from early definitive treatment versus observation [5]. A recent study of ibrutinib in early-stage chronic lymphocytic leukemia was ultimately unable to justify early treatment [6]. In addition, some individuals with hematologic diseases such as smoldering myeloma or low-grade lymphoma may be clinically managed with close observation [7,8]. Moreover, in asymptomatic metastatic solid tumors, there are at least four randomized trials evaluating early versus delayed treatment in colorectal cancer and recurrent ovarian cancer [9]. Most of these trials (75%, three out of four) in asymptomatic metastatic malignancies have not demonstrated a survival benefit with early treatment. While there is scarce data on when to initiate treatment across multiple cancers, there is a greater paucity of data on when to stop cancer-directed treatment (Table 1).

3. When to stop therapy

In order to determine the efficacy of an oncologic therapy for most malignancies, clinicians and researchers currently rely on radiographic studies that employ the assessment method Response Evaluation Criteria in Solid Tumors (RECIST). According to RECIST version 1.1, a partial response is defined by a decrease by 30% in the sum of longest diameters

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Table 1
Randomized trials of early versus delayed initiation of treatment.

Tumor Type	Setting	Intervention	Number of Participants	Survival Outcomes	Conclusion	Year of Publication	Citation
Colorectal	Asymptomatic, Metastatic	Early or delayed chemotherapy with MFL (methotrexate, 5-FU, leucovorin)	183	Approximately 5 month survival benefit with early treatment ($p = 0.13$)	No statistically significant benefit with early treatment of asymptomatic metastatic colorectal cancer	1992	[17]
Colorectal	Asymptomatic, Metastatic	Early or delayed chemotherapy (5-FU plus leucovorin or daily Mayo Clinic schedule)	168	13.0 months with early treatment versus 11.0 months (HR 1.15, 95% CI 0.79–1.72, $p = 0.49$)	No survival benefit with early treatment for asymptomatic metastatic colorectal cancer	2005	[18]
Ovarian	Complete remission after first-line platinum-based chemotherapy; monitored by CA-125	Early or delayed chemotherapy	529 (265 early treatment, 264 delayed treatment)	Median survival 25.7 months for early treatment versus 27.1 months for delayed treatment (HR 0.98, 95% CI 0.80–1.20, $p = 0.85$)	No evidence of survival benefit with early treatment of relapse on basis of elevated CA-125	2010	[19]
Multiple myeloma (stage I)	Asymptomatic, previously untreated	Early or delayed treatment with melphalan plus prednisone	50	No difference in survival	No evidence of survival benefit with early treatment of asymptomatic myeloma	1993	[20]
Multiple myeloma	Asymptomatic, previously untreated	Early treatment with pamidronate versus observation	177	Overall survival was similar between both groups	No evidence of survival benefit with use of bisphosphonate in asymptomatic myeloma	2011	[21]

(SLD) in target lesions whereas disease progression is defined by an increase in 20% in the SLD from nadir in target lesions or the development of new lesions [10]. Given the widespread use of RECIST and the substantial implications associated with its evaluation of the disease status of millions of individuals with cancer globally, it is critical to understand the historical basis for evaluating cancer treatment response and RECIST.

The treatment of advanced Hodgkin lymphoma drastically changed in the 1970s with several chemotherapy combinations including MOPP and ABVD [11]. As more individuals with Hodgkin lymphoma developed clinical responses to these regimens, physicians encountered a common dilemma: how to best characterize and quantify treatment response. Consequently, cancer researchers Charles Moertel and James Hanley assembled 16 experienced oncologists to determine how to reliably measure tumor response to treatment. The 16 oncologists used calipers or rulers to measure the size of 12 solid spheres placed on a mattress and covered by foam. Moertel and Hanley also used two spheres of the same size to determine the reproducibility of measurements from the same oncologist and different oncologists. Moertel found that a measurement error occurred in 6.8–7.8% of instances in measuring the same sized sphere when using a 50% reduction in the product of the perpendicular diameters, whereas a measurement error occurred in 19–25% of the times when using a reduction criterion of 25% [12]. Moertel ultimately concluded that in "the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5–10% due to human error in tumor measurement." Notably, Moertel stated that a change in 25% "should not necessarily be regarded as influencing the management of the patient." These size cutoffs were not chosen because they best predicted which drugs improved survival or quality of life; the cutoffs were chosen for operational reasons—because using the tools of the era (i.e. palpation), these differences could be somewhat reliably distinguished by diverse clinicians.

