The cancer wars 2

Rethinking the war on cancer

Douglas Hanahan

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This is the second in a Series of three papers about the cancer wars

Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences. Swiss Federal Institute of Technology Lausanne (EPFL), CH-1015 Lausanne, Switzerland (Prof D Hanahan PhD)

Correspondence to: Prof Douglas Hanahan, Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, Swiss Federal Institute of Technology Lausanne (EPFL), SV 2816 (Bâtiment SV), Station 19, CH-1015 Lausanne, Switzerland
dh@epfl.ch

Some 40 years ago a metaphor was posed that cancer was such an insidious adversary that a declaration of war on the disease was justified. Although this statement was a useful inspiration for enlistment of resources, despite extraordinary progress in our understanding of disease pathogenesis, in most cases and for most forms of cancer this war has not been won. A second metaphor was about magic bullets—targeted therapies based on knowledge of mechanisms that were envisaged to strike with devastating consequences for the disease. The reality, however, is that targeted therapies are generally not curative or even enduringly effective, because of the adaptive and evasive resistance strategies developed by cancers under attack. In this Series paper, I suggest that, much like in modern warfare, the war on cancer needs to have a battlespace vision.

Introduction

A "war on cancer" was launched by the US congress[1] and declared by US President Richard Nixon in 1971, with a vision that, by raising public awareness of the devastating disease and presenting it as a dangerous enemy that posed a serious threat to societies, diverse forces and resources could be assembled to successfully counter-attack and win the war. The resulting investments and initiatives, and the metaphor itself, helped to catalyse international commitments to research and drug development, leading to extraordinary advances in our knowledge about the nature and mechanisms of the disease. Diverse organisations—academic research institutions, hospitals, medical centres, the biopharmaceutical industry, governments, and philanthropic organisations—have come together in various alliances to attack different aspects of the threat.

We now know that cancer manifests as hundreds of types and subtypes, collectively affecting most organs and tissues. The war on cancer has taught us about the tremendous diversity in the characteristics of cancers arising in different organs from cell types distinctive to those organs. The instrumental mutations and rearrangements of the human genome in the transformed cancer cells are extremely complex. These transformed cells drive the expansive growth of different cancers, via genetic and epigenetic reprogramming of regulatory circuits, which corrupt normal cells to become chronically proliferating cancer cells. Further diversity is seen in the recruitment, indoctrination, and integration of ostensibly normal supporting cells—vascular cells, immune inflammatory cells, and fibroblasts. Diversity is also evident in rates of disease progression and the disease's effects on the individual. Finally, disconcerting incongruity exists in the types of therapy to which particular cancers respond (or do not respond), and in the duration of clinical benefit from such therapies; sadly, few cancers can be cured unless detected early and surgically excised.

Although progress towards understanding the nature and logical basis of cancer has been impressive, the essential premise of the war on cancer was to apply new knowledge of mechanisms to greatly improve the treatment and prevention of the disease. At a gathering of thought-leaders from across cancer research and treatment at the World Oncology Forum, in Lugano, Switzerland, in late 2012, a question was asked: are we winning the war on cancer, 40 years on? The conclusion was, in general, no. Despite the introduction of hundreds of new anticancer drugs, including advanced therapies (so-called magic bullets) aimed at particular weapons in the enemy's armamentarium, the consensus was that, for most forms of cancer, enduring disease-free responses are rare, and cures even rarer. Notable exceptions include some forms of leukaemia and of breast cancer, testicular cancer, and particular tumours—eg, colorectal—amenable in early stages to total surgical resection.

Another sobering issue discussed at the Forum was the reality that many exciting new cancer treatments are very expensive (largely due to the high cost of drug development and clinical testing), despite in many cases producing only transitory clinical benefit, posing serious cost–benefit dilemmas for patients, health insurers, and governments.

Moreover, the war is expanding on the world map of cancer. Incidences of lifestyle-associated cancers are rising in developing countries as populations adopt diets and lifestyles associated with risks of cancer in high-income countries, without commensurate reductions in cancers elicited by preventable infectious disease (eg, papillomavirus-induced cervical cancer) still occurring.

