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Cancer as a Chronic Disease

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Et al.

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Summary and Key Points

1. Patients and families (and some health care providers) often think of cancer as a single disease. However, cancer is actually many diseases; each referred to as a malignancy.
2. Some malignancies behave indolently and may not require active treatment or have an impact on a patient's life span.
3. Some malignancies, even when metastatic, may have a long natural history and be managed as a chronic disease.
4. In individual patients, cancers which are normally rapidly fatal may have a prolonged natural history. For example, only a few metastases may appear, or only one at a time, a phenomenon referred to as oligometastatic disease.
5. Long term management of some malignancies may require successive management strategies including a variety of different therapies such as hormonal, immune or chemotherapies, surgery or radiation to extend survival or palliate symptoms.
6. Targeted therapies, which exploit specific tumor targets such as hormone receptors or cell signaling pathways, have led to extended survivals in some cancers and have changed the natural history of some biologically aggressive malignancies.
7. Immune therapies help to interfere with a tumor's ability to suppress the immune system, leading to longer survivals and chronic management in some malignancies.
8. Tumor gene profiling, looking for ‘‘driver mutations" that may be involved with malignant transformation and proliferation, may increase our therapeutic targets and lead to more effective therapies and chronic management.

Clinical Cases

Case #1: A 33-year-old female presents with a locally advanced estrogen receptor positive HER2/neu-positive breast cancer. She is treated with surgery, chemotherapy and radiation. Two years after treatment completion she develops progressively severe right arm pain and presents with a pathological fracture requiring surgical fixation and radiation. She begins treatment with anti-HER2/neu therapy and ovarian suppression. Two years later imaging shows progression of bony metastatic disease. She is treated with a succession of different anti-HER2-neu based therapies with each sign of progression and remains alive with minimal bony metastatic disease 10 years after diagnosis working full time and caring for her family.

Case #2: A 70-year-old female, a never smoker, presents with cough and weight loss. Chest imaging reveals multiple bilateral pulmonary nodules. Biopsy of a lung nodule reveals well-differentiated adenocarcinoma, with Epidermal Growth Factor Receptor (EGFR) mutation. Patient is started on a tyrosine kinase inhibitor (TKI) targeting the EGFR receptor with radiographic resolution of lung disease. She continues on oral targeted therapy for three years symptom free until she develops a persistent cough with new pulmonary nodules seen on imaging. Patient is treated with six cycles of chemotherapy and placed back on a TKI. She remains disease free for 17 months and then develops progressive pulmonary disease. She is switched to another TKI. At nine months the patient develops brain metastases and expires. Time from diagnosis to death–six years.

Case #3: A 45-year-old male presents with rectal bleeding. Colonoscopy reveals a partially fixed mass six cm from the anal verge. Biopsy reveals moderately differentiated adenocarcinoma. Staging workup otherwise is negative for metastatic disease. Patient is treated with preoperative chemotherapy and radiotherapy followed by surgery and six months of post-operative chemotherapy. Patient does well for five years until he is found to have a new liver lesion. Biopsy of lesion shows adenocarcinoma

consistent with a rectal primary. Patient undergoes partial liver resection followed by six months of additional chemotherapy. Two years later he is found to have a two cm left upper lobe lung nodule. Again biopsy is consistent with his rectal primary. Patient undergoes surgical resection of his lung lesion and now remains cancer free eight years after his original diagnosis.

Case #4: A 70-year-old man presents with pain in the lumbar spine, five years after radical prostatectomy for a Stage II T2cN0M0 Gleason's 7(3+4), PSA prior to treatment = 9, adenocarcinoma of the prostate. At this time, PSA is 20. MRI demonstrates tumor growing from the vertebral body into the canal, compressing the cord at L1. A course of palliative radiation therapy relieves his pain, and he remains neurologically intact. He is started on Lupron injections for suppression of testosterone and his PSA goes down to 2. Six months later, he reports pain in his right shoulder; PSA is 10, bone scan is positive in 10 different areas. Again, radiation relieves his pain, but then his left hip becomes painful. He is administered a dose of Radium-223 and radiation therapy to the left hip. Three years later, the right hip hurts. PSA is 30 and bone scan is positive in multiple areas. Chemotherapy, right hip radiation and next generation hormonal suppression is administered. Four years later he is symptom free, but bone scan is positive in new areas and PSA is 59.

Introduction

When a patient or family member hears the diagnosis of a cancer, they immediately assume that it is an immediate sentence of death. The above cases demonstrate that even widely metastatic disease may be managed for long term survival with good quality of life. They exemplify a new paradigm of treating cancer as a chronic disease, like diabetes or human immunodeficiency virus (HIV) infection.

