Drug rechallenge and treatment beyond progression—implications for drug resistance

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Abstract | The established dogma in oncology for managing recurrent or refractory disease dictates that therapy is changed at disease progression, because the cancer is assumed to have become drug-resistant. Drug resistance, whether pre-existing or acquired, is largely thought to be a stable and heritable process; thus, reuse of therapeutic agents that have failed is generally contraindicated. Over the past few decades, clinical evidence has suggested a role for unstable, non-heritable mechanisms of acquired drug resistance pertaining to chemotherapy and targeted agents. There are many examples of circumstances where patients respond to reintroduction of the same therapy (drug rechallenge) after a drug holiday following disease relapse or progression during therapy. Additional, albeit limited, evidence suggests that, in certain circumstances, continuing a therapy beyond disease progression can also have antitumour activity. In this Review, we describe the anticancer agents used in these treatment strategies and discuss the potential mechanisms explaining the apparent tumour re-sensitization with reintroduced or continued therapy. The extensive number of malignancies and drugs that challenge the custom of permanently switching to different drugs at each line of therapy warrants a more in-depth examination of the definitions of disease progression and drug resistance and the resulting implications for patient care.

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Introduction

Historically, the most important factor to limit the success of systemic anticancer therapy in achieving cure or prolonged overall survival has been drug resistance. This situation is apparent after using chemotherapy drugs for more than half a century, and continues to be a formidable problem in the current era of molecularly targeted drugs and personalized medicine. There are two types of cancer drug resistance: intrinsic (also called innate or primary resistance) and acquired (also called evasive, adaptive, or secondary resistance). In this Review we will focus on acquired resistance, particularly with regard to the stability—or lack thereof—of the acquired drug-resistant phenotype.

In the clinic, resistant disease describes cancer that is found to have progressed since the time of treatment initiation. The term 'drug resistant' is often used synonymously with 'progressive disease' when referring to a treated tumour. Once a patient develops acquired resistance to a given agent, the usual accepted strategy is to initiate a different therapy on resistant (refractory) disease using non-cross-resistant drugs. The underlying assumption is that previously used agents are obselete, and it is on this premise that treatment guidelines (such as from the National Comprehensive Cancer Network, NCCN) for nearly all cancers are built. According to the classic Goldie–Coldman hypothesis of drug resistance,[1] mutations are spontaneously acquired by the tumour over time leading to an accumulation of drug-resistant clones. Resistant variants in a heterogeneous tumour can be selected for in a Darwinian evolutionary process,[2] or a quiescent subpopulation of intrinsically drug-resistant cancer stem cells might cause regrowth or spread of the tumour at progression.[3] A tumour that has progressed on therapy is assumed to have permanently changed, necessitating a different treatment plan.

The view that acquired drug resistance is almost always stable and irreversible stems from a number of reasons. First, many of the early pioneering studies of drug resistance undertook the selection and analysis of drug-resistant mutant cell clones in cell culture, usually using prolonged stepwise treatments of cell monolayers with ultimately very high concentrations of cytotoxic agents.[4,5] This technique can create a severe and sometimes artifactual selection pressure that is unlike the clinical situation. Such procedures led to the discovery in the 1970s of the multidrug-resistant (MDR) phenotype caused by overexpression of the P-glycoprotein drug efflux transporter;[6] however, the clinical relevance of MDR was questioned when multiple phase III trials of specific P-glycoprotein antagonists subsequently failed

Competing interests
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Key points

- Reuse of the same anticancer therapy following disease progression is often considered to be futile owing to drug resistance; however, many cancers show sensitivity to therapy reintroduction after disease progression
- Spontaneous, reversible and epigenetic resistance mechanisms might explain the retreatment phenomenon; alternatively, cancer cells might proliferate independently of drug resistance
- Selection of drug-resistant clones is not necessarily a major contributor to response to therapy in many patients
- Drug resistance definitions need to be re-evaluated; for example, disease progression based on RECIST criteria might be a poor indicator of drug resistance and when to change a course of treatment
- Applying transient drug-resistance mechanisms to clinical practice could offer advantages over traditional therapy regimens, including increased therapeutic options, reduced costs, and improvements in quality of life, without compromising efficacy

Box 1 | Unstable, non-heritable cytotoxic and hormonal drug resistance

Chemotherapy rechallenge dates back to the 1970s with the retreatment using combination chemotherapy in patients with Hodgkin lymphoma[166] and multiple myeloma.[167] Early studies primarily reported on drug rechallenge in small-cell lung cancer, various leukaemias and following adjuvant treatment of breast cancer.[12] More recently, rechallenge-like regimens used for retreatment include anthracyclines and taxanes in adjuvant or metastatic breast cancer,[150] platinum-based therapy in ovarian cancer,[13] tamoxifen in oestrogen receptor-positive breast cancer,[168] and diethylstilbesterone or maximum androgen blockade in androgen-independent prostate cancer.[28,169,170] Specific experiences with chemotherapy rechallenge have changed definitions of drug resistance to exclude relapses that occur after a prolonged period off therapy.[13–15]

to show any efficacy.[7] Second, defined mutations were identified in genes encoding molecular drug targets, such as *EGFR*, *BCR–ABL*, or *KIT*, which can explain acquired resistance to drugs such as the small-molecule tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, or imatinib.[8,9] Third, deep-sequencing genomic studies that revealed the enormous extent of genetic heterogeneity of human tumours has added to the perception of fixed pre-existing (or induced) gene mutations being primarily responsible for acquired drug resistance in cancer.[10,11] Finally, the act of permanently stopping a particular therapy on the emergence of radiographic disease progression reinforces the belief of permanent drug resistance. Stopping a treatment at the time of disease progression is the current dominant paradigm of clinical trial conduct; therefore, available data from clinical trials are routinely not able to provide any information that could challenge this notion of permanent drug resistance.

Unstable, non-heritable resistance

There are many examples from the clinic that compete with the archetype of managing recurrent or refractory disease, in that patients' tumours can be sensitive to the agent(s) they had originally experienced disease progression on (Box 1, Figure 1). First, a patient relapses (has progressive disease after initially responding to a therapy) following discontinuation of therapy and is rechallenged with the same therapy—typically with the same dose and regimen—after a treatment-free interval. Second, a patient experiences disease progression during a course of therapy and is rechallenged with the same therapy following an intervening therapy. Third, a patient experiences disease progression during a course of therapy, but continues the therapy—typically in combination with a new agent—without stopping.

These treatment strategies have demonstrated activity in a wide variety of malignancies using conventional chemotherapeutic drugs as well as many of the newer and older (hormonal) molecular targeted therapies. Drug rechallenge and continuation of treatment following progression on therapy are strategies that have emerged over the past decade. Rechallenging a tumour that has relapsed when the patient is not receiving therapy is an old concept (Box 1). This topic was reviewed over a decade ago, with the conclusion that many seemingly drug-resistant cancers might not be resistant.[12] In a few specific cases for the treatment of ovarian,[13] colorectal[14] and small-cell lung carcinoma,[15] this concept has led to the development of new, more flexible definitions of drug resistance. Relapses may be termed 'sensitive' or 'partially sensitive' rather than 'resistant' if the treatment-free interval from therapy discontinuation to relapse is of long (or intermediate) duration, since the longer the time to progression, the greater the chance of a response to retreatment.[13–15] These definitions also add confusion to the debate on what constitutes true drug resistance.

Although the treatment scenarios described above are biologically and clinically distinct, their antitumour activity implies that many ostensibly resistant tumours were either not resistant at initial progression, or that the resistant phenotype was transient. Thus, heritable mechanisms driving drug resistance and response to future therapy can be ruled out. Indeed, recent evidence suggests that many characteristics of tumours, such as persistence of clones, altered tumour dynamics, tumour heterogeneity and response to therapy, might be derived from genomically similar clones and not necessarily by mutations.[16] Despite its apparent prevalence, unstable or transient resistance has received little attention as a major concept in medical oncology.

In this Review, we discuss the therapeutic agents from the past decade that have been used to rechallenge patients with cancer who have progressed during therapy or at relapse, or that have been continued in patients beyond disease progression. In many cases, these strategies are routinely being used in the clinic or incorporated into the standard of care. The differences between each retreatment strategy and its implication for drug resistance, and possible mechanisms of non-heritable or reversible drug resistance are examined. Finally, the implications that unstable acquired resistance might have for patient care, clinical benefit, clinical practice, and cost of cancer therapy are discussed. For example, if a patient who has progressed on therapy has merely developed a transient insensitivity to that agent, the possibility of retreatment increases the number of therapeutic options available, raising the issue of how to identify true resistance and establish when treatment with a drug has become futile. The abundant examples that counter the long-standing convention of changing therapies at traditional disease progression

should not be dismissed as exceptional cases. A re-evaluation of the definition of drug resistance, as well as the standard treatment dogma in oncology, is warranted.