In 1979, the World Health Organization (WHO) released recommendations on evaluating cancer treatment efficacy. The WHO set cutoffs of clinical response as a reduction by 50% in the sum of products of dimension measures and disease progression as an increase in 25%, and by doing so, used cut-off values that Moertel had originally intended as a measure of reproducibility of measurements as opposed to clinical efficacy from a treatment [13].

By 2000, several international cancer organizations including the National Cancer Institute (NCI) developed RECIST in order to further refine evaluation of cancer response [13]. RECIST moved away from the WHO's response criteria which involved two dimensions to one dimension in RECIST. In doing so, a partial response was defined as a reduction in 30% in one dimension as opposed to 50% reduction in two dimensions, and disease progression was defined by an increase in 20% in one dimension as opposed to 25% in two dimensions. Notably, using the formula for spherical volume ($\frac{4}{3}\pi r^3$) these cutoffs are nearly exactly Moertel's original value.

RECIST provided additional guidance including the number of target lesions to measure in determining treatment response. As such, RECIST came to use Moertel's two-dimensional measurements intended for reproducibility that has been transformed into a one-dimensional measurement intended to represent tumor response. Although several meta-analyses have suggested that tumor shrinkage correlates with survival outcomes such as progression-free survival and overall survival, no randomized controlled trials to date have demonstrated correlation between RECIST and survival.

Since the development of response criteria, most individuals with radiographic disease progression are switched to a new therapy or referred to comfort care services if unable to tolerate additional treatment. Given the historical basis for defining disease progression and in an attempt to identify other measures of clinical efficacy, studies have endeavored to evaluate the efficacy of continuing cancer-directed treatment beyond the widely accepted definition of disease progression based off RECIST.

4. The case for continuing treatment post-progression

Traditionally, the concept of switching therapy at the time of disease progression was rooted in the concern that cytotoxic therapies can encounter drug resistance. As such, once it was clear that a tumor was growing despite therapy, oncologists historically concluded the cancer was resistant to the therapy. Thus, further therapy was believed to add toxicity without any clinical benefit. However, this logic has been extended to multiple drugs across different classes and mechanisms of action and has never been formally and rigorously tested across cancers.

Using phase III study data of men undergoing treatment for prostate cancer, Tito Fojo and then colleagues at the NCI developed a mathematical model to derive tumor growth rates that correlated with patient survival [14]. Subsequently, Fojo and colleagues determined growth and regression rates for 321 patients with metastatic renal cell

Table 2
Data on continuing therapies following radiographic progression.

Tumor Type	Setting	Intervention	Number of Participants	Survival Outcomes	Conclusion	Year of Publication	Citation
Renal cell carcinoma	Advanced	Sunitinib	321	Estimated median time to second progression of 7.3 months	Sunitinib can be continued beyond radiographic disease progression particularly in patients with stable rate of growth	2014	[15]
Renal cell carcinoma	Advanced	Nivolumab	36	Not reported	25 patients (69%) experienced subsequent tumor reduction or stabilization of target lesion	2016	[16]

carcinoma who were treated with either sunitinib or interferon. Utilizing the basis that tumors were only "relatively resistant" and not "absolutely resistant" to sunitinib at the time of radiographic progression, the study revealed that in most patients (94.4%, 303 out of 321 patients), the growth constant remained stable when allowing patients to continue treatment with sunitinib beyond the first scan demonstrating progressive disease [15]. Moreover, at 100, 200 and 300 days after starting therapy, an estimated 47%, 27% and 13% of tumor remained sensitive to sunitinib. Ultimately, the study demonstrated an estimated median time to second progression of 7.3 months. As the standard-of-care for metastatic RCC now includes immunotherapy, a similar study evaluating nivolumab beyond progression was undertaken. The study found that among 36 patients treated beyond progression, 5 patients (14%) had a subsequent partial response while 21 patients (58%) had stable disease [16]. These studies revealed that some patients derive clinical benefit beyond radiographic progression.

