A call for integrated metastatic management

Metastatic disease remains invariably fatal. Until truly curative therapies are developed, can clinical oncology benefit from lessons learned in pest management?

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Unfortunately, the overall survival for metastatic cancer has changed little since 1991 in spite of the large number of new drugs approved by the Food and Drug Administration (FDA) for treatment of metastatic disease[1]. While these drugs can be highly effective in temporarily suppressing disease growth, the proliferation of resistant clones invariably leads to tumor progression and treatment failure. These evolutionary dynamics of resistance have proven to be a significant barrier to survival in patients with metastatic disease[2,3].

A similar 'resistance crisis' occurred during the initial attempts of the agriculture industry to eradicate major pests[4]. The development of a large variety of synthetic pesticides and their subsequent widespread usage began in the 1940s. While the impact on the pest population was initially dramatically successful, use of pesticides in high doses resulted in maximal selection pressure for resistance and eliminated competing phenotypes, actually accelerating the proliferation of resistant pest populations[5].

In response, the agricultural industry recognized the key role of the evolution of resistance and transitioned away from an exclusive focus on developing new, more lethal insecticides to a more nuanced approach, coined integrated pest management, or IPM[6]. The main goal of IPM is not to achieve 'clean' fields, but instead to maintain pests below levels that cause serious damage by delaying or preventing growth of resistant pest populations. Significant differences certainly exist between agricultural pests and disseminated cancer, such as how genetic variability is created and transferred (sexual versus asexual)[7] or how the fitness cost of resistance inhibits growth (r versus K selection)[8]. While these will require modifications to the precise tactics that are used against cancer, the overarching strategy of IPM remains highly relevant in transforming metastatic cancer into a chronic disease.

In 2015, Barzman et al.[9], on the basis of 50 years of agricultural experience, formalized the fundamental principles of IPM that proved most successful in obtaining long-term control of pest populations. These eight principles, discussed within the context of cancer biology, provide a framework to build and develop a long-term management paradigm for metastatic disease (Fig. 1). Until truly curative therapies for metastatic disease are developed, the similarity to the 1950s resistance crisis leads to a compelling question: can clinical oncology benefit from lessons learned in pest management?

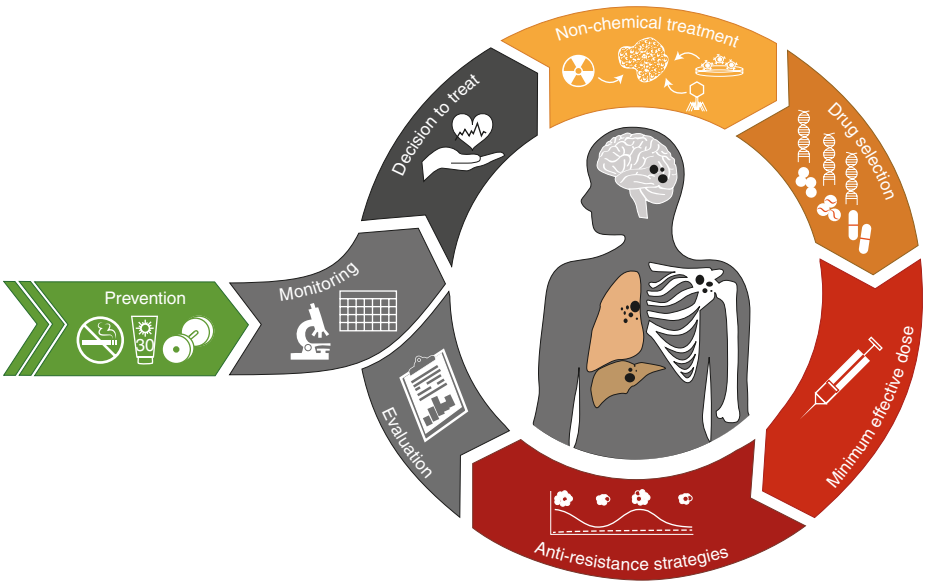

Fig. 1 | Integrated metastatic management. Barzman's eight principles of integrated pest management provide a formal process to successfully manage metastatic disease as a long-term chronic illness. Implementation of these eight principles in the clinic could drastically reduce drug usage, delay or completely prevent evolution of resistance to available drugs, and lengthen the overall survival of patients with metastatic disease. Credit: Web & Moss Studio