Rechallenge after progression off therapy

Most rechallenge studies are performed in patients experiencing disease progression off therapy and likely do not constitute rechallenge of resistant disease. The durable responses of several months to years in length achieved by retreatment therapy (Supplementary Tables 1–3 and Supplementary online text) indicate a minor role for acquired permanent drug resistance in these settings. Drug rechallenge can be assessed by observing a prolonged time to secondary progression or positive anti-tumour response following therapy reintroduction and by comparing these to initial drug exposure within the same patient or patient cohort (Figure 2). Some examples are discussed below while others are included in the Supplementary text online. Retrospective and prospective studies for all treatment strategies are summarized online in Supplementary Tables 1–3.

Oxaliplatin-based chemotherapy in CRC

Combining 5-fluorouracil (5-FU) and leucovorin with newer agents such as oxaliplatin (FOLFOX), irinotecan, or the monoclonal antibodies bevacizumab or cetuximab has led to an increase in survival in patients with advanced-stage colorectal cancer (CRC) from 12 months to several years.[17,18] Consequently, incorporating chemotherapy-free intervals into treatment algorithms has become important for the management of patient quality of life, particularly with regard to oxaliplatin treatment, which can cause an accumulation of neurological toxic effects.[19] Retrospective data indicate a benefit of interrupting FOLFOX therapy and reintroducing it at relapse, typically with a different regimen, with a high rate of response or disease stabilization at reintroduction.[19,20] Compared to other follow-up therapies, rechallenge with FOLFOXIRI (FOLFOX plus irinotecan) was shown to yield a significantly longer progression-free survival (PFS; 8.2 months rechallenge versus 6.3 months for other therapies, $P = 0.003$) and overall survival (19.3 versus 14.0 months, respectively, $P = 0.02$).[21]

Chemotherapy-free intervals can result in improved efficacy in comparison with continuous treatment using well-established chemotherapy regimens and drugs in patients with CRC.[15,22] Rechallenge strategies with newer agents have also been studied in patients with metastatic CRC in prospective, randomized phase III (OPTIMOX1) and phase II (OPTIMOX2) trials.[23,24] In the OPTIMOX1 trial, 620 previously untreated patients received either continuous FOLFOX4 administered every 2 weeks until disease progression (arm A), or six cycles of FOLFOX7 followed by a simplified regimen of maintenance 5-FU and leucovorin for 12 cycles and then reintroduction of FOLFOX7 (arm B). FOLFOX7 is a more dose-intensive regimen of oxaliplatin than FOLFOX4. Oxaliplatin was reintroduced in only 40.1% of patients in arm B: those who experienced progressive disease prior to FOLFOX7 reintroduction (89 patients) experienced a lower response rate and rate of disease stabilization (6.7% and 42.7%) than patients who did not first experience disease progression (33 patients; 24.2% versus 54.4%, respectively).[23] Overall survival was not found to be significantly better in the FOLFOX7 reintroduction arm (21.2 months versus 19.3 months in arm A; $P = 0.49$), but after accounting for biases in the original trial,[23] a subsequent analysis found that reintroduction of oxaliplatin had an independent significant positive impact on overall survival (hazard ratio [HR] = 0.56, $P = 0.009$).[25]

In OPTIMOX2, 202 patients with previously untreated metastatic CRC received six cycles of modified FOLFOX7 and were randomly assigned to stop chemotherapy or receive maintenance chemotherapy without oxaliplatin until disease progression.[24] At progression, another six

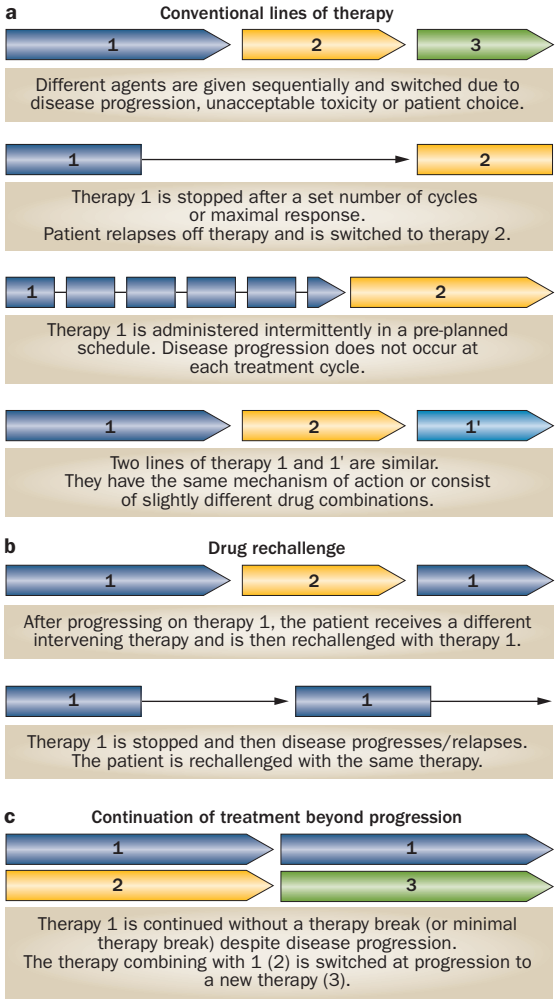
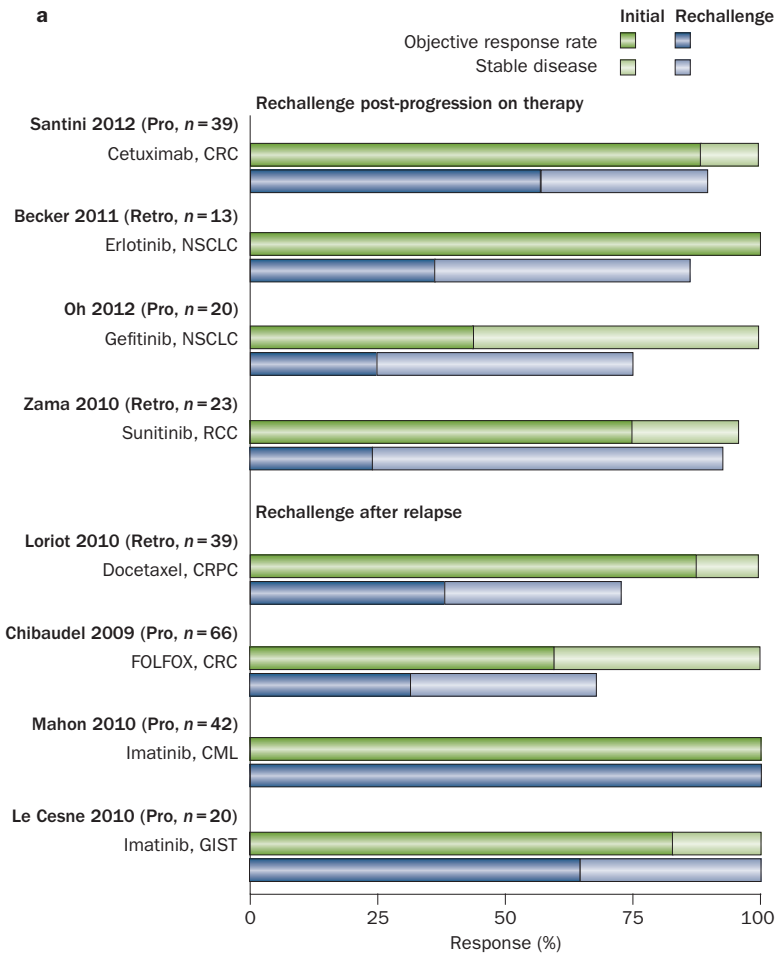


Figure 1 | Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology. **a** | Typical sequences of therapy in relation to disease progression. **b** | Two major types of drug rechallenge. In drug rechallenge, treatment with a previously used agent(s) is repeated despite prior failure of the treatment, consisting of disease progression on therapy or after discontinuation of the therapy. **c** | In treatment beyond progression a therapy is continued with no break or a minimal break at disease progression. Arrowheads: progressive disease. Black lines: drug-free interval.