It is projected that by 2020, there will be 1.9 million new cancer cases per year. Of these, approximately 600,000 patients will die of their disease.[1] Many metastatic cancers remain lethal with short median survivals despite intensive treatment. However, in contrast to these alarming numbers and facts, over the last thirty years survival rates have continued to improve from roughly 45% to 65% for all cancers combined.[2] This is felt to be due to earlier detection and improved therapeutic options.[3] Novel treatments have prolonged survival in many types of malignancies. Cancers which were once fatal are increasingly able to be managed as chronic diseases. While most metastatic cancers in adults may not be curable, they often can be controlled for long periods of time with a succession of treatments. In this chapter, we will examine those cancers with longer natural histories and those with extended survivals due to therapeutic advances.

Important Concepts

Some malignancies are by nature biologically indolent, having long natural histories and requiring minimal intervention over the course of the illness. In addition, a variety of different approaches have led to the ability to manage some cancers as chronic disease.

Some cancers may be managed by sequential surgical procedures to remove sites of metastases as they arise to extend survival. In other malignancies, drugs have been developed that interfere with specific targets within cells to interfere with proliferation. The ability to genetically sequence tumors to look for mutations that may be used as therapeutic targets has made it possible to identify which cancers might be successfully treated with such drugs. Finally, the exciting advent of immune therapies, which harness the body's own immune system to fight cancer, is showing clinical promise with activity in a variety of different malignancies.

Biologically Indolent Malignancies

There are several malignancies that behave indolently and often do not impact overall mortality. Some patients may be diagnosed with a cancer that is completely asymptomatic for many years and never requires therapy. In many cases, there is no evidence that early intervention prolongs overall survival. Two examples of these malignancies are chronic lymphocytic leukemia (CLL) and prostate cancer.

Chronic lymphocytic leukemia - CLL is the most common type of leukemia (malignant population of white blood cells) in adults. The median age at diagnosis is 71 and most patients are asymptomatic at presentation with the diagnosis made on routine blood tests revealing lymphocytosis.[4] In patients diagnosed over the age of 70, this disease often does not impact on life expectancy. For symptomatic patients, treatment options include cytotoxic chemotherapy, monoclonal antibodies or oral drugs that target specific proteins within CLL cells. Treatment is often sequential, utilizing each of these modalities at various points in the disease. While the natural history of this disease is long with median survival greater than 10 years, cure is rare.[4] Since therapy is not curative, the goal of any treatment is to maintain quality of life in these patients and to minimize side effects of therapy.

Prostate Cancer – The natural history of this malignancy varies dramatically from very indolent with prolonged median survival without therapy to very aggressive, requiring multiple therapeutic interventions. Aggressive prostate cancers occur most commonly in younger men. Many men have indolent disease, however, with five year survival in the US of 99%.[2] In addition, a majority of cases are diagnosed in men over the age of 70. Older men may have multiple comorbidities, so treatment of an early stage prostate cancer may be delayed or avoided.[5] Many men remain asymptomatic without treatment for many years.

In men who develop metastatic disease, prostate cancer is generally initially exquisitely sensitive to hormone deprivation therapy. Suppressing testosterone interrupts proliferation and induces apoptosis of prostate cancer cells, leading to disease regression. Patients may be on hormone therapy for several years to control disease. In patients who develop resistance to hormone therapy, chemotherapy may play a role to control disease. Radiation therapy is frequently utilized to palliate symptoms and improve the quality of life. According to most recent data, the 5-year survival rate for metastatic prostate cancer is about 30%.[1] This extended survival implies that a substantial number of men with metastatic disease will require management of their disease for many years.

Some cancers which are often aggressive may behave indolently in certain patients. For example, both breast cancer and prostate cancer sometimes metastasize only to bone. So long as no soft tissue metastases are present, patients can live a long time. For these patients, one important goal of treatment is relief of symptoms.

In addition, some cancers will spread to only one or a few spots at a time, usually to a single organ, a pattern referred to as oligometastatic disease.[3] Aggressive management of these metastases may offer another chance for long term control of the cancer. For example, sarcomas tend to spread to lung parenchyma. Resection of a single or a few lung metastases from a sarcoma may result in long term control of the disease; sometimes patients will benefit from repeated thoracotomies for metastasectomies, or repeated ablative procedures. In addition to surgical resection of oligometastatic tumors, a variety of other ablative techniques have been used to eradicate limited numbers of metastases. Among other techniques, these include radio frequency ablation, cryosurgery, and stereotactic body radiotherapy. At this time each technique has its own unique advantages and risks. To date, there are no comparative data to suggest that one technique results in better clinical outcomes than another.

