

Resistance is not the end: lessons from pest management

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Abstract

The “war on cancer” began over 40 years ago with the signing of the National Cancer Act of 1971. Currently, complete eradication has proven possible in early stage premetastatic disease with increasingly successful early detection and surgery protocols; however, late stage metastatic disease remains invariably fatal. One of the main causes of treatment failure in metastatic disease is the ability of cancer cells to evolve resistance to currently available therapies. Evolution of resistance to control measures is a universal problem. While it may seem that the mechanisms of resistance employed by cancer cells are impossible to control, we show that many of the resistance mechanisms are mirrored in agricultural pests. In this way, we argue that measures developed in the agricultural industry to slow or prevent pesticide resistance could be adopted in clinical cancer biology to do the same. The agriculture industry recognized the problem of pesticide resistance and responded by developing and enforcing guidelines on resistance management and prevention. These guidelines, known as integrated pest management (IPM), do not encourage eradication of pests but instead strive to maintain pests, even with the presence of resistant strains, at a level that does not cause economic damage to the crops. Integrated pest management inspired management of metastatic cancer could result in the slowing or curtailing of widespread resistance to treatment, reducing overall drug usage, and increasing the survival and quality of life of patients with cancer. Using IPM principles as a foundation and shifting the goal of treatment of metastatic disease to long-term management will require close monitoring of evolving tumor populations, judicious application of currently available therapies, and development of new criteria of success.

Keywords

chemoresistance, chemotherapy, evolution, pesticide, resistance

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Introduction

The “war on cancer” began over 40 years ago with the signing of the National Cancer Act of 1971. While the legislation itself did not use the language of “war,” this adopted terminology reflects the long-standing psychological drive to eradicate every cancer cell in the body. Currently, complete eradication has proven possible in early stage premetastatic disease with increasingly successful early detection and surgery protocols; however, late-stage metastatic disease remains invariably fatal.

One of the main causes of treatment failure in metastatic disease is the ability of cancer cells to evolve resistance to currently available therapies. Evolution of resistance to control measures is a universal problem. The ability to evolve is what allows all life to adapt and survive, and it is the main cause of

control failure in a wide range of disciplines including invasive species, pest management, bacterial infections, and viral vectors to name a few. While it may seem that the mechanisms of

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resistance employed by cancer cells are impossible to control, we show that many of the resistance mechanisms are mirrored in agricultural pests. In this way, we argue that measures developed in the agricultural industry to slow or prevent pesticide resistance could be adopted in clinical cancer biology to do the same.

Current clinical protocols for metastatic disease generally give a single drug at maximum tolerable dose until the disease relapses. Unfortunately, this general strategy does not consider the dynamics of the ecology and evolution of the growing cancer populations. This dose dense strategy mimics the initial high concentration use of synthetic pesticides in the 1940s and 1950s that resulted in toxicity issues as well as widespread evolution of resistance. In the coming decades, the agriculture industry responded by developing and enforcing guidelines on prevention and management of pesticide resistance. These guidelines, generally known as integrated pest management (IPM), do not encourage eradication of pests but instead strive to maintain pests, even with the presence of resistant strains, at a level that does not cause economic damage to the crops. Since the introduction of the concept of IPM¹ in 1959 as an integration of biological, natural predators, and chemical control, IPM has succeeded in providing long-term health of a wide variety of crop systems.²

Until therapies are developed that can truly cure metastatic disease, it may be more beneficial to focus on increasing overall survival while maintaining quality of life, irrespective of the presence of resistant cells or the total tumor burden. Integrated pest management inspired management of metastatic cancer could result in the slowing or curtailing of widespread resistance to treatment, reducing overall drug usage, and increasing the survival and quality of life of patients with cancer. Using IPM principles as a foundation and shifting the goal of treatment of metastatic disease to long-term management will require close monitoring of evolving tumor populations, judicious application of currently available therapies, and development of new criteria of success.

History of Pesticide Use in Agriculture

Humans developed agriculture independently in several geographical areas around the world from 12 000 to 8000 years Before Present (BP).^{3,4} These developments were almost certainly preceded by hundreds, if not thousands of years of trial and error efforts leading up to what we now recognize as a crop domesticate.⁵ And probably as soon as humans were tending crops, pests were attacking them. Application of pesticides to protect crops appears about 4000 years BP,^{6,7} and it seems reasonable to suspect that resistance to even these ancient pesticides arose shortly after. The first known reports^{8,9} of pesticide resistance in arthropods appeared in 1897, as seen in Forgash.¹⁰ Amazingly, Melander's prescient 1914 publication on resistance of San Jose scale (*Quadraspidotus perniciosus* [Comstock]) to lime sulfur¹¹ included many initial suggestions that are foundational to current pest management techniques.