Another disconcerting theme of this Forum was our inability to effectively fight cancer in the developing world, where important new drugs and modern technologies are generally unaffordable or logistically impractical to deliver to patients. Some have argued that we are losing, and will continue to lose, major battles against cancer in developing countries. The importance of incorporation of a global perspective[2,3] into the strategic plan for the war on cancer has been raised in reports from this forum[4] and from another timely forum held at

the US National Institutes of Health in 2012.[5] The economic cost of cancer is a global problem. Cancer costs the European economy more than €50 billion (US$67·55 billion) every year in care, treatment, and lost productivity—more than 15% of that cost is due to smoking-induced lung cancer.[6] In this Series paper I focus on fighting the war on cancer, prevention being discussed in Series paper 1.

Although we have won some battles, we have not won the war on cancer. Despite remarkable progress in our understanding of the disease and in treatment of some forms of it, some observers have passionately argued that we are losing this war,[7,8] suggesting radical prescriptions for change in how the war is fought. However, most would agree that we have not lost the war. Historic progress has been made, and remarkable opportunities exist to turn the tide. Refined and potentially more-effective tactical strategies are being developed and tested.[9] With respect to regrouping of and improvement of our tactical forces' ability to fight this evolving war, perhaps now is also time to rethink the strategy for this useful metaphor of fighting a war on cancer. To take a lesson from the evolving theories of modern conventional warfare, in which individual battlefields, armies, and armaments are integrated into an overarching, holistic so-called battlespace that guides strategic war plans,[10] perhaps an analogous battlespace plan for cancer should now be considered.

The notion of stepping back from the front lines of the battles against specific forms of cancer, looking instead at the larger picture across the manifestations of the disease, is integral to the concept—called the hallmarks of cancer—that has been put forward in an attempt to rationalise the complexity of human cancer pathogenesis.[11,12] The proposition was that most lethal cancers acquire a similar armamentarium of capabilities, albeit empowered with specific mechanistic underpinnings and characteristics that can differ substantially from one cancer battlefield to another, much as weapons of conventional war can be similar in function but distinctive in design and application in particular war zones. The distinctive constitutions of several forms of human cancer are being shown by interrogation, with increasingly advanced research methods, of the enemy's weapons and modes of operation in different organs, producing a wealth of new information; in turn, the use of approaches such as the hallmarks of cancer formulation might help to integrate these specific details about different manifestations of the enemy into a common framework. In this Series paper I suggest that this organising principle might be applicable to development of a battlespace plan for the war on cancer that integrates knowledge about the weapons, capabilities, strategies of expansive growth, resilience of adaptive resistance, and evasion of therapeutic attacks into what could become a new doctrine for the metaphorical war on cancer.

The cancer battlespace

A military battlespace is a strategic approach that takes an integrative, holistic view of war, incorporating information about the enemy's characteristics and armamentarium, precise topographical maps of all potential battlefields and war zones, the weather, and other environmental factors, along with a census of friendly forces and their capabilities, in all relevant geographical locations. The metaphorical war on cancer needs to adopt an analogous cancer battlespace plan, integrating knowledge about similar variables, including: a census of a cancer's variously specialised cells, the basis of their corruptions (eg, genetic mutations, reprogrammed regulatory circuitry), their lines of communication, and the nature of their functional contributions to the war machine; the mechanistic composition of the armamentarium in a particular form of cancer that collectively supplies the hallmark capabilities necessary for tumour growth, invasion, and dissemination; the distinctive histological features of a cancer's assemblage in different tissue landscapes; and the characteristics and potential value of friendly forces that might be enlisted as part of tactical attacks throughout the many battlefields of disease.

From the cancer-hallmarks perspective, three strategically distinct battlespace-guided plans can be envisaged to attack cancer with our increasingly powerful drugs and other weapons, with the use of increasingly advanced therapeutic strategies. Each approach takes a different perspective, potentially complementary to each other, of the landscape of war afforded by a cancer battlespace philosophy.

This three-dimensional cancer battlespace plan can be envisaged to include disruption of several capabilities of the enemy, neutralisation of specialised divisions of the enemy's armed forces, and integration of the distinctive geographies of the often-multiple tissue and organ battlefields.