Despite the clinical successes of immunotherapy across multiple cancers, a common clinical dilemma revolves around how long immunotherapy should be administered to a patient. Exploratory analysis attempted to identify any survival benefit of fixed duration (one year) versus continuous nivolumab as studied in CheckMate 153, a phase IIIb/IV study that evaluated the efficacy of nivolumab in previously treated non-small cell lung cancer. Among 1428 patients who were treated, 252 were randomly assigned to continuous treatment (n = 127) or 1-year fixed duration treatment (n = 125). Patients still on treatment at 1 year, including those who had radiographic progression but were perceived to still derive clinical benefit, were randomly assigned to continuing nivolumab until disease progression or retreatment after disease progression (1-year fixed duration). The analysis revealed that individuals assigned to continuous treatment had a longer median OS (HR 0.61, 95% CI 0.37–0.99) than individuals on fixed duration treatment. This finding underscores the necessity to prospectively study the appropriate duration of treatment for therapies across drug classes and tumor types.

Putting this together, the Figure shows a prototypical treatment scenario. Patients often undergo a series of cancer treatments, typically started after periods of tumor growth. Drugs can shrink tumors or slow the growth rate. Once the arbitrary threshold of progression is passed, therapy is switched. Our core observation is that none of these time points are evidence based. Neither the starting point nor stopping point has not been chosen for optimal outcomes. Very likely the optimal treatment duration depends both on the absolute tumor dimensions, but also the pace of tumor change; however, counterintuitive results are possible.

5. Policy recommendations: towards precision timing of cancer drugs

The two studies in metastatic RCC demonstrated that antineoplastic therapies can be continued in individuals who met the traditional criteria of disease progression, and in a subset of patients, continued clinical benefit may be derived especially in those with a constant rate of tumor growth. These findings are particularly relevant in clinical settings with a lack of access to additional subsequent line therapies due to lack of regulatory approval or due to high cost, as well as to patients who prefer to remain on the same treatment due to tolerability. Given the lack of prospective data validating RECIST-defined response with survival, randomized trials evaluating tumor growth and regression may provide more informed data on when to stop a cancer therapy.

Moving towards precision initiation and discontinuation will require a coordinate effort and set of randomized trials. In many disease settings, we lack randomized trials assessing survival and quality of life based on the timing of initiating therapy. We believe that this must be part of our research agenda. Such trials warrant promotion by industry sponsors as well as those in academia. While funding may be a potential challenge for conducting these trials, recognition of the value of these studies by regulators may address these obstacles. Moreover, patient education by physicians will be critical for successful enrollment in these trials. In 2014, the SLIM criteria were added to the definition of myeloma implying treatment, but to date these factors have been disputed as grounds to initiate therapy [7]. We propose formal randomized study of this, and related dilemmas in low volume, asymptomatic solid cancers. Similarly, current randomized trials evaluating therapies, should consider factorial randomization to discontinue or continue therapies at prespecified cutoffs, such as 1 year or 2 years of therapy, as well as factorial randomization to continue post progression. Such studies may reveal two insights that indefinitely treatment till progression is not always needed, and that treatment post progression is sometimes warranted.

Evaluating the optimal starting and stopping point of therapies represents the next phase in precision oncology. Potential gains include improve survival, decreased toxicity and cost, and the magnitude of these gains is yet inestimable due to limited studies to date (Tables 1 and 2).

Declaration of Competing Interest

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References

[1] C.S. Won, N.H. Oberlies, M.F. Paine, Mechanisms underlying food-drug interactions: inhibition of intestinal metabolism and transport, Pharm. Ther. 136 (2) (2012) 186–201, https://doi.org/10.1016/j.pharmthera.2012.08.001.
[2] R.P. Riechelmann, A.D. Giglio, Drug interactions in oncology: how common are they, Ann. Oncol. 20 (12) (2009) 1907–1912, https://doi.org/10.1093/annonc/mdp369.
[3] E. Bangi, P. Smibert, A.V. Uzilov, et al., A Drosophila platform identifies a novel, personalized therapy for a patient with adenoid cystic carcinoma, iScience 24 (3) (2021), https://doi.org/10.1016/j.isci.2021.102212.
[4] A. Letai, P. Bhola, A.L. Welm, Functional precision oncology: testing tumors with drugs to identify vulnerabilities and novel combinations, Cancer Cell 40 (1) (2022) 26–35, https://doi.org/10.1016/j.ccell.2021.12.004.
[5] F.C. Hamdy, J.L. Donovan, J.A. Lane, et al., Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer, N. Engl. J. Med 0 (0) (2023), https://doi.org/10.1056/NEJMoa2214122.
[6] P. Langerbeins, C. Zhang, S. Robrecht, et al., The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia, Blood 139 (2) (2022) 177–187, https://doi.org/10.1182/blood.2021010845.