◀ **Figure 2** | Efficacy of drug rechallenge following disease progression on or off therapy. **a** | Examples of response rates at initial treatment and rechallenge. Tumour control rates are good, although generally weaker at rechallenge, and fewer objective responses are achieved. **b** | PFS or TTP at initial therapy and at rechallenge in relation to the length of treatment-free interval. The rate of disease progression at rechallenge is favourable, although shorter at rechallenge. A longer treatment-free interval is often related to the rechallenge PFS or TTP. Treatment-free interval consists of an intervening treatment if rechallenge is post-progression on therapy. In the study by Mahon 2010, rechallenge ORR includes 62% of patients with complete molecular response and 38% of patients with declining *BCR–ABL* transcripts. In the study by Loriot 2012, ORR is defined as PSA decline ≥ 50%, at rechallenge SD is defined as PS decline between 30–50%. Abbreviations: B-CLL, B-cell chronic lymphocytic leukaemia; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; GIST, gastrointestinal stromal tumour; MM, multiple myeloma; NSCLC, non-small-cell lung cancer; ORR, overall response rate; Pro, prospective study; PFS, progression-free survival; RCC, renal cell carcinoma; Retro, retrospective study; SD, stable disease; TTP, time to progression.[24,34,41,44,58,67,69,79,81,148,152]

cycles of FOLFOX7 were reintroduced in both treatment arms. The chemotherapy-free interval had a negative impact on PFS (6.6 months versus 8.6 months in the maintenance arm, $P = 0.0017$) and overall survival (19.5 months versus 23.8 months, respectively, $P = 0.42$).[24] An analysis of data from both trials found that a prolonged interval between courses of FOLFOX or a longer initial PFS might be predictive of the efficacy of this strategy, with median survival from reintroduction of therapy of 8.9 months, 16.6 months and 22.1 months if the FOLFOX-free interval was <6 months, 6–12 months or ≥12 months, respectively ($P < 0.0001$).[26] To determine whether continuous or intermittent therapy is superior, the phase III MRC COIN trial (a three-armed trial in previously untreated patients) was conducted, and included a continuous oxaliplatin and 5-FU or capecitabine arm as well as an intermittent therapy arm in which patients were rechallenged after progression following 12 weeks of initial chemotherapy (815 patients per group).[27] Of the 268 patients who were rechallenged and assessable 33% of patients had a partial response, and 38% had stable disease. Overall, this trial failed to show non-inferiority with rechallenge compared to continuous oxaliplatin-based chemotherapy (overall survival 14.4 months versus 15.8 months, respectively), but rechallenge did improve quality of life, reduced time on chemotherapy and hospital visits (of note, pain was worse in the intermittent arm).[27] Overall, oxaliplatin rechallenge demonstrates similar efficacy to continuous regimens, but rechallenge might be preferred for the long-term management of CRC given its improved tolerability.[19]

Docetaxel in prostate cancer

Docetaxel chemotherapy is standard first-line therapy in metastatic castration-resistant prostate cancer (CRPC). The possibility of intermittent therapy has been examined to alleviate excessive toxicity and avoid

unnecessary treatment in responding patients, a strategy shown to be successful in hormonal therapy for prostate cancer.[28] Multiple retrospective studies have shown that incorporating a therapy break could lead to objective responses and, occasionally, improvements in quality of life if patients are rechallenged after relapse.[29–33] In the largest of these studies, 48% of initially responding patients ($n = 50$) achieved a biochemical response (≥50% decline in prostate-specific antigen [PSA]) at re-exposure to docetaxel, which is comparable to other therapies after docetaxel failure.[31] Moreover, an initial biochemical response[30] or prolonged docetaxel-free period[34] have been found to correlate significantly with PFS or overall survival at rechallenge. Additionally, greater than two rechallenges after subsequent relapses seem to induce PSA responses in certain patients.[30,35,36]

Two prospective trials have assessed the efficacy of rechallenge following a profound initial response to docetaxel.[35,37] In the ASCENT phase III clinical trial comparing calcitriol plus docetaxel to docetaxel alone, patients with progressive disease were later re-exposed to docetaxel therapy.[35] Of 36 patients rechallenged after one drug holiday, 45.5% had a reduction of PSA ≥50% and 45.5% had stable disease. Quality-of-life improvements were also noted in these patients, although rechallenged patients had more-favourable prognoses than patients who were not rechallenged. In a multicentre phase II trial, 45 patients with CRPC who initially responded to docetaxel and then had disease progression after a period of biochemical remission of at least 5 months were retreated with docetaxel.[37] A partial biochemical response (defined as >50% PSA decline) was observed in 24.5% of patients and minor PSA reductions (>25–49% PSA decline) or stable disease (<25% PSA decrease or increase) were observed in 22.2% of patients.[37] Retreatment with docetaxel has become a standard of care in patients with CRPC since alternative treatment strategies have not been defined; however, an ongoing phase III trial will help to establish whether continuous or intermittent docetaxel regimens are superior.[38]

Imatinib in GIST and CML

First-line imatinib, an oral TKI targeting KIT, PDGFRα and BCR–ABL, is the standard of care for patients with advanced-stage gastrointestinal stromal tumours (GIST) and is normally given long-term and continuously. Most patients with controlled GIST who discontinue imatinib rapidly experience disease progression.[39] The phase III BFR14 trial was conducted to determine the optimum duration of imatinib therapy and whether introducing therapy breaks influenced the onset of acquired resistance.[40] Patients with non-progressing GIST after 1 year, 3 years or 5 years of imatinib treatment were randomly assigned to either continue or discontinue the drug. Following re-introduction of imatinib at disease progression patients regained tumour control. This was observed in 92% of patients previously treated for 1 year (32) with imatinib, and in 100% of patients previously treated for 3 or 5 years (25 and 14 patients, respectively).[39,41,42] There was no significant difference in overall survival or rates of progression on therapy (that is, development of resistance) between discontinuation and continuous groups at the first two randomizations.[39,41] Interestingly, regardless of the length of initial treatment, most patients experienced disease progression off therapy at the same rate, although patients who progressed rapidly after imatinib discontinuation had the poorest prognosis and had disease progression sooner during imatinib rechallenge (2-year PFS was 30%, 62% and 75% for patients who relapse in the first 6 months after discontinuation, 6–12 months after discontinuation and 12 months after discontinuation, respectively).[40] Results from this trial also suggest that patients experiencing stronger initial responses to imatinib have a longer time to relapse after therapy discontinuation; however, patients experiencing a complete response after long duration of treatment still have residual persistent sensitive tumour cells.[40] Similar findings for rechallenge after adjuvant imatinib treatment suggest that recurrent disease is imatinib-sensitive and prior exposure does not limit the efficacy of imatinib.[43]

Imatinib is also used to treat chronic myelocytic leukaemia (CML), through inhibition of BCR–ABL, and complete remissions are not uncommon. Disease recurs in a subset of patients with CML who discontinue imatinib following periods of durable remission.[44] The results of a phase II trial (TWISTER) that followed 40 patients with CML with sustained undetectable minimal residual disease for 2 years (based on quantitative PCR of BCR–ABL) have recently been reported.[45] Approximately 40% of patients remained in deep remission for 24 months following imatinib discontinuation. If relapses occurred most were observed within the first 4 months after therapy discontinuation, and all patients (22) regained undetectable minimal residual disease status at imatinib reintroduction upon early detection of relapse. Surprisingly, the BCR–BL DNA remained stable without mutation at relapse. All five patients who relapsed within 5 months regained a complete molecular response when rechallenged with imatinib.[45] In another small study of 26 patients who discontinued imatinib after achieving complete remission, all 23 patients who relapsed and resumed imatinib treatment achieved a complete molecular or cytogenetic response of prolonged duration.[46] The largest study that has investigated imatinib rechallenge is the multicentre phase II STIM (Stop Imatinib) trial.[44] Of 69 patients with CML who discontinued imatinib after 2 years, 42 patients relapsed. All the relapsed patients responded to imatinib reintroduction, with prolonged complete molecular remission observed in 26 patients, and declining BCR–ABL levels seen in 16 patients.[44] The finding that both patients with GIST and CML respond remarkably well to reintroduction of imatinib suggests that permanent acquired resistance does not occur. Of note, the duration and intensity of responses seen with imatinib treatment of GIST and CML are not typical of other targeted therapies in other diseases. Despite the impressive tumour responses seen with imatinib reintroduction in both malignancies, imatinib discontinuation is not recommended if disease control is achieved unless patients experience significant toxic effects.[39,44]

Temozolomide in glioblastoma

The alkylating agent temozolomide is used as a front-line therapy in combination with radiotherapy and as salvage therapy in high-grade recurrent malignant glioma. Temozolomide has been tested in various rechallenge settings—following disease progression on therapy and following relapse after temozolomide discontinuation—since there is no consensus on subsequent therapies.[47] The focus of rechallenge has been on using an alternative dosing strategy in an effort to overcome initial temozolomide resistance. Depleting methylguanine-DNA methyltransferase (MGMT) levels or inhibiting angiogenesis are both hypothesized to be affected through more-protracted and dose-intensified regimens following an initial standard schedule.[48,49] Retreatment with different temozolomide schedules is well-tolerated and response rates seem to be comparable to other therapies.[47,49–52] Switching to a dose-intensified continuous 50 mg/m^2 temozolomide regimen at disease progression immediately or following a drug-free period from conventional 150–200 mg/m^2 5-day temozolomide both seem to be active strategies. Perry *et al.*[49] observed a clinical benefit rate of 47% and 6-month PFS of 17% with immediate switching in 21 patients and, in 14 patients relapsing after adjuvant or radiation plus concomitant temozolomide, a 79% clinical benefit rate and 6-month PFS of 57% was observed. In a retrospective study of patients with recurrent glioma rechallenged with the same or one of various different regimens of temozolomide (mostly dose-intensified), PFS at 6 months was 57.9% in patients with anaplastic glioma (19 patients) and 28.6% in patients with glioblastoma multiforme (28 patients) who had relapsed after a temozolomide-free interval.[47] PFS at 6 months in patients who had been rechallenged after having disease progression when receiving temozolomide (without a break) was 16.7% (six patients with anaplastic glioma) and 26.3% (19 patients with glioblastoma multiforme).[47]