Disruption of the enemy's many capabilities

Specialists in cancer medicine have long been anticipating the development and introduction into clinical practice—beginning in the late 1990s—of treatments intended to disrupt specific mechanisms (and hallmark capabilities) that drive tumour formation, growth, and malignant progression. The hope and expectation was that such magic bullets would stop cancers in their tracks. Some heartening examples exist—eg, biological therapies targeting the hallmark capability for evasion of immune destruction—which are producing remarkable responses in patients with metastatic melanoma.[13,14] The reality check, however, has been that designer drugs targeting particular mechanisms and hallmark capabilities have not proved to be magic bullets. Rather, most targeted therapies are only transiently effective; after taking some losses, the cancer adapts and becomes resistant to, or otherwise evades, the treatment, and disease progression resumes,

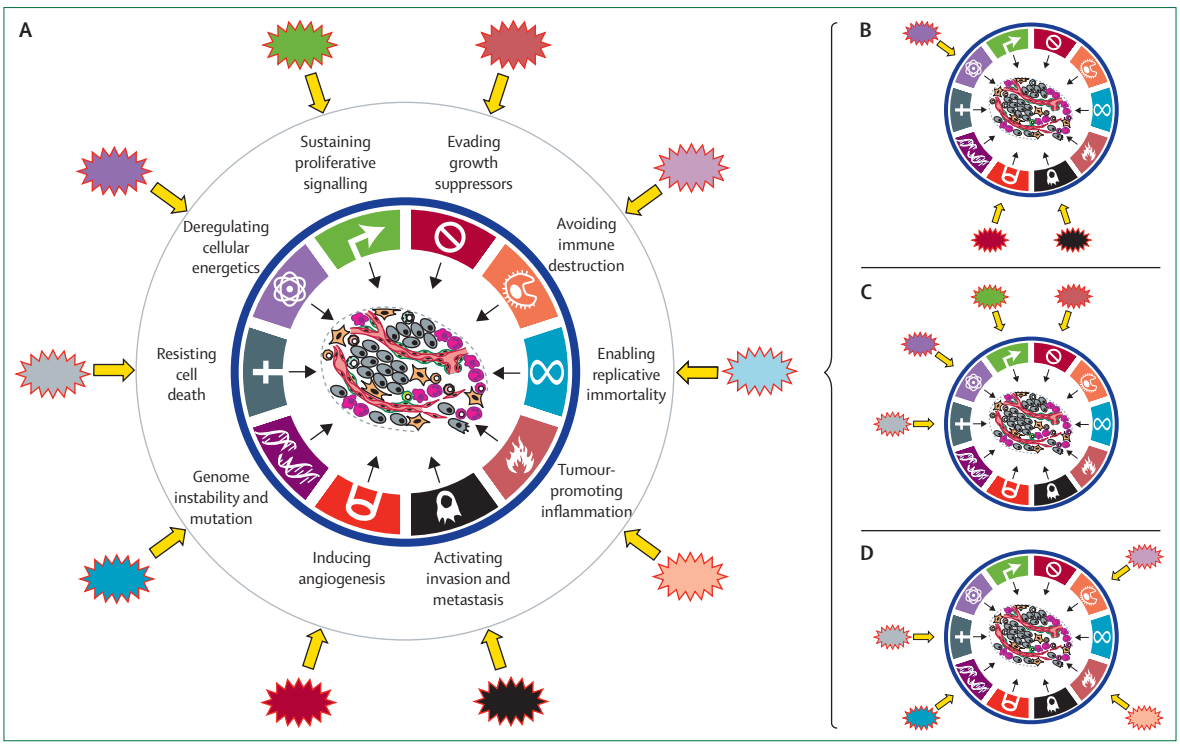

***Figure 1*: Disruption of a cancer's capabilities**

Cancers acquire ten damaging functional capabilities and facilitators (shown in white ring and indicated by symbols in coloured ring) that collectively manifest successful attacks on the affected individual.[11,12] Each capability can be counteracted by various mechanism-targeted treatments[12] (shown figuratively as explosion shapes) which, generally, do not act as curative magic bullets because of the countervailing development of advanced strategies of resistance. One battlespace plan involves multitargeting of all of these capabilities and facilitators (A). A major challenge, however, is limitation of collateral damage—toxicity to normal tissue and physiological functions. Realistically, tactical variations will involve more selective multitargeting (exemplified in B, C, and D), fine-tuned both by enabling of military intelligence of a patient's tumour afforded by increasingly accurate, high-resolution molecular diagnostics, and by the nature of the drugs and the tactical regimens in which they are launched, to optimise effectiveness while restricting toxicity. Adapted from figure 6 of Hanahan and Weinberg.[12]

often with renewed vigour.[15–17] One pattern of resistance involves activation of new mechanisms that convey, via alternative strategies, the particular functional capability being targeted.[15–18] A second pattern is to increasingly rely on other hallmark capabilities—eg, a cancer's resistance to angiogenesis inhibition by becoming more invasive and metastatic,[19,20] enabling cancer cells to grow by co-opting normal tissue vasculature.

If one accepts the premise that most cancers acquire a similar armamentarium of capabilities, then a logical strategy is to remove as many of these capabilities as possible, rather than merely to target a single mechanism. Such a strategic shift can be thought of as a plan, of co-targeting of multiple capabilities, especially cotargeting of hallmarks that can provide cross-support, whereby the power of one hallmark capability can help to compensate for the therapeutic impairment of another. Importantly, drugs have been developed that disrupt each one of the eight hallmark capabilities and both associated facilitators.