Modern synthetic pesticides came of age in the mid-20th century. The poster child synthetic is dichlorodiphenyltrichloroethane (DDT). First synthesized in a laboratory by Othmar

Zeidler in 1874, its insecticidal properties were discovered by Paul Hermann Müller in 1939 (Müller won the Nobel Prize in Physiology and Medicine in 1948 for this discovery). Dichlorodiphenyltrichloroethane was initially highly effective, and it is attributed for saving countless lives from its use against mosquitoes, vectors of malaria, and other zoonotic diseases. However, we now recognize that overuse of DDT, to the exclusion of any other control measure, selected quickly for mosquitoes and flies to evolve resistance to DDT by 1947, a mere 8 years after its discovery as a powerful and lethal insecticide. Since this time, many more synthetic pesticides, including insecticides, herbicides, fungicides, and so on, were developed, and more and more pesticide targets continued to evolve resistance.¹²

Types of Resistance

A multitude of mechanisms of resistance are known for all types of agricultural pests (animal, plant, fungi, etc). Interestingly, these mechanisms of resistance are mirrored in the common resistance mechanisms cancer cells exhibit in response to therapeutic agents. To illustrate, we highlight several mechanisms found in arthropods, where they are perhaps best understood. We couple this with examples of similar mechanisms known to operate in cancer. By drawing these parallels, we may better understand how to translate the strategies used in agricultural pest management to prevent or overcome resistance into clinical oncology.

Genetic Variability

Genetic heterogeneity among individuals is common in all ecological systems (eg, study by Lewontin¹³). Arthropods have been shown to sustain genetic heterogeneity that provides baseline variability in their sensitivity to multiple insecticides.¹⁴ Furthermore, epigenetics also plays a role in evolution of resistance to pesticides in insects.^{15,16} Both genetic variability and epigenetics are well established in tumor biology as a cause of treatment failure due to either the existence of resistant clones before treatment or the evolution of new resistance mechanisms during treatment.¹⁷⁻²⁰

Target Site of Action

Almost all arthropod pesticides operate by binding to a macromolecule within the pest organism. A common mechanism of resistance is an alteration of the function or structure of this target binding site, rendering the pesticide nontoxic or less toxic.²¹ Such target site alterations are well-known in cancer resistance to chemotherapies.²² An example is a mutation of the topoisomerase II gene, rendering a topoisomerase II-inhibiting drug ineffective. Some anticancer drugs target signaling kinases (eg, epidermal growth factor receptor), and prolonged use of drugs targeting such kinases promotes evolution of resistance through mutations or chromosomal rearrangements.

Decreased Cuticular Penetration

Known since the 1960s, decreased cuticular penetration of a pesticide provides only modest levels of resistance—in the order of 3-fold or less²³ (as seen in the study by Plapp²⁴). Nonetheless, this resistance mechanism works broadly against many pesticides,²³ and it may augment effects of other resistance mechanisms.²⁵ In cancer, the most obvious analog is the decrease in drug influx²⁶ that may occur via decreased expression of carrier proteins or mutations that inactivate carriers. Similarly, drug efflux via P-glycoprotein and multidrug resistance-associated proteins transport chemotoxic agents out of tumor cells, thus conveying resistance.^{27,28}

Biotransformation or Detoxification

Arthropods evolved metabolic adaptations that identify and metabolically destroy potentially xenobiotic toxins. These mechanisms also recognize and biotransform many pesticides to less toxic molecular forms. Three major classes of metabolic enzymes, esterases, cytochrome P450 monooxygenases, and glutathione transferases are primarily involved.²⁵ Similar metabolic biotransformation also provides a mechanism of resistance in cancer.²⁹ In contrast to metabolic transformation of pesticides in arthropod pests, little is known about these mechanisms of resistance in cancer, and more research into these mechanisms is critically needed in cancer.³⁰

Behavioral

In some cases, insect pests evolve behavioral tactics that allow them to avoid exposure to pesticides.³¹ For instance, pest species may detect the presence of the pesticide and avoid it, or they may evolve aversions for landing on structures (eg, protective nets) to which the pesticide is applied. We suggest that it is not a stretch to consider processes such as the epithelial to mesenchymal transition³² or the upregulation of angiogenesis or glucose uptake in cancer cells as behavioral changes.

Pesticide Industry and Governmental Response to Resistance

In response to the agricultural “resistance crisis,” industries associated with pesticide manufacturing recognized the threat of evolved resistance to their economic success. In 1967, these manufacturers formed a trade organization now called CropLife International. The purpose of this trade organization is to represent the pesticide industry in a government lobbying capacity and to promote crop protection technologies. In 1984, a second industry organization formed. The explicit objective of this group, the Insecticide Resistance Action Committee (IRAC), was to coordinate industry response to prevent or delay development of resistance in agricultural pests. IRAC is clearly a trade organization motivated by industry self-interest with a goal of prolonging effectiveness of pesticides.

The United States Department of Agriculture (USDA) became involved in efforts to counter evolution of pesticide

resistance in 1999, when the United States congress allocated funding for a network of IPM centers in Section 406 of the Agricultural Research, Extension, and Education Reform Act of 1998. This partnership of IRAC and the USDA solidified the commitment to applying IPM principles to develop a variety of strategies that specifically aim to slow or preclude the evolution of pesticide resistance.