Small prospective trials have demonstrated successful outcomes when drug rechallenge of different temozolomide regimens was used, even in patients with poor prognosis[53,54] and in patients whose tumours expressed MGMT or had unmethylated *MGMT* promoters.[54,55] The largest of these trials, the RESCUE study, prospectively stratified 120 patients with recurrent anaplastic astrocytoma or glioblastoma multiforme who had previously received 5-day adjuvant temozolomide, into groups to receive 50 mg/m^2 temozolomide treatment based on the type of progression, including glioblastoma multiforme patients who had progressed following disease progression on adjuvant temozolomide (early or extended progression) or rechallenge after a treatment-free interval of more than 2 months.[55] Patients rechallenged with daily temozolomide after a prolonged treatment-free interval benefited the most from the new schedule compared to those who progressed earlier (PFS 3.7 months for the treatment-free interval group, 3.6 months early and 1.8 months late progression). The ongoing DIRECTOR phase II trial will further compare two dosing regimens of temozolomide in patients with relapsed or progressive glioblastoma.[56] It has been suggested that repeating the same regimen and administering therapy breaks is not necessary,[54] but the necessity of changing the regimen of temozolomide at disease progression has not yet been tested.

Rechallenge after progression on therapy

Disease progression on therapy represents a newer setting for drug rechallenge, likely owing to the increased use of molecular-targeted agents that enable extended treatment duration (Figure 2), and involves retreatment of what might be considered to be truly drug-resistant disease.

Cetuximab-based therapy in CRC

Cetuximab is an EGFR monoclonal antibody that is used to treat metastatic CRC. A case series of four patients with CRC showed that rechallenge with the same cetuximab-containing therapy was effective following the development of progressive disease on therapy and treatment with an intervening therapy.[57] A single-arm phase II multicentre trial in patients with *KRAS* wild-type CRC was conducted to examine the benefit of cetuximab rechallenge after progression on cetuximab-based therapy.[58] This strategy was hypothesized to be effective because *KRAS* mutation status was not expected to change during treatment and, therefore, impact the efficacy of later exposures.[58] Indeed, of 39 patients rechallenged following disease progression on intervening therapy, 53.8% achieved an objective response, 35.9% had stable disease, and 51.2% of patients achieved the same or better response as initial treatment. Stable disease of greater than 6 months and detection of a partial response at initial therapy were predictive of clinical benefit. The authors suggested that intervening therapy caused an increase in the proportion of sensitive tumour cells prior to cetuximab re-exposure.[57,58]

EGFR inhibitors in NSCLC

Gefitinib is a selective EGFR oral TKI given continuously as monotherapy to patients with non-small-cell lung cancer (NSCLC). Although FDA approval was withdrawn for new users in 2005 following the approval of erlotinib, it is still widely used in Europe and Asia.[59] Patients with NSCLC have been shown to retain sensitivity to EGFR TKIs when they are switched to erlotinib after gefitinib failure.[60] However, numerous case reports suggest that retained sensitivity occurs when gefitinib is reused after disease progression.[61–63] In a retrospective analysis of 27 patients with NSCLC who showed an initial response to gefitinib, rechallenge with the drug in five evaluable patients resulted in a partial response in one patient and stable disease in three patients.[64] In another study of 20 patients with NSCLC, a partial response was observed in 16 patients and stable disease in four patients after initial treatment with gefitinib.[65] Re-exposure of all patients (following a median of 7.2 months of cytotoxic therapy) led to a partial response in five patients and stable disease in eight patients.[65] A few small single-arm phase II trials have investigated the efficacy of gefitinib rechallenge.[66,67] In a study of 16 patients with advanced-stage NSCLC who initially

responded to gefitinib, retreatment with gefitinib did not shrink tumours; however, it stabilized disease in seven patients, and in four of these patients this response lasted for 6 months or longer.[66] In another trial of 23 patients with NSCLC, 43.5% of patients had a partial response and 56.5% had stable disease after initial treatment with gefitinib.[67] Following rechallenge, a partial response was observed in 21.7% of patients and 43.5% had stable disease. Patients who initially exhibited a partial response had a better response to re-exposure and a longer time to disease progression (TTP) than those with stable disease (median TTP of 109 days versus 42 days, $P = 0.010$), but had no significant improvement in overall survival (337 days versus 372 days, respectively, $P = 0.685$). Pre-existing acquired *EGFR* mutations were not associated with response to rechallenge.[67]

Erlotinib has also demonstrated success when used in a rechallenge regimen.[68–70] In medical reports of 14 patients with stage IV NSCLC who initially responded and then had disease progression on erlotinib, remarkably, a partial response was observed in 36% of patients and stable disease in 50% following erlotinib retreatment, with responses observed even in patients with T790M *EGFR* mutations (eight of these patients received erlotinib monotherapy at both exposures).[69] The median interval between TKI exposures was 9.5 months and the initial and rechallenge median PFS were 12.5 months and 6.5 months, respectively. The EGFR TKI-free period has been proposed to enable regrowth of EGFR-sensitive cells and actually benefit patients with NSCLC that initially responded to the TKI.[68,69] At this time, only retrospective data suggest a survival benefit of rechallenge with gefitinib versus cytotoxic therapy,[71] but rechallenge regimens have not been prospectively compared with non-rechallenge regimens. Retreatment seems to be a promising opportunity in NSCLC, particularly since subsequent lines of therapy are undefined.

Imatinib in GIST

If early discontinuation and subsequent rechallenge of imatinib in GIST does not cause an expansion of drug-resistant clones, how would responses differ if patients' disease initially progressed while taking imatinib? In a small retrospective study of 26 patients with imatinib-refractory or intolerant GIST, re-induction of stable disease was observed with imatinib treatment in 21% of 14 patients, and overall survival was non-significantly improved compared to 12 patients treated with best-supportive care (22 months versus 4 months, $P = 0.059$).[72] A review of medical records for 223 patients with GIST resistant to first-line imatinib and second-line sunitinib revealed that third-line treatment with an alternate TKI, nilotinib (67 patients) or sorafenib (55 patients), provided the greatest overall survival (11.8 months and 10.4 months, respectively).[73] However, after adjusting for prognostic factors in a multivariate analysis, rechallenge with imatinib (40 patients) was associated with improved overall survival compared to best-supportive care (18 patients; overall survival 7.5 months versus 2.4 months, HR = 0.2, $P = 0.001$).[73] The efficacy of retreating resistant GIST has been confirmed by prospective data.[74] In the phase III RIGHT study, 81 patients with GIST refractory to both imatinib and sunitinib were randomly assigned to receive either placebo or imatinib.[74] Compared to the placebo group, patients rechallenged with imatinib had a significantly greater PFS (1.8 months versus 0.9 months, $P = 0.002$) and disease control rate (32% versus 5%, $P = 0.003$) at 12 weeks. A modest but not statistically significant improvement in overall survival was observed with imatinib compared to placebo (8.2 months versus 7.5 months); this lack of significance might be because 92% of patients in the placebo arm crossed over to the imatinib arm after disease progression. Although subsequent responses to imatinib are weaker if the patient had initial disease progression on therapy rather than off therapy,[40,74] a clinically meaningful proportion of cells seem to continue to remain imatinib-sensitive at progression. Guidelines from the NCCN recommend rechallenge with imatinib in GIST, if tolerable, as late-line palliative therapy after response failure on other TKIs.[75,76]

VEGFR kinase inhibitors in RCC

Multiple antiangiogenic TKIs that primarily target VEGFRs and PDGFRs, such as sunitinib, sorafenib, pazopanib and axitinib, are approved as monotherapy for the treatment of metastatic renal cell carcinoma (RCC). After progression on therapy, patients with RCC are frequently switched to an alternative antiangiogenic TKI, mainly because of the abundance of drug therapies. Surprisingly, this strategy is effective and suggests an absence of complete cross-resistance between TKIs.[77] A similar strategy has also demonstrated activity in patients with hepatocellular carcinoma.[78] Zama *et al.*[79] retrospectively examined whether rechallenge with the same agent could have a similar effect in patients with RCC; 23 patients with metastatic RCC who had disease progression after an initial response to sunitinib (PFS 13.7 months) were rechallenged after intervening therapy (primarily sorafenib with or without bevacizumab or an mTOR inhibitor) and experienced a second PFS of 7.2 months. Although retreatment generally yielded fewer objective responses ($P = 0.006$) and a shorter PFS ($P = 0.04$), PFS was significantly longer in patients with more than 6 months between exposures compared to patients with an interval between sunitinib treatments of 6 months or less (16.5 months versus 6.0 months, respectively, $P = 0.03$).[79] In a second study, 13 patients with metastatic RCC were re-exposed to sunitinib after first-line sunitinib and second-line treatment with mTOR inhibitors (temsirolimus or everolimus).[80] In this study, 92% of patients achieved either a partial response or stable disease with sunitinib rechallenge, and failure to respond to an mTOR inhibitor was not associated with the outcome of rechallenge. In another study of patients with metastatic RCC, stable disease was observed in six out of eight patients who originally discontinued sorafenib because of progressive disease and were then retreated with the same drug.[81] In these studies, antiangiogenic TKI rechallenge seems to have