Biologically Aggressive Malignancies with Therapeutic Targets

Many cancers behave aggressively with potential for widespread metastases and short median survival. However, chemotherapy, molecular biology, immunology and cytogenetics have improved the treatment of certain aggressive malignancies, increasing the median survival of some cancers. In many malignancies, one or more exploitable targets have been discovered at the molecular level to interfere with clonal proliferation of cancer cells. Patients who once would have died within one to two years of diagnosis are now living many years. Human epidermal growth factor receptor-2 (HER2/neu)-positive breast cancer and Philadelphia chromosome-positive chronic myeloid leukemia (CML) are two malignancies that exemplify these impressive advances.

HER2-Positive Breast Cancer – Breast cancer is the most commonly diagnosed malignancy in women, aside from skin cancer, and is the second leading cause of cancer death in women after lung cancer. Approximately 20% of all invasive breast cancers are HER2-positive.[6] The

Apoptosis - Genetically determined programmed cell death that occurs as a normal part of cell cycle

protein product of the HER2 gene is a member of the epidermal growth factor receptor family. The HER2 gene is amplified in patients with HER2-positive breast cancer, resulting in an increased number of HER2 receptors within the membrane of cancer cells. This causes increased proliferation of these cells. These cancers are biologically aggressive with increased potential for early nodal involvement and distant spread.

The HER2 receptor became recognized as a potential therapeutic target in the late 1980's leading to the development of multiple agents targeting the HER2 receptor. Added to chemotherapeutic regimens, these have been shown to increase the disease free and overall survival in patients with both localized and metastatic disease.[6] Many women with metastatic HER2-positive breast cancer can now live for five years or more since the advent of these highly effective targeted therapies.[7]

Chronic Myeloid Leukemia (CML) – A relatively uncommon hematologic malignancy, it is estimated that 9500 new cases will be diagnosed in the United States in 2018. The Philadelphia chromosome, the cytogenetic definition of CML, is the result of translocation of chromosomes 9 and 22. This translocation produces a fusion gene, bcr-abl leading to unregulated expression of an activated ABL protein. The activated ABL protein leads to proliferation of CML cells. Prior to 2000, the eight year survival rate for this disease was less than 20%.[8] The tyrosine kinase activity of ABL was identified as a therapeutic target in the late 1990's, leading to drugs that would dramatically improve the median survival of this chronic disease.[8] Although these drugs usually do not lead to eradication of the leukemic cells, they greatly inhibit clonal proliferation. Studies showed improved response rates and overall survivals compared to standard chemotherapy alone. The eight-year survival of CML has increased from historic rates of 20% to almost 90% in recent years.[9]

Advent of Immune Therapies

Recent investigations have led to a better understanding of the interaction between cancer cells and the normal immune response. Activated T cells normally play a role in fighting infection and cancer surveillance. Programmed cell death protein 1 (PD-1) is a protein on the surface of activated T cells.[10] Many tumor cells express a blocking protein that binds to the PD-1 receptor on activated T cells, rendering them inactive and unable to attack tumors cells.[9] This discovery has led to the development of various drugs that suppress the tumor blocking proteins on cancer cells that would otherwise suppress the immune response. Several immune-modulatory drugs have been identified that have shown activity in a number of malignancies- lung, melanoma, head and neck cancers to name a few. This new class of drugs, referred to as "immune checkpoint inhibitors", appears to have tremendous potential to extend survival of many different malignant subtypes.[11]

Tumor Gene Profiling

Intensive research in cancer genomics has led to the ability to entirely sequence tumors to look for alterations in genes that may be involved with malignant transformation and proliferation. The hope is that exploitable targets will be found which will make it possible to target these genetic alternations in a therapeutic way. For example, alterations in genes such as HER2, braf, egfr, mek, and others can be found with next generation sequencing of a variety of cancers. Drugs exist that can target the protein products of these various genes.[12] For example, osimertinib is a potent inhibitor of the tyrosine kinase activity of EGFR and improves outcomes in patients with EGFR activated non-small cell lung cancer.[13] It is conceivable that cancers of different histology that harbor mutations in egfr may also respond to a drug like osimertinib. Studies are ongoing that assign patients to "targeted" treatment based on gene profiling. The discovery of specific genetic abnormalities within individual cancers may open up new therapeutic options for patients. Note that this represents a fundamental change from thinking of cancer as an organ-based disease. In 2017 the FDA approved pembrolizumab for treatment of any metastatic cancer that possesses a defect in one of the DNA mismatch repair enzymes. This represented the first time a drug had been approved to treat cancer on the basis of a molecular defect and not on the basis of the cancer cell of origin. It is expected that many more drug approvals will follow this same path. Hence, simply identifying a cancer as a "breast" or "lung" cancer may not be adequate in the future. It may be necessary to identify cancers based on their unique genetic profiles.[14] These new therapies are often better tolerated than conventional chemotherapy.[15]