Since then, IPM practices have achieved dramatic success, both as a means of slowing or preventing evolution of resistance of pests to pesticides³³ and in decreasing pesticide use while maintaining high crop yields.³⁴ Successful IPM measures include managing the landscape to boost populations of natural predators³⁵ and deployment of pest traps, field sanitation, and biopesticides.³⁴ Furthermore, scouting for pest density coupled with economic thresholds to determine use of chemical pesticide³⁶ and use of pesticide-free refuges to maintain susceptible individuals within the pest populations has proven highly successful.³⁷

Pharmaceutical Industry and Clinical Response to Resistance

It is important to note that these success stories are in systems that have the same complex, wide-ranging, and numerous types of resistance mechanisms observed in tumor biology described above. In this way, even in the face of the overwhelming threat of resistance to the success of treatment in metastatic disease, a broad set of general guiding principles could greatly affect treatment outcomes. Unfortunately, the “war on cancer” has historically been waged without the same sort of forethought and practicality regarding evolution of resistance. While pesticide manufacturers led the charge of changing the pest management paradigm to long-term management, pharmaceutical industries have yet to develop and implement treatment protocols that could greatly prolong the effectiveness of their products.

Interestingly, several IPM principles have been recently tested in clinical oncology. For example, decision-making in IPM requires exhaustive and judicious monitoring on an ecological time scale in order to decide whether and when to apply control measures and specifically which control measures to use. This has proven useful in metastatic breast cancer, where 9 of 24 patients with HER-2-negative primary tumors were shown to acquire HER-2 gene amplification during treatment by frequent circulating tumor cell analysis. This frequent monitoring allowed for a change in treatment to add a targeted therapy for the HER-2 gene resulting in complete or partial response in a number of patients.³⁸

Furthermore, IPM strongly advocates against the dose dense model used in clinical cancer treatment and instead suggests using minimum effective doses and adaptive anti-resistance strategies to prioritize overall quality of life over eliminating tumor burden. These have shown promise in metastatic lung cancer, where the use of an anti-resistance strategy known as a double bind using a p53 vaccine increased the response rate of chemotherapy from 8% to 62% and in metastatic prostate cancer where the mean time to progression increased from 17

months to at least 27 months using only 47% of the standard dose of abiraterone by using adaptive application based on frequent monitoring.^{39,40}

A particularly effective IPM strategy, management of agricultural landscapes to recruit natural predators,⁴¹ has direct analogy with therapies that manipulate the tumor microenvironment to recruit antitumor immune surveillance for cancer treatment.⁴² Immunomodulatory approaches boost both innate and adaptive immune responses by defeating checkpoint inhibitors, activating pathways using chimeric antigen receptor T cells or bispecific antibodies,⁴² or using radiation therapy to boost antitumor immunity.⁴³ A complementary approach targets the acidity of the tumor microenvironment.⁴⁴ Therapeutically increasing the pH of the tumor microenvironment may help defeat the suppressive effects of acidity on immune surveillance.⁴⁵ Although immunotherapy has not yet achieved the success in delivering successful cancer therapy once thought possible, strategies to manipulate the tumor landscape to boost immune function hold great promise for the future.

While the differences between pests and cancer make translating all of the principles of IPM into the clinic difficult, such as leveraging sexual reproduction and rotating crops, many of the principles can be applied easily and readily.⁴¹ These examples above show that implementation of monitoring, deciding whether and when to treat, informed drug selection, minimizing drug usage, and employing one or more anti-resistance strategy can greatly affect clinical outcomes. With the success of these individual examples, it is possible to see that irrespective of the presence of resistant phenotypes, simple changes to the way we approach treatment of metastatic disease could increase overall survival and the quality of life of metastatic patients with cancer.

Summary and Conclusions

In the simplest sense, the ultimate goal of treating cancer is for the patient to remain alive. Defining success as cumulative quality of life regardless of tumor burden and presence of resistant clones allows for the development and implementation of long-term disease management techniques. It is critical to remember that “The development of resistance does not automatically lead to impairment of pest control” and similarly does not have to mean the loss of therapeutic control in metastatic disease.¹² Both the pharmaceutical industry and oncologists could greatly benefit from an Integrated Cancer/Metastatic Management paradigm modeled on pesticide resistance strategies, particularly IPM, developed in the pesticide and agricultural industries.

Of most immediate importance is to learn from the long history and experience in agriculture and discontinue treatment application practices that strongly select for the evolution of resistance. Paramount among these are (1) frequent application of a single pesticide or multiple pesticides with similar modes of action targeting a single pest species, creating strong selection for resistance (DDT being the classic example) and (2) failure to incorporate non-pesticide control agents or practices, especially the recruitment of natural predators, into pest control

measures. In this way, a strict management of drug application to prevent or at least slow the evolution of resistance should be established.

Promoting complementary measures to control and manage metastatic cancer may prolong life while minimizing or precluding evolution of resistance. Rather than a universal application of “maximum tolerated dose” of a series of chemotherapies, we need “a formal process that incorporates the plethora of therapies that are already available into an integrated clinical paradigm.”⁴⁶ To paraphrase Dr Robert A. Gatenby: We do not need more bullets, we need strategies.⁴⁷ Developing the formal process called for here will necessarily require the joint cooperation and integration of many fields, including practitioners, funding agencies, universities, and the pharmaceutical industry itself.

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