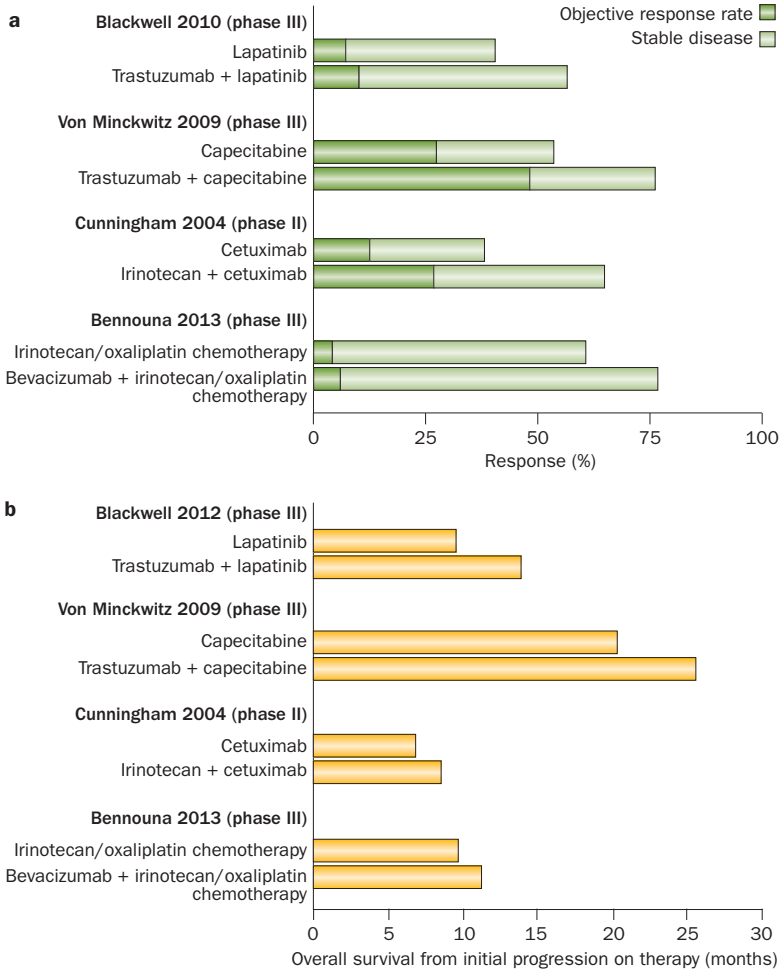


Figure 3 | Efficacy of treatment beyond progression in four randomized phase II or III clinical trials. **a** | Objective response rate and stable disease (%). **b** | Median overall survival following disease progression on trastuzumab, irinotecan and bevacizumab-based chemotherapy when treatment is continued (or not) beyond progression. Continuing a therapy is associated with significant improvements in survival and objective tumour responses.[89–91,94,97]

activity in RCC—and possibly in other malignancies, as observed in GIST case studies[82,83]—suggesting that resistance to sunitinib or sorafenib might be transient, at least in some individuals.[80]

Treatment beyond progression

Randomized studies in which patients either continue or discontinue an agent after disease progression are essential to establish whether continuing an agent beyond progression is efficacious. Whereas patients who are rechallenged serve as their own controls (initial versus subsequent response to treatment), patients who continue a treatment might have very different characteristics compared to those who discontinue treatment. For example, a patient with a minor disease progression (such as a 20% increase in the diameter of a small nodule) is more likely to continue and benefit from therapy than a patient whose disease has progressed rapidly with new extensive metastases. Randomized studies of treatment beyond progression (Figure 3) are discussed below.

Trastuzumab in breast cancer

Trastuzumab is a monoclonal anti-HER2 antibody approved for the treatment of *HER2*-overexpressing metastatic breast cancer in both the adjuvant and metastatic treatment settings. The safety and ability to combine trastuzumab with other agents has led to the practice of continuing trastuzumab treatment beyond progression while switching to other lines of chemotherapy. Since 2004, a number of observational or retrospective studies have indicated that continuing trastuzumab treatment beyond disease progression is superior in terms of response rates, PFS and overall survival than discontinuing trastuzumab and switching to chemotherapy.[84–87] For example, a large observational study observed that in 177 patients with metastatic breast cancer receiving first-line trastuzumab, overall survival measured from the time of first progression was 4.6 months in patients who discontinued trastuzumab and 21.3 months if treatment was continued ($P<0.001$).[88] Prospective data from randomized phase III trials investigating the continuation of trastuzumab treatment beyond disease progression have been reported.[89,90] The German Breast Group 26/Breast International Group 03-05 study demonstrated an improvement in response rate and TTP when patients with metastatic breast cancer who had progressed on trastuzumab-based therapies continued the combination of capecitabine plus trastuzumab (78 patients; treatment beyond progression regimen) versus capecitabine alone (78 patients) at disease progression (response rate, 48.1% versus 27.0%, odds ratio 2.50, $P=0.0115$ and TTP, 8.2 months versus 5.6 months, HR = 0.69, $P=0.0338$, respectively).[89] Although underpowered, this trial demonstrated a trend toward improving survival with the treatment beyond progression regimen. In another phase III trial of heavily pretreated patients on trastuzumab therapy with metastatic breast cancer, the combination of lapatinib plus trastuzumab compared to single-agent lapatinib significantly improved PFS (HR = 0.73, $P=0.008$) and the clinical benefit rate (24.7% versus 12.4%, $P=0.01$).[90] Further analysis of the results from this trial revealed that continuing trastuzumab beyond disease progression significantly improved overall survival by 4.5 months (overall survival 51.6 weeks TBP versus 39.0 weeks lapatinib alone; HR = 0.74, $P=0.026$).[91] Results with this drug combination suggest that enhanced blockade of HER2 can overcome resistance, and that trastuzumab still has activity beyond progression. Ongoing trials are exploring the use of trastuzumab in successive treatments and current NCCN guidelines recommend continued HER2 suppression after disease progression.[92]

Bevacizumab in CRC

Bevacizumab in combination with chemotherapy improves survival in metastatic CRC when used in the first-line and second-line setting. Two large observational studies have seen a benefit when bevacizumab treatment is continued beyond disease progression. The BRiTE study assessed 1,445 previously untreated CRC patients who experienced disease progression

on a bevacizumab-containing regimen.[18] In this study, continuation of bevacizumab treatment beyond disease progression (642 patients) was significantly associated with an improvement in overall survival of 31.8 months versus 19.9 months in patients who discontinued bevacizumab (531 patients), or 12.6 months if they had no treatment (253 patients; treatment beyond progression versus no treatment beyond progression HR = 0.48, P <0.001).[18] These results were confirmed in the ARIES study, which enrolled 1,546 patients receiving first-line or second-line bevacizumab plus chemotherapy.[93] In first-line patients experiencing progressive disease, 539 patients continuing bevacizumab beyond progression had a median beyond progression survival of 16.3 months versus 8.5 months if only bevacizumab was discontinued (417 patients) versus 5.2 months if all therapy was discontinued (127 patients). Treatment beyond progression was independently associated with improved survival after disease progression (HR = 0.41, P <0.001).[93] However, owing to their observational design, it is likely that these studies were biased.

The concept of treatment beyond progression has been validated in the randomized phase III Treatment Across Multiple Lines (TML) trial.[94] In this study, 820 patients with metastatic CRC who had disease progression up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were assigned to receive second-line chemotherapy with or without bevacizumab. Continuation of bevacizumab led to a significant improvement in overall survival from 9.8 months to 11.2 months (HR = 0.81, P = 0.0062).[94] Although the magnitude of benefit associated with continuing bevacizumab treatment beyond progression observed in this trial was much less than suggested by the ARIES and BRiTE studies, this trial provided strong evidence that stable resistance to bevacizumab had not developed. Interestingly, bevacizumab treatment beyond disease progression has been associated with an overall survival benefit in a retrospective study of 23 patients with recurrent glioblastoma,[95] and single-agent bevacizumab has been shown to be effective in five patients with relapsed epithelial ovarian carcinoma who had received first-line maintenance bevacizumab.[96] This finding indicates that VEGF expression might continue to be important for tumour growth despite progression, potentially in several tumour types.

