Generalizations of a generalist — common themes among systemic therapies for common cancers

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Oncology, along with the rest of medicine, is becoming increasingly subspecialized. Early leaders in the development of medical oncology trained and practiced as generalists, but that generation has been replaced by the current generation of academic oncologists who start specialization early on, often while still in fellowship. The advantages of being able to concentrate on just one area of oncology, or even just one disease, are obvious in terms of the ability to gain expertise and to advance research. As a result, most of the current literature is written by subspecialists.

However, such focused specialization may deprive oncologists of a potentially useful, broader perspective. Indeed, most of medical oncology is still delivered by generalists. An advantage of treating the full spectrum of neoplasms is that one can see common themes that occur across different cancers in both tumor behavior and treatment. And a generalist can gain experience with therapies in a variety of diseases, rather than just one. Bevacizumab, imatinib, and everolimus are examples of agents that are used in multiple cancers.

So while the trend is to fragment specialties and diseases even further, it may be useful to look in the opposite direction at commonalities that occur across tumor types. I have observed that the dilemmas patients with different cancer types face and the discussions I have with them are often quite similar. Although there are exceptions for each of the views below, they often hold true as teaching points, and I have found them particularly useful in instructing fellows.

When to start treatment

A common scenario is dealing with an incurable, slowly growing cancer in an asymptomatic patient and deciding whether or when to start therapy. This occurs with both hematologic malignancies (chronic lymphocytic leukemia, follicular and other low-grade lymphomas, a subset of mantle cell lymphomas, smoldering or indolent myeloma), but also with some metastatic solid tumors (carcinoid and islet-cell tumors, and well-differentiated thyroid, biochemically relapsed prostate, indolent renal cell, and some lung cancers). For all of these diseases, treatment can improve the patient's quality of life, progression-free survival, and often overall survival (OS).[1] However, it is not clear that starting therapy sooner is better than starting it later. You don't have to start treatment immediately just because you can. In the absence of proof that earlier therapy is better, the right time to start treatment would seem to be just before the patient becomes symptomatic from their disease, so they never do. The hard part is judging when that will be.

Does sequencing of systemic palliative treatments make a difference?

As more agents become available to treat a variety of incurable cancers, we have to choose which agents to use and in what order. In hormone refractory breast cancer, how do we decide between a taxane, capecitabine, vinorelbine, eribulin, ixabepilone, and so on? Likewise, for castrate-resistant prostate cancer, which is better – abiraterone, enzalutamide, sipuleucel-T, docetaxel, cabazitaxel, or radium 223? There can be similar debates about other solid tumors and for hematologic malignancies such as myeloma, chronic lymphocytic leukemia, and indolent lymphomas.

It seems that for OS, the sequencing of therapies has generally not been proven to make a difference, and that we most likely get the same benefit regardless of the order we use the agents, as long as we get to use them. Common sense would dictate using your most active and least toxic therapies first, with selection also mitigated by underlying patient concerns, comorbidities, convenience, and cost.

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Taking a break: maintenance vs chemotherapy 'holiday'

One of the largest shifts in approaching incurable metastatic cancers in recent decades has been the option to take a "chemotherapy holiday." Before the shift, patients with stable or responding disease were generally treated until progression or unacceptable toxicity. If you knew the patient had a fatal disease and therapy was helping, why would you stop treating? However, there is no greater gift for a patient who is receiving palliative treatment than to be put in remission and given a prolonged period off therapy. The question is whether these chemotherapy holidays compromise survival. Studies have addressed this in hormone-refractory breast cancer, colon cancer, non-small-cell lung cancer, ovarian cancer, hormone-sensitive prostate cancer, as well as low-grade lymphomas, myeloma, and chronic myelogenous leukemia.[2,3] Results are consistently inconsistent, with some studies suggesting a modest survival benefit for continued treatment, but others not. Certainly, if you are giving active agents, progression-free survival and disease-related symptoms are improved, but this is counterbalanced by treatment-related toxicities. Hormonal agents and targeted therapies for maintenance are generally much less toxic and thus more acceptable than cytotoxic chemotherapies. If there is a difference, findings from randomized trials suggest it is probably small and may be offset by quality of life issues and cost. In all these situations, I find it generally comes down to a discussion with the patient about the goals of care and perceptions about the disease and toxicity of the treatment.

For cancers that are potentially curable with systemic treatment (Hodgkin and aggressive non-Hodgkin lymphomas, and ovarian, small-cell lung, and testicular cancers) we either cure them in the first 3-6 months of therapy or we do not. With the exception of acute lymphoblastic leukemia, maintenance therapy has not improved results. I often find that these studies are so old that younger oncologists are not even aware the question was ever asked.

Adjuvant chemotherapy for (nearly) all

Early on in the development of adjuvant systemic therapy, there was debate as to whether adjuvant therapy after surgical resection was beneficial for many tumors. It became established initially for breast and then colon cancer, but now adjuvant treatment is also commonly offered to sarcomas (both bone and soft tissue), and lung, esophageal, gastric, pancreatic, bladder, uterine, ovarian, and testicular cancers.[4]

The more sensitive a tumor is to systemic treatment when metastatic , the greater the magnitude of benefit that will be seen in the adjuvant setting. The relative benefit of adjuvant chemotherapy is roughly proportional to the complete response rate seen in metastatic disease.

Neoadjuvant chemotherapy, response rates, and recurrent disease

Response rates are much higher in patients who receive neoadjuvant (primary or induction) chemotherapy than in those with recurrent disease. This is most striking for head and neck and breast cancers, where response rates to neoadjuvant treatment are often over 80%, but is also seen in sarcomas, and esophageal, non-small-cell lung, colorectal, and gastric cancers.[5] Explanations for this generally doubling of response rates have been proposed, but the cause of this large discrepancy is unclear.

What is even more perplexing is that these significant increases in response rate – despite improving options for organ preservation or resectability – do not necessarily translate into improved survival, with head and neck cancer being the strongest example. Furthermore, in diseases in which neoadjuvant therapy and postoperative adjuvant therapy have been compared, studies indicate no difference in OS whether the chemotherapy is given before or after surgery, as studied in breast, lung, and ovarian cancer.[5]

Benefits of combination chemotherapy and radiation therapy

Many studies show a benefit for combining chemotherapy and radiation therapy as definitive treatment for a range of solid tumors. Chemotherapy agents function as