[12] In a perfect attack, one would simultaneously target all ten capabilities (figure 1A). Practically, however, cumulative toxicities will probably render this simplistic strategy unrealistic. Instead, we will need to consider the battlespace—ie, how specific forms of cancer use particular capabilities, and how such cancers can adapt to therapeutic attack, either by circumventing the functional blockade of the targeted capability, or by shifting to rely on some other capabilities. In a shifting approach, therapeutic co-targeting of interdependent hallmarks could seriously weaken the enemy. Thus, for example, one can envision futuristic war plans cotargeting hallmark capabilities and enabling characteristics by one of several strategic attacks: inhibition of tumour angiogenesis, together with inhibition of invasion and metastasis, and disruption of cancer energetics and metabolism (fuelling) (figure 1B); inhibition of proliferative signalling with reactivation of disabled mechanisms for programmed cell death and for growth suppression, along with disruption of cancer-cell fuelling (figure 1C); or inhibition of tumour-promoting inflammation and hyperactivation of immunological destruction of tumours by killer T lymphocytes, concomitant with damage to the cancer cell genome and accentuation of immunogenic forms of programmed cell death using potent chemical weapons (figure 1D).

Realistically, interim steps—now in use in some cases[17,18,21–23]—will involve even fewer (pairwise) combinatorial attacks to test the value and feasibility of this

strategy. Additional factors in successful application of such a battlespace plan will probably entail timing of particular therapeutic attacks, because it could prove more effective (and less toxic) to design regimens with rational sequences of hallmark-targeting drugs, abrogating components of the cancer's armamentarium at optimum times on the basis of knowledge, both of the enemy's war machine (typically solid tumours) and of how the machine adapts when attacked.

Importantly, this strategy of concomitant targeting of multiple hallmark capabilities to circumvent adaptive or evasive resistance and other limitations of target effectiveness is not the only possible strategy for improvement of the success of hallmark targeting. Another active line of development necessitates second and third-generation weapons, and many weapons aimed at different components with the same capability. Thus, for example, simultaneous targeting of two of the oncogenic signal transducers driving the proliferative hallmark in metastatic melanoma (mutant *BRAF* and its downstream relay partner *MEK*) produces exciting responses.[18] Another tactic is to use so-called synthetic lethal strategies, whereby to hit one target is ineffectual by itself, but produces an underlying sensitivity to the abrogation of a second target, such that dual targeting of both is synergistically effective at killing cancer cells.[24,25] Some of these weak points could transcend multiple hallmark capabilities rather than focus on one.[24–26] Irrespectively, one can envision an evolving war plan that will both target individual hallmarks more effectively, and cotarget several hallmarks so as to cripple the war machine.