Irinotecan in CRC

At the start of the past decade, new biological agents were being tested in novel combinations in patients with chemotherapy-refractory CRC. The randomized phase II BOND trial[97] had an interesting trial design that demonstrated the validity of treatment beyond disease progression, even if it was not designed with this outcome in mind. In this trial, 329 patients with metastatic CRC who had experienced disease progression on irinotecan-based therapy prior to enrolment were assigned to receive cetuximab monotherapy or cetuximab plus irinotecan. Interestingly, compared to cetuximab monotherapy, treatment beyond progression with cetuximab and irinotecan led to significant improvements in overall response rate (22.9% versus 10.8%, P = 0.007), TTP (4.1 months versus 1.5 months, P <0.001) and a trend towards improved overall survival (8.6 months versus 6.9 months, P = 0.48). This trial led to the FDA approval of cetuximab in 2004 for the treatment of metastatic CRC. It was suggested that cetuximab resensitized tumours to irinotecan,[97] but an alternative explanation is that irinotecan resistance had not developed at initial disease progression.

Other examples

Additional randomized data for continuing treatment beyond progression is unavailable; however, this area is being explored in situations where drug rechallenge has demonstrated efficacy. In a retrospective study of 64 patients with NSCLC, a significant improvement in overall survival was observed in patients who continued erlotinib therapy beyond disease progression compared to those who switched to chemotherapy (32.3 months versus 23.0 months, P = 0.005).[98] A single institution case control study of patients with NSCLC treated with erlotinib showed that patients who continued erlotinib treatment beyond progression (n = 25) had a longer overall survival from the start of progression compared to patients who discontinued erlotinib (n = 16; 14.5 months versus 2.0 months, HR = 0.154, P = 0.0003).[99] This benefit was not dependent on *EGFR* mutation status. The phase III IMPRESS trial will compare erlotinib plus chemotherapy treatment beyond progression versus chemotherapy alone after disease progression in NSCLC.[100] It has also been observed that patients with RCC who remain on sunitinib after disease progression experience prolonged disease control[101] or better survival than patients who discontinue the drug.[102] Recently, a detailed analysis of the sunitinib registration trial revealed that the growth rates of tumours in the vast majority of patients with RCC do not increase for hundreds of days on therapy indicating the existence of intrinsic rather than acquired resistance.[103] Where progressive disease is documented, continued sunitinib might be favourable compared to switching to other less-effective antiangiogenic TKIs,[103] but this remains to be assessed in clinical trials.

Resistance mechanisms

If heritable changes in the tumour dictate drug response in patients, how can use of the same therapy after disease progression sometimes be effective? There are limited data showing a lack of correlation between absolute drug resistance and mutations associated with drug resistance.[67,69,104] Of note, the presence of an alleged resistance-inducing mutation at disease progression does not imply causation of resistance.[105] A false assumption that the tumour was resistant at initial treatment and/or transient resistance mechanisms have developed might explain the apparent clinical benefits derived from drug rechallenge and treatment beyond progression strategies. Since very little preclinical research has been undertaken to replicate these clinical treatment strategies and define the mechanisms involved, a number of hypotheses have been proposed (Table 1 and Figure 4), some of which are discussed in the following sections.

Table 1 | Mechanisms of acquired resistance during drug rechallenge and treatment beyond progression

Possible mechanism(s)	Drug rechallenge (progression off therapy/relapse)	Drug rechallenge (progression on therapy)	Continuation of treatment beyond progression
Permanent or mutational resistance mechanism driving initial progression to agent	No	No (unless residual sensitive cells are fast growing)	No (unless new combination acts synergistically by new mechanism)
Tumours are not resistant to agent at initial progression	Yes	Yes	Yes
Reversible resistance caused by tumour cell adaptation to a drug-free environment	Yes	Yes	Unlikely (yes if treatment discontinuous)
Tumour cells spontaneously cycle between resistant and sensitive states	Yes	Unlikely	Unlikely
Drugs combine synergistically after progression	No	No	Yes

Disease progression, not necessarily resistance

RECIST, progression and drug resistance

In solid tumours, the current dominating paradigm for declaring resistance is the classification of progressive disease using the RECIST criteria.[106,107] These criteria define progression as the growth of a tumour's unidimensional longest axis of at least 20% from baseline (or the sum of diameters of multiple target lesions) or the appearance of one or more new lesions. A response is defined as the opposite, that is, tumour shrinkage, regardless of the time to that event. The RECIST criteria for disease progression based on tumour dimensions were defined through several iterations based on measurement precision, but not how this is associated with survival. These definitions create problems for interpreting clinical data. First, the failure to observe progressive disease might not imply drug sensitivity, but instead might indicate that the tumour is in a natural state of stability, regardless of treatment. Second, the baseline from which to evaluate tumour response is 'reset' when sequential treatments are evaluated. This re-evaluation means that a tumour growing at a constant rate regardless of therapy might take longer to achieve a 20% increase in size in subsequent lines of treatment. Third, it is certainly possible, even likely, that at the time of a 20% tumour growth some patients with extended TTP are achieving clinical benefit through antitumour activity of attenuated tumour growth.

Response evaluation criteria can overestimate the effect of therapy—or lack thereof—while having little to do with the inherent drug sensitivity of a tumour, unless, perhaps, the progression on therapy is considered dramatic. On the one hand, the efficacy of drug rechallenge beyond disease progression in certain cases might be slightly exaggerated; on the other hand, discontinuing therapy in the case of a minor progression is ill-advised. Changes in morphological imaging of the longest diameter of a tumour might be an inadequate assessment of the aggressiveness of a tumour; instead, volumetric or functional imaging might be better approaches, as has been shown for multiple types of cancer.[108–112]

Relapse and drug resistance

For tumours that respond to drug rechallenge after relapse, the simplest explanation is that the tumour cells were not resistant when therapy was discontinued. If treatment had continued indefinitely, progression on therapy would eventually develop in the absence of cure. Relapses that occur shortly after stopping a course of chemotherapy (tumour repopulation) require no inherent change in the chemosensitivity of cells.[113] Indeed even 'resistant' relapses in ovarian,[13] CRC,[15] and small-cell lung carcinomas[14] show some sensitivity to retreatment. The generalization that relapses are not drug resistant is a complex and controversial issue. Increasing the duration or intensity of chemotherapy does not always improve clinical outcome, and if it does the benefit is often marginal.[114–116] Additionally, undetectable, persistent tumour cells that remain following a complete response or adjuvant therapy cannot be eradicated by treatment (as functionally, they are resistant), but patients who subsequently relapse are often sensitive to drug rechallenge.[12] By contrast, if some relapses are because of resistance, these mechanisms of resistance may be transient, as discussed below.

Partial resistance or drug synergism

When disease progression occurs while a patient is on a combination of drugs, it is impossible to determine if resistance has developed to one, some, all (or none) of the agents. The effect of trastuzumab treatment beyond progression in breast cancer or bevacizumab in CRC might be explained by assuming that the cancer had developed resistance to cytotoxic chemotherapy only. Alternatively, if resistance had developed to the initial drug combination, the continued agent could retain some benefit if it combines synergistically with a newly introduced agent. In preclinical models, trastuzumab demonstrated synergistic activity when combined with different chemotherapy agents,[117,118] perhaps explaining its efficacy in multiple lines of therapy. This synergy is difficult to observe in patients if the individual effects of each agent cannot be tested. Interestingly, such a trial has been inadvertently conducted in patients with CRC.[119] The three-arm phase III EFC4584 trial assessed 463 patients with metastatic CRC who had progressed on or soon after receiving the combination of irinotecan, 5-FU and leucovorin. These patients were randomly assigned to one of three regimens: continued treatment

of 5-FU and leucovorin in combination with oxaliplatin, 5-FU plus leucovorin, or single-agent oxaliplatin. The triplet chemotherapy combination provided the greatest survival benefit; for triplet chemotherapy TTP was 4.6 months, for doublet chemotherapy it was 2.7 months ($P<0.0001$ versus triplet chemotherapy), and for single-agent oxaliplatin TTP was 1.6 months ($P=0.03$ versus triplet chemotherapy).[119] This trend was also seen for the overall response rate, which was 9.9%, 0% and 1.3%, for triplet, doublet and single chemotherapy, respectively ($P<0.0001$ for triplet versus doublet therapy).[119,120] Thus, 'synergy beyond progression' might result in efficacy for an agent to which a tumour had previously become resistant.