When modern cancer chemotherapy first appeared in the decades after World War II, there was a perception that cancer treatment might follow a model like that seen with infections and antibiotics. Perhaps, it was thought, with the right chemotherapy drugs, a relatively short course of treatment could permanently eradicate cancer in a patient. Unfortunately, over the last seventy years that goal has only been achieved in a few adult cancers. At this time, a better model for treatment of metastatic adult

cancers may be that used in diabetes or, to stay with an infectious disease analogy, HIV. Current treatments do not cure either condition. However, treatments of diabetes and HIV do an excellent job of controlling disease and permitting patients to live for decades. It is hoped that some of the newer drugs available to treat cancer will, if not cure, at least permit long term control of cancer.

Conclusion

Cancer is many diseases, each with its own natural history and expected prognosis. But within each cancer, individual cases will behave independently. While there are clinical oncology principles that are generally applicable to a population of patients with cancer, it is important to appreciate that any individual patient may have a cancer that has a natural history that is significantly longer than the average for that malignancy. For such a patient, the goal of cancer therapy is long term control of the disease, with as little toxicity as possible.

Even when cure is not possible, many patients will experience long term survival when cancer is managed as a chronic disease, using any or all of the tools in the armamentarium – surgery, radiation therapy, chemotherapy, immunotherapy, and nuclear medicine.

It is important that all physicians be aware of the possibility of achieving long term survival with even the most aggressive cancers so that they can help patients through the initial shock of a cancer diagnosis to an understanding of their situation and so they can manage symptoms in an appropriate manner, based on a realistic perception of the patient's life expectancy.

Thought Questions

1. Why do some patients with prostate cancer succumb very quickly even with aggressive treatment, while others will survive for years with no treatment at all and some will experience years of progression of bony metastatic disease?

   Your answer:

Expert Answer

Prostate cancer, like most cancers, is really several different diseases, arising from the same organ, with very different natural histories. Differences in cancer behavior is almost certainly due to different DNA mutations or epigenetic changes within different clones of cancers. The histologic diagnosis of cancer is based on the microscopic appearance of cells and the presence of tissue invasion. While some aspects of histology – grade, for example – can hint at biologic aggressiveness, conventional pathologic definition of cancer does not provide an accurate assessment of the behavior of individual cancers.

2. What characteristics would make a molecule a useful target for cancer therapies? What characteristics would preclude use of a molecule as a therapy target?

   Your answer:

   Expert Answer:

   Expert Answer: A good target will play a vital role in some aspect of cancer growth. For example, targets of some current anti-cancer drugs include growth factor receptors, enzymes that control the cell cycle, and proteins that block apoptosis. Another broad class of “targeted” drugs interferes with angiogenesis. Ideally a target of a cancer drug would be restricted to the cancer. In reality, this almost never occurs. Many side effects of ""“targeted” therapies arise because the cell target is expressed on normal cells as well as cancer cells. For example, the estrogen receptor is expressed in about 70% of breast cancers. Tamoxifen and aromatase inhibitors are effective drugs for treatment of estrogen receptor positive breast cancer. However, the estrogen receptor is also present in a variety of other tissues. Many of the side effects of tamoxifen and aromatase inhibitors arise as a direct result of effects on estrogen receptors in normal cells. Needless to say, if a drug targeted a vital function in a cancer cell but also caused life-threatening toxicity by interfering with the same vital function in normal cell, that drug would be unlikely to be useful in cancer treatment.

3. Why would a cancer which has been controlled by a certain chemotherapy regimen or hormonal suppression agent become resistant to this regimen, as hormone responsive prostate cancer usually will after a while?

   Your answer:

   Expert Answer:

4. Describe mechanisms by which cancer cells may interfere with the normal immune response?

   Your answer:

Expert Answer

Normal immune function includes “checkpoint inhibition” that turns off an immune response once it is no longer needed. Some cancers are able to make the protein signals that function to activate checkpoint inhibition to block an immune response to the cancer.

Glossary

Ablative procedure – procedure to cause necrosis of tumor deposit, such as with stereotactic radiosurgery, freezing or high heat deposition.

Apoptosis - Genetically determined programmed cell death that occurs as a normal part of cell cycle

HER2/neu - One of the four epidermal growth factor genes involved in cellular proliferation

Metastasectomy - surgical removal of metastases

Oligometastatic disease- a transitional zone between localized and widely metastatic disease

Ovarian suppression - Blocking ovulation in premenopausal patients which may be therapeutic in some cancers, particularly breast cancer

Targeted therapy – Treatment that is able to exploit some difference between cancer cells and normal cells, generally utilizing a unique cellular antigen or mutation, to improve effectiveness and decrease toxicity of treatment

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