Defence against cancer's armed forces

Another important dimension to a battlespace perspective of cancer is refined knowledge about the armed forces of the enemy—ie, the cells attacking the host—and the contributions that each type of cell makes to the war machine. We now know that most cancers are outlaw organs, composed of hierarchies of mutant cancer cells of different rank and character, which are supported by once-normal (stromal) cells that they recruit and reprogramme. Much as in a conventional war, the skills and contributions of these distinctive populations of cells are crucial to the enemy's war machine. The war on cancer has largely focused on mutant cancer cells, via chemotherapy and radiotherapy and, more recently, targeted therapy based on knowledge of the driver mutations that force the chronic proliferation that is the basis of the disease. Most of the time, however, cancers eventually find ways to circumvent such targeted strikes, adapting and then re-emerging as expansive and often more aggressive growths. Several mechanistic explanations exist for this resilience in the face of a seemingly lethal attack on hyperproliferating cancer cells.

Proliferative dormancy—a capability of cells to hibernate before emerging from therapeutic attack to resume growth—is, in some cases, preferentially vested in a distinctive subclass of cancer cell—slowly proliferating cancer stem cells. Additionally, conscripted stromal cells can nurture and protect cancer cells (and cancer stem cells) from the effects of therapeutic attack in special cave-like tissue niches. There is increasing reason to believe that such guerrilla-like hibernation, in the context of a cancer suffering major losses of conventional cancer cells, enables the cancer to survive and re-emerge to launch new expansive growth. Thus, the cancer battlespace should consider all classes of constituent cell in a cancerous growth and their distinctive contributions to the war machine,[27,28] beyond the obvious assemblage of conventional cancer cells.

Drugs and strategic targeting regimens will need to be developed that kill, inactivate, or otherwise neutralise all component cells of a cancer (figure 2). For some soldiers (cancer cells, and the endothelial cells and pericytes of the tumour vasculature), drugs are available to target them or their contributions to the cancer war machine,[12,27] although substantial potential remains to develop more refined and effective agents. For cancer stem cells, cancer-associated fibroblasts, and tumour-promoting inflammatory cells, new mechanism-guided agents are needed, and can be anticipated.[27,29] To have an enduring effect, an almost-certain necessity will be to establish advanced combinations and temporal regimens of drugs that effectively target several classes of cellular soldier, so as to avoid adaptive resistance with use of tactical shifts among them, while limiting collateral tissue damage (toxicity). Moreover, it will be important to delineate potential variations in the abundance and characteristics of constituent cells in the tumour microenvironments of distinctive tissue and organ battlefields for a particular cancer.

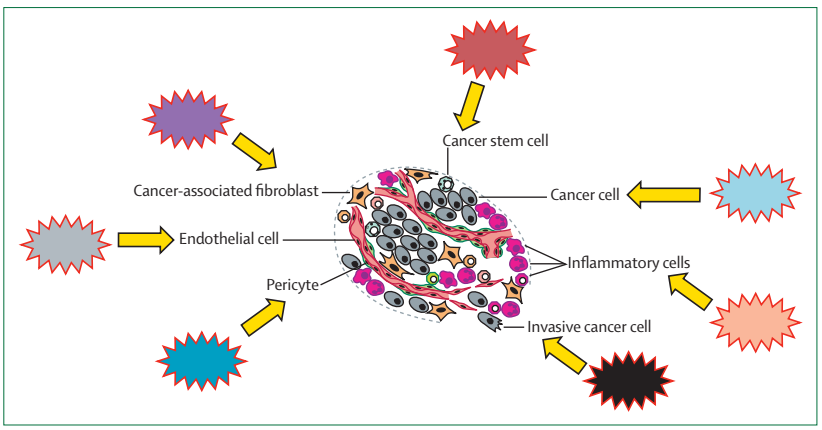

***Figure 2*: Targeting of cancer's armed forces**
The enemy uses specialised soldiers—corrupted and conscripted cells of the body that serve the cancer's war machine. Each of these distinctive cell types can, in principle, be targeted, probably in various tactical combinations and temporal regimens to maximise effect and to restrict toxicity, guided by intelligent diagnostics that inform with great accuracy the constitution of targetable constituent cell types in a patient's tumour. Each of the cell types comprising a cancer's armed forces can be targeted by different so-called smart drugs, shown as explosion shapes.