Spontaneous reversal of resistance

In the absence of drug selection or other exogenous stimuli, clonal cells might spontaneously become heterogeneous in their intracellular signalling patterns, proliferation rates and drug sensitivity.[121–124] Even cancer stem cells, the minority subpopulation of cells proposed to persist during drug treatment, might not be stable.[125–128] For instance, tumorigenic cells derived from melanoma patients were found to be highly prevalent and tumorigenic independent of the expression of several putative stem cell markers, and moreover, had surface markers that were reversibly expressed within lineages of cells, without a hierarchical organization, as proposed by the cancer stem cell model.[125] Cycling populations of drug-resistant and drug-sensitive stem-like cells can occur in the presence[126] or absence of drug selection *in vitro* and *in vivo*.[127,128] Sharma *et al.*[127] identified a small subpopulation of stem-like 'persister' cells from NSCLC cell lines that could survive a near-lethal treatment with erlotinib. Persister cells were found to be transiently tolerant to drugs through epigenetic chromatin modifications: cells spontaneously re-acquired drug-sensitivity in drug-free media, and similar drug-tolerant cells could arise *de novo*, even in the absence of lethal treatment.[127] Thus, populations of tumour cells, putative stem cells or otherwise, might be dynamically drug-resistant and phenotypically unstable. Such dynamic tumour heterogeneity could serve as a survival tactic for a tumour in fluctuating environmental conditions, but this same instability could conceivably be exploited by drug rechallenge to enable additional tumour responses.[127]

Drug holiday-mediated tumour resensitization

Reversal of resistance mechanisms

A drug holiday is a major reason cited for causing tumours to become resensitized to therapy. Indeed, loss of drug resistance is occasionally reported following drug withdrawal *in vitro*,[127,129–133] although this mechanism is difficult to demonstrate *in vivo*. In xenograft models of RCC and hepatocellular carcinoma, tumours that had acquired resistance to sorafenib or sunitinib were shown to become resensitized to treatment after being transplanted into new hosts.[134–136] Long time periods are sometimes necessary to develop *in vivo* resistance, and the short doubling times of cancer cells in these hosts make drug holidays at disease progression ineffective interventions to improve therapeutic efficacy. Treatment interruption for 6 weeks was possible in mice that had developed resistance to the aromatase inhibitor letrozole in a model of hormone-dependent breast cancer.[137] Stopping therapy was found to restore tumour oestrogen receptor-α levels allowing effective rechallenge. This strategy has been adapted for the ongoing SOLE (Study of Letrozole Extension) phase III clinical trial.[138]

In preclinical studies, treatment strategies using pre-planned pulsed regimens are often used. Although the planned drug holidays are not influenced by disease progression, this strategy has shown enhanced and prolonged antitumour activity compared to continuous drug administration in numerous animal models.[139–141] Melanoma tumour cells with acquired resistance to the BRAF inhibitor vemurafenib were found to depend on

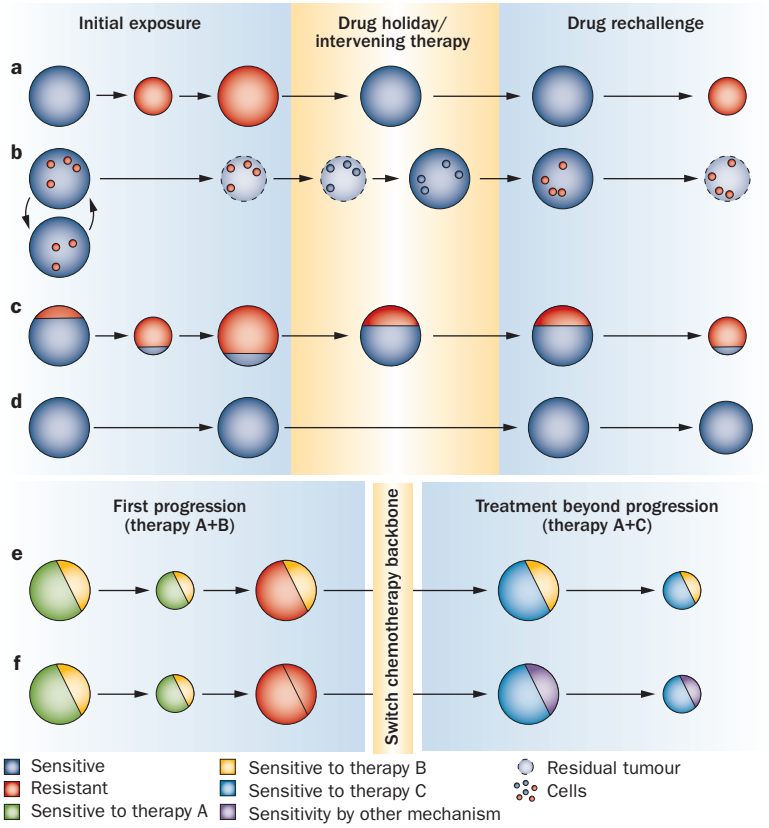


Figure 4 | Mechanisms of drug resistance during drug rechallenge (panels a–d) and treatment beyond progression regimens (panels e–f). **a** | Resistance caused by non-heritable cellular adaptation might be reversed by a drug holiday. **b** | Cells spontaneously cycle between drug-resistant and drug-sensitive states enabling cell survival at initial treatment and resensitization after therapy rechallenge. **c** | Altered proportions of fast-growing/sensitive and slow-growing/resistant cells results in tumour regrowth during a drug holiday or intervening therapy, but drug sensitivity at retreatment. **d** | A slow-growing tumour, that had not yet acquired resistance, might be mistakenly classified as progressive disease based on RECIST; therefore, it is sensitive to rechallenge therapy. **e** | At first progression the tumour had not yet acquired resistance to the agent used for treatment beyond progression; therefore, switching the chemotherapy backbone, but continuing the other agent or rechallenging with an old agent could be beneficial. **f** | The tumour becomes resistant to both agents at disease progression. The agent continued beyond progression combines synergistically with a newly introduced agent, thus bypassing previous resistance mechanisms.

the presence of vemurafenib for continued proliferation, but, counterintuitively, suffered a growth disadvantage upon drug withdrawal leading to tumour regression.[142] Intermittent treatment was found to delay the onset of drug resistance *in vivo* as cells were sensitive to reintroduction of vemurafenib. This finding suggests that adaptation to a drug-free environment might reverse or delay the onset of drug resistance and could explain resistance to drug rechallenge. This mechanism could also be relevant during treatment beyond progression when therapy is not given continuously.[18,89,94,97] For example, 30.8% of all patients who continued treatment beyond progression in the BRiTE study discontinued bevacizumab for more than 28 days prior to its reintroduction.[18] In the TML study, therapy breaks of up to 3 months were allowed, even if they preceded initial disease progression.[94]

Altered tumour kinetics

Therapeutic intervention and subsequent drug withdrawal could favour or limit the growth of different populations of cells within a heterogeneous tumour in a way that could be manipulated by drug rechallenge. Initial treatment of a tumour consisting of fast-growing and slow-growing cells will mostly affect the fast-growing cells, inducing a clinical response. Eventually, the slow-growing cells will cause tumour progression and, if therapy is discontinued, regrowth of fast-growing cells provides an opportunity for the tumour to respond to retreatment. An intervening therapy, rather than a therapy break, might also allow regrowth of drug-sensitive cells.[58,68,80] A similar explanation has been proposed to explain sensitivity to EGFR TKI rechallenge in NSCLC, in which acquired resistance is often thought to be due to *EGFR* mutations, such as the T790M mutation. A loss of T790M during a TKI-free interval has been observed in patients resistant to EGFR TKIs who presented at disease progression with the mutation. Moreover, these patients were sensitive to rechallenge.[143,144] Thus TKI withdrawal might reduce the proportion of T790M mutant cells.[132] Even tumours consisting of a mixture of sensitive and resistant cells could behave more like sensitive tumours in response to treatment as the higher degree of growth inhibition and shorter doubling times of sensitive cells might mask therapeutic effects on resistant cells.[145] This theory suggests that even genetic resistance mechanisms might be reversible.