The implementation of IPM is broken into three major parts: prevention, decision-making and intervention. In oncology, prevention is already well recognized and identified as the principal initiative of the most recent World Cancer Declaration[10]. On the other hand, the decision-making process in oncology can take from IPM and include continuous monitoring of ongoing evolution of tumour subpopulations, allowing a decision as to whether immediate treatment is truly necessary and prioritizing overall survival above eliminating tumour burden. Lastly, if decision-making warrants an intervention, IPM suggests the use of a wide variety of control methods used within what is known as a resistance management plan. This is perhaps the most significant divergence from current cancer therapy, as IPM rejects the traditional view that the best treatment is 'hit them hard and fast' (for example, the Norton–Simon model[11]). Instead, a resistance management plan prescribes using the minimum effective dose in adaptive therapy protocols[12], expanding precision oncology efforts and identifying additional anti-resistance strategies in an attempt to explicitly prevent or delay the evolution of resistance to treatment.

Decision-making

Monitoring. The success of IPM is greatly facilitated by the availability of accurate data on the ongoing evolution of pests within a treated region. In contrast to sophisticated sampling in fields, there are no currently available biomarkers that

can unambiguously define intratumoral evolution of a cancer cell population during treatment. After initial histological and molecular analysis, tumour monitoring is performed only episodically through serum biomarkers and imaging studies[13]. Thus, while the evolutionary dynamics of cancer cells occur continuously, clinical measures are, at best, available in intervals of weeks or months. Thus, virtually all treatment decisions are made in the absence of critical information concerning the evolution of resistant tumour subpopulations. To enable effective monitoring of the underlying evolutionary landscape of the disease during treatment, technologies using circulating tumour cells[14], cell-free tumour DNA[15], plasma DNA[16] and radiomics[17] should be expanded.

Decision to treat. In IPM, it is common practice to decide whether and when to treat the identified pest, with the decision often being to not treat at this time. To implement a successful long-term management strategy in metastatic disease, it will be necessary to re-define the tolerable threshold of cancer cell burden to a nonzero value. This threshold will be patient-specific and will depend on a number of factors not limited to demographic, primary cancer type, dissemination pattern and individual quality-of-life measurements. Prioritizing long-term quality of life over short-term minimization of disease burden will fundamentally change the treatment approach to metastatic disease.

Evaluation. In order to evaluate if a process is successful, it is important to precisely identify the definition of success. In IPM, the definition of success has shifted away from prioritizing making fields completely free of pests toward instead prioritizing crop yield, stability and profit over multiple years. In metastatic disease, the definition of success will have to shift in the same way away from a 'clean', complete cure to instead maximizing quantity and quality of life.

Resistance management plan

Non-chemical treatment. IPM strategies for indirect methods of control fall into two main categories — 'live biologic controls' and conditioning of the environment. First, IPM uses live biologic controls by introducing predators, pathogens and parasites. In general, these non-chemical strategies can be more effective than chemical insecticides because they require a significantly greater investment in resources to evolve resistance[18]. The recent success of immunotherapies and development of other live biologic controls, such as oncolytic agents and bacterial therapies, are likely governed by similar properties of evolutionary dynamics[19–21].

Second, IPM suggests conditioning the soil itself to resist pests. Several adjunctive cancer therapies have applied this type of environmental conditioning, such as bevacizumab, the anti-VEGF antibody, which is approved to inhibit angiogenesis in several cancer types[22]. Anti-resorptive agents have been used to slow growth and metastasis in cancers that metastasize to bone, with mixed results[23]. Multiple agents, including those that target acidic and hypoxic environments, have not yet been integrated into clinical treatment strategies[24,25]. Proven radiation therapy techniques likely fall within both categories[26]. Use of these non-chemical treatments in IPM shows that these strategies may produce perturbations that substantially improve tumour control when given in combination with currently available chemotherapy, hormonal therapy, targeted therapy and immunotherapy. Furthermore, these methods generally damage the healthy cells less than conventional cytotoxics and can therefore be used more regularly and for longer periods of time in a long-term management scenario.