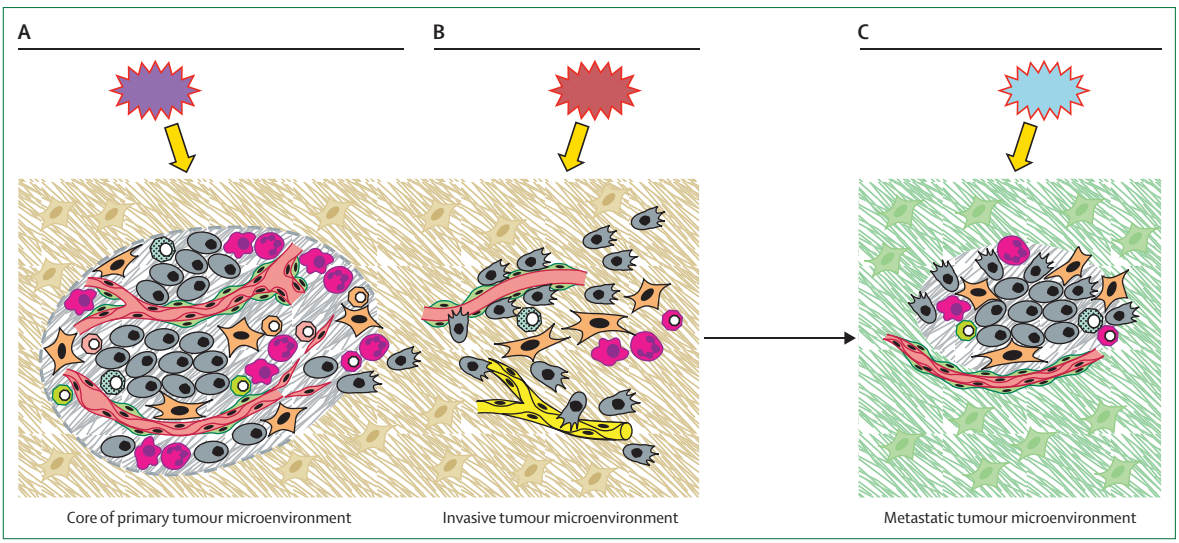

Figure 3: **Integration of the geographies of several active battlefields**
As cancers grow and become more aggressive, many invade both local and distant tissues; the resultant cancerous landscapes are increasingly appreciated to be qualitatively distinct, both in their composition of cell types (as shown in A, B, and C), and in their reliance on particular hallmark capabilities. Thus, successful counterattacks that produce enduring effectiveness, and perhaps in some cases cures, will necessarily mean effective targeting of each of the distinctive battlefields in the body of a cancer patient, which will also need improved capabilities to gather intelligence about these battlefields with high-resolution diagnostics. Thus different weapons and targeting strategies (shown as explosion shapes) might be needed to effectively target different cancer battlefields in the same individual. Adapted from Hanahan and Weinberg.[12]

Integration of the geographies of the battlefields

A third dimension to the war on cancer entails consideration of the geography of the conflict. Even for a particular form of cancer, the cancer can grow and gather strength in many locations of the body, becoming more aggressive (figure 3). Most simply, for solid tumours the distinctive battle zones that are encountered when counterattacking a cancer begin at the initial site, the primary battlefield, where the cancer arose, assembling the core tumour microenvironment. Secondly is the battlefield created in which cancer cells become guerillas, invading from the primary tumour mass, intercalating into adjacent normal tissue, coopting vasculature for fuel and nutrients, and disrupting architecture and organ function. Distant war zones erupt after cancer cells disseminate through blood or lymphatic vessels to draining lymph nodes or distant organs, seeding new conflicts.

That these various battlefields have distinctive characteristics that can affect the success or failure of a therapeutic strategy is increasingly apparent. A cancer can have several armies, each distinctive for a particular war zone, differing in the abundance and characteristics of the various classes of corrupted and conscripted cell types comprising its armed forces.

Although these notions are speculative, improved understanding of the distinctive battlefields to create a battlespace is arguably a sensible and feasible strategic goal. Improvement of knowledge of the different anatomical, histological, cellular, and molecular genetic landscapes and their effects on cancer will be crucial to the design of more effective battlespace plans. Different drugs could be aimed at the particular vulnerabilities of a specific battlefield or war zone (figure 3), collectively shifting the balance of war in favour of enduring therapeutic responses.

A refined battlespace-guided war on cancer

In this Series paper I propose a hypothesis that, although the metaphorical war on cancer has not been won, even if specific battles have succeeded, there is good reason to not abandon the metaphor, but rather to refine and modernise it into an overarching and holistic battlespace war plan against cancer. Strategically, many dimensions exist to such a vision. Prevention of cancer by changes in lifestyle and global health is one dimension, albeit with many cultural and socioeconomic impediments—eg, cessation of smoking tobacco, which would have an enormous effect on prevention of the most prevalent and one of the most lethal forms of human cancer worldwide). Another dimension is to take a world view of the enemy, thereby seeking to fight prevention and therapeutic battles not only in wealthy, developed countries but also in the developing countries where cancer is becoming a plague.[2–5] A third dimension, argued in this Series paper, is that the therapeutic war plan needs to be refined. Although applied cancer research is regularly adding to our armamentarium of weapons, which are increasingly effective against those of the enemy, the resilience and adaptability of human cancers make singular assaults generally destined for failure.

The proposition, still to be thoroughly explored conceptually and practically, is that we should seek to adopt a

battlespace plan of war, recognising the multiple dimensions of the enemy and its modes of operation in different battlegrounds and war zones of the human body (figures 1–3). Importantly, much as military intelligence is crucial for formulation of battlespace plans, so too will improved intelligence be important in fighting cancer. Thus, all three of these strategic approaches need specific detailed and up-to-date intelligence to best design and implement the respective battle plan. One of the major elements in our future arsenal must be new generations of molecularly-based in-vivo and in-vitro diagnostics that can guide the creation of an optimum battlespace therapeutic plan for each patient, at the specific timepoint in his or her disease progression, factoring in any ongoing responses or adaptations to a previous therapeutic attack.

Perhaps then, with a broader perspective of the battlespace and its dimensions, and with better means for gathering of intelligence via sophisticated molecular diagnostics, new therapeutic strategies can be implemented that will prove to be more effective initially, and, even more importantly, better able to block the circumventing adaptive resistance mechanisms that render the effectiveness of most therapies transitory. Of course, a serious qualification to such multipronged and aggressive attacks will be in management of collateral damage—the toxicity of complex combinatorial regimens, already extant as an issue with many treatments. An increasingly important avenue is likely to be the insightful use (while recognising their limitations) of preclinical models of human cancer—genetically engineered cancer-prone mice and patient-derived cancer xenograft mice (avatars), and testing of a patient's biopsy specimen in organ culture—to advance knowledge about the battlespaces of different forms of cancer,[21,22,30] and provide guidance about comparative effectiveness and toxicity of alternative battlespace-guided therapeutic regimens, aiming to then take the best plans into the clinic.

Conclusion

Although the dual metaphors of the war on cancer and of magic bullets to kill cancers have been useful, now is the time to refine them, factoring in extraordinary advances in knowledge about cancer science and medicine. The premise of this Series paper is that a refined metaphor involving a multidimensional cancer battlespace vision could prove useful in strategic designs of more effective cancer therapies. Such an integrative and dynamically refined cancer battlespace philosophy—by factoring in the diversity of cancer's armamentarium of weapons, the organisation of its specialised armed forces, and its distinctive battlefields and war zones within a cancer patient, integrated across the spectrum of cancer types and subtypes and, in turn, patient individuality—could contribute to substantial progress in the treatment of cancer, enabling more battles and even certain wars to be won.

Conflicts of interest

I declare that I have no conflicts of interest.

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