Discussion

Summary of clinical findings

As discussed above and previously,[12] drug rechallenge and treatment beyond progression strategies can be efficacious for a surprising number of patients with metastatic cancer. A number of interesting observations or implications emerge from these data. First, further clinical benefit can be achieved from reuse of the same drug after disease progression whether disease progression occurred on therapy[58,67,74,79] or after its discontinuation.[26,35,40,44,55,146,147] Based on the limited available data, continuation of treatment beyond progression might yield an overall survival benefit,[91,94] whereas certain drug rechallenge regimens offer long-term benefits that are similar to continuous treatment.[26,27,39,41] These observations must be confirmed in randomized studies for additional malignancies and drug treatments to understand the true scale of this potential efficacy, and to assess how retreatment compares with changing to an alternate therapy.[73] Second, rechallenge strategies seem to be broadly effective (Figure 2) and do not seem to discriminate between the class of anticancer therapy used,[27,34,57,67,79,148,149] the tumour type,[13,23,37,44,55,67,74,79,150,151] the compartment targeted (the genetically unstable tumour versus the genetically stable stromal cells)[27,44,57,79,96] or the type of progression (on or off therapy).[44,79] Treatment beyond progression has shown activity in a variety of tumour types with both targeted agents and chemotherapy (Figure 3).[90,91,94] Third, based on the high response rates achieved, rechallenge regimens do not seem to select resistant clones or accelerate acquired secondary resistance. This finding could be particularly true of disease that recurs after therapy discontinuation in which rechallenge tends to elicit the strongest responses; however, there are limited data available comparing rechallenge responses following different types of progressions to confirm this.[40,44,55,74] Although data are immature on treatment beyond progression, classic resistance mechanisms do not seem to apply here either.[89,94,97] Fourth, the length of the interval between rechallenge treatments, in relapse and progression on therapy settings, has been positively associated with the response to rechallenge (Figure 2b),[26,34,40,79,147,151] similar to what has been established with rechallenge of platinum therapy in patients with relapsed ovarian carcinoma.[13] It is tempting to think that a prolonged interval between exposures increases the magnitude of the 'reversal effect' on drug resistance. However, it should be noted that patients with a shorter intervening period might have more-aggressive disease such that any therapy could lead to weaker responses of shorter duration. Fifth, the degree of the initial objective response is also associated with a positive response to rechallenge.[30,40,58,67,146,151] Therefore, highlighting the importance of primary or intrinsic resistance rather than acquired resistance in response to therapy. Sixth, PFS is almost always shorter and objective responses weaker at rechallenge (Figure 2a,b),[20,34,40,58,67,79,152] suggesting that resistant cells eventually dominate a tumour rendering treatment less effective—or this underscores how subsequent lines of therapy are less effective compared to previous ones while the tumour becomes increasingly aggressive over time (Figure 2b). Finally, patients that tolerate a first course of therapy are likely to tolerate a second course of the same therapy. Toxicity is typically non-cumulative at rechallenge exposure,[27,35,39,55,67,72,79,146,151] although neurotoxic drugs might be an exception.[23]

Implications for drug resistance

The data suggest that the definitions and implications of clinical drug resistance must be used and applied carefully. When early single-arm clinical trials tested P-glycoprotein antagonists in combination with

cytotoxic chemotherapy—the same chemotherapy that tumours had previously become resistant to—the high response rates that were observed were interpreted as evidence of a reversal of multidrug resistance, sparking hundreds of millions of dollars of further research and development.[153,154] Subsequent randomized phase III trials demonstrated no benefit of these antagonists,[7,155,156] suggesting that the earlier observed efficacy might have been due to unintentional drug rechallenge. Although most oncologists would likely agree that rapid tumour progression during a course of therapy signifies drug resistance, the reasons for minor progressions after sustained therapy or progression off therapy are more controversial. Based on the available evidence, early discontinuation of therapy (for reasons other than progressive disease) does not seem to select for drug-resistant clones at relapse. If therapy had been continued until disease progression one cannot, however, be certain that a tumour is truly and permanently drug resistant unless it is shown to no longer be responsive to the same therapy. It is clear that RECIST-defined progression does not denote a meaningful selection of drug-resistant clones nor is it a gold standard indicator for when to change a course of therapy. We suggest that these concepts, along with the notion of reversible or unstable drug resistance, should be given greater emphasis in oncology research and in clinical practice.

Implications for clinical practice

The main implication of transient or reversible drug resistance is that an old agent should not be uniformly excluded from further use in a patient if previously found to be effective and well-tolerated. This possibility has many potential benefits. First, if a patient on long-term therapy is suffering from adverse events or desires a drug holiday, early interruption of therapy might be considered without the concern of accelerating drug resistance, worsening toxicity and potentially compromising overall survival. With a high likelihood of response at re-exposure, further quality-of-life benefits are possible through reduced number of overall treatments and hospital visits. Second, the option of repeating or continuing a therapy considerably improves the availability of therapeutic options. If all other treatment options have been exhausted or there is no standard of care, continuing the same therapy indefinitely or drug rechallenge could be viable options. This option could also be desirable even if other agents are available—consider a new agent with unclear real-world efficacy and a new toxicity profile. This new agent might offer only a marginal benefit in PFS or overall survival with potential reductions in quality of life. Third, if a previously used drug is off-patent and inexpensive, and/or the new agent is expensive, a cost–benefit assessment might favour retreatment with the less-expensive agent. Strategies to make cancer care more affordable and accessible are in high demand given the rapidly rising cost of many new cancer drugs and patient care.[157,158] Continuing a high-cost drug, such as bevacizumab or trastuzumab, beyond progression can be troubling to some given the modest improvements in survival that these agents provide. Finally, if continuing therapy after progression incrementally improves patient outcome, there are clear implications for clinical trial design. In a trial of a novel agent or strategy seeking an overall survival benefit, consideration should be given to allowing therapy continuation in instances of minor (to be prospectively defined) progression in the absence of demonstrated benefit of alternate therapies.

Limitations

Is it possible that retreatment or continuation of treatment could potentially be active in all tumour types and with all drugs? There are clinical examples in which non-heritable resistance mechanisms might have a role, for example, when tumours display a lack of cross-resistance to agents within the same drug class, or different taxane and platinum agents in breast cancer and ovarian cancer treatments, respectively,[13,150] or antiangiogenic TKIs in RCC.[77] The overall success of these strategies across a broad spectrum of malignancies and anticancer agents—and that we were unable to find any evidence of absolute inactivity—suggests that unstable and non-heritable resistance mechanisms have a significant role in medical oncology. Of note, much of the present literature consists of anecdotal studies clearly subject to various biases. The selection bias of prospective trials—patients selected for retreatment often have good performance status and prognosis, and experience good initial responses to treatment—might cause an overestimation of the activity of the treatment strategy. Furthermore, publication bias may further skew this apparent efficacy.

Conclusions

Although a few phase III clinical trials demonstrate that continuous conventional maximum tolerated dose chemotherapy offers no survival benefit and poorer quality of life compared to rechallenge-like regimens,[13,22,159,160] one can only speculate on the true efficacy of drug rechallenge using most of the newer therapies. Further research is needed to address this area. If research effort focuses only on identifying and targeting robust and stable changes that occur in the tumour cell, more subtle explanations for resistance will be missed. Preclinical studies of drug rechallenge and treatment beyond progression, which are rare, are necessary. Such studies require that questionably relevant experimental models of cancer, such as *in vitro* dose escalation and selection of clones, are used with caution and that models reflecting the clinical situation, such as models of advanced-stage metastatic disease,[161] genetically engineered mouse models or patient-derived tumour xenografts[162] treated with relevant drugs and regimens, are implemented.

Future clinical studies are required to assess the impact of RECIST-determined progression with subsequent survival and to consider whether alternative growth percentages, time-based rates of change, or newer measures are more predictive of long-term outcomes. Well-designed prospective phase III clinical trials with appropriate controls are necessary to compare if switching to a new therapy (conventional therapy) is better than

a retreatment strategy. Based on this Review, and as suggested for trials in RCC,[103] an appropriate control arm for testing a new therapy could be continuing or repeating an old therapy. Unfortunately, it might be difficult to accrue patients into a clinical trial if therapy is discontinued temporarily or a new agent is not offered. A number of questions should be addressed in future studies. When 'resistance' develops to an initially effective long-term continuous low-dose metronomic chemotherapy, would a break in therapy at disease progression similarly reverse the resistant phenotype? How do therapy dose (maximum tolerated dose versus low-dose chemotherapy) and regimen (dose dense versus continuous and protracted or metronomic dosing) contribute to delaying or preventing the onset of stable acquired resistance?[163] When is some sort of maintenance therapy, during what would otherwise be a therapy break, be superior to a true drug holiday in terms of resensitizing a tumour to therapy?[24,164,165] Would continuing all agents beyond progression be of equal benefit to switching the chemotherapy backbone? Is continuous (beyond progression) treatment superior to a treat-as-needed approach?

In conclusion, there are abundant clinical examples in medical oncology of transient resistance or progression that do not equate to resistance. Despite the development of disease progression on or after discontinuing therapy, a large number of patients remain sensitive to therapy that is continued or reintroduced at a later time. Such treatment strategies have major implications for patient care, the choice and timing of therapies, and the overall quality and cost of treatment. These considerations simply serve to highlight the shortcomings of present concepts of drug resistance and how progressive disease is characterized and managed.

Review criteria

The PubMed and MEDLINE databases and Google were searched for publications in English with search terms such as "rechallenge", "reintroduction", "retreatment", "intermittent", "beyond progression", "transient resistance", "reversible resistance" in addition to "therapy", "cancer", "chemotherapy" and "drug". Citations from relevant publications, ClinicalTrials.gov and abstracts from annual scientific meetings, including ASCO and ESMO, were also considered. The drugs focused on for this Review were selected on the basis that they were first documented in a rechallenge or beyond progression study since 2000, and up to June 2013. Readers are directed to the literature for older agents found in new rechallenge studies.

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