Drug selection. IPM emphasizes the role of appropriate matching of pesticides to the specific pests within the treated area. In many ways this is identical to 'precision oncology' initiatives that base therapy on specific molecular aberrations[27]. There is, however, an important difference — using current precision-medicine strategies, oncologists in general make an initial treatment decision on the basis of the primary tumour characteristics and continue to give the same treatment until the tumour progresses. In contrast, IPM calls for the use of information gained from continuous monitoring of the treated population and rapid rotation of pesticides if the pest population changes in response to treatment. In a study of patients with HER-2-negative primary breast cancer, monitoring circulating tumour cells as a real-time biopsy showed that *HER2* gene amplification can be acquired during treatment of metastatic disease. These patients would rarely receive anti-HER-2 therapy as a standard of care; however, the addition of anti-HER-2 therapy in these patients resulted in complete or partial response in a number of patients[28]. Developing technology that allows precision oncology to continually modify therapy throughout the course of the disease could greatly enhance our ability to contend with the evolutionary dynamics of metastatic disease.

Minimum effective dose. To prevent cancer cells from acquiring new resistance strategies, reducing overall drug dose is an immediately implementable first step. Traditional oncology approaches often are based on the premise that maximum patient benefit is obtained by killing the largest possible number of cancer cells. While this aggressive strategy is intuitively appealing, it is evolutionarily unwise because it causes strong selection pressure for novel resistance mechanisms and permits unconstrained growth of any resistant population by removing the sensitive population — this recapitulates the competitive release dynamics in pest management. By reducing the intensity of treatment, IPM aims to reduce the pest population below some threshold of crop damage — but no further! In essence, the IPM strategy maintains a population of individuals that can be controlled (that is, treatment-sensitive individuals) so that they can use their fitness advantage to suppress growth of individuals that are resistant and, therefore, uncontrollable. While sublethal effects are possible[29,30], initial clinical implementation of what is known as 'adaptive therapy' is provocatively demonstrating improved progression-free survival in metastatic prostate cancer.

Adaptive therapy exploits the fact that evolutionary resistance mechanisms draw resources away from cell proliferation. In this way, during therapy, the benefits of resistance outweigh the costs, but in the absence of therapy the resistant cells become less fit than the sensitive phenotype[31]. Intentional withdrawal of treatment can allow sensitive cells to remain in the population, controlling the population of resistant cells and extending the time that the drug remains effective[32]. In a clinical trial of metastatic prostate cancer, the mean time to progression using adaptive therapy is at least 27 months (versus 17 months), with reduced cumulative drug use of 47% of the standard dose[33].

Anti-resistance strategies. IPM includes in resistance management plans the combination of therapies with orthogonal modes of action. While combining multiple drug therapies in cancer is common, identification of 'evolutionary double binds', where two therapies are used in combination such that evolving resistance to one leaves individuals more susceptible to the other, and vice-versa, could provide long-term control. An interesting example of a successful double bind may exist with the p53 cancer vaccine and chemotherapy in patients with lung cancer[34]. While the p53 vaccine did not yield a significant clinical

response, follow-up chemotherapy, which historically achieves an 8% response rate, achieved a response rate of 62%. As the best chemotherapy response was seen in patients who had the best immune response to the p53 vaccine, it is likely that the tumour cells adapted to the immunotherapy by down-regulating p53, rendering them more vulnerable to the chemotherapy. An effort to identify double-binds using currently available drugs would improve long-term control of metastatic disease.

Conclusion

Most current treatments for metastatic cancers use the maximum tolerated dose of a series of drugs regardless of the individual disease characteristics of a patient. However, this rigid therapy using maximum tolerated doses does not typically produce cures in metastatic cancers, and emergence of resistance is universally observed. Similar to the failure of high-dose synthetic pesticides in pest management, the treatment of metastatic disease is not in need of more lethal drugs, but instead demands the development of a formal process that incorporates the plethora of therapies that are already available into an integrated clinical paradigm. As cancer is re-defined as an eco-evolutionary system, this new clinical paradigm can and very much should be built upon the mistakes and successes of other disciplines that suffer from the evolution of resistance to control techniques.

Here, lessons from pest management serve as guidelines to achieve long-term clinical management of metastatic disease, but this is just one example[35]. The success of the long-term management of HIV provides confidence to overcome the psychological implications of living with a disease while maintaining quality of life[36]. Lessons from the management of multidrug-resistant bacterial infections suggest enhanced monitoring and using collateral sensitivity[37,38]. In veterinary and livestock management, there has been success with a wide variety of prevention techniques and non-chemical methods, including biologics[39]. In 2004, the WHO adopted 'integrated vector management' globally for the control of all vector-borne diseases[40]. Coined here as 'integrated metastatic management', this novel clinical paradigm that exploits proven IPM techniques could drastically reduce drug usage, delay or completely prevent evolution of resistance to available drugs, and lengthen the overall survival of patients with metastatic disease. ❐

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Competing interests

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