[7] A.M. Goodman, M.S. Kim, V. Prasad, Persistent challenges with treating multiple myeloma early, Blood 137 (4) (2021) 456–458, https://doi.org/10.1182/blood.2020009752.
[8] J.O. Armitage, D.L. Longo, Is watch and wait still acceptable for patients with low-grade follicular lymphoma, Blood 127 (23) (2016) 2804–2808, https://doi.org/10.1182/blood-2015-11-632745.
[9] S. Augustinus, G. Thurairajah, M.G. Besselink, et al., Delayed versus immediate start of chemotherapy in asymptomatic patients with metastatic cancer: A systematic review and meta-analysis, J. Clin. Oncol. 40 (16_suppl) (2022) 12126, https://doi.org/10.1200/JCO.2022.40.16_suppl.12126.
[10] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer Oxf. Engl. 1990 45 (2) (2009) 228–247, https://doi.org/10.1016/j.ejca.2008.10.026.
[11] G.P. Canellos, S.A. Rosenberg, J.W. Friedberg, T.A. Lister, V.T. DeVita, Treatment of Hodgkin lymphoma: a 50-year perspective, J. Clin. Oncol. 32 (3) (2014) 163–168, https://doi.org/10.1200/JCO.2013.53.1194.
[12] C.G. Moertel, J.A. Hanley, The effect of measuring error on the results of therapeutic trials in advanced cancer, Cancer 38 (1) (1976) 388–394, https://doi.org/10.1002/1097-0142(197607)38:1<388::aid-cncr2820380156>3.0.co;2-a.
[13] P. Therasse, S.G. Arbuck, E.A. Eisenhauer, et al., New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada, J. Natl. Cancer Inst. 92 (3) (2000) 205–216, https://doi.org/10.1093/jnci/92.3.205.
[14] W.D. Stein, W.D. Figg, W. Dahut, et al., Tumor growth rates derived from data for patients in a clinical trial correlate strongly with patient survival: a novel strategy for evaluation of clinical trial data, Oncologist 13 (10) (2008) 1046–1054, https://doi.org/10.1634/theoncologist.2008-0075.
[15] M. Burotto, J. Wilkerson, W. Stein, R. Motzer, S. Bates, T. Fojo, Continuing a cancer treatment despite tumor growth may be valuable: sunitinib in renal cell carcinoma as example, PLoS ONE 9 (5) (2014), e96316, https://doi.org/10.1371/journal.pone.0096316.
[16] S. George, R.J. Motzer, H.J. Hammers, et al., Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression: a subgroup analysis of a randomized clinical trial, JAMA Oncol. 2 (9) (2016) 1179–1186, https://doi.org/10.1001/jamaoncol.2016.0775.
[17] Nordic Gastrointestinal Tumor Adjuvant Therapy Group, Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial, J. Clin. Oncol. J. Am. Soc. Clin. Oncol. 10 (6) (1992) 904–911, https://doi.org/10.1200/JCO.1992.10.6.904.
[18] S.P. Ackland, M. Jones, D. Tu, et al., A meta-analysis of two randomised trials of early chemotherapy in asymptomatic metastatic colorectal cancer, Br. J. Cancer 93 (11) (2005) 1236–1243, https://doi.org/10.1038/sj.bjc.6602841.
[19] G.J. Rustin, M.E. Burg, C.L. van der, Griffin, et al., Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial, Lancet 376 (9747) (2010) 1155–1163, https://doi.org/10.1016/S0140-6736(10)61268-8.
[20] M. Hjorth, L. Hellquist, E. Holmberg, B. Magnusson, S. Rödjer, J. Westin, Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I–a randomized study. Myeloma Group of Western Sweden, Eur. J. Haematol. 50 (2) (1993) 95–102, https://doi.org/10.1111/j.1600-0609.1993.tb00148.x.
[21] G. D'Arena, P.G. Gobbi, C. Broglia, et al., Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study, Leuk. Lymphoma 52 (5) (2011) 771–775, https://doi.org/10.3109/10428194.2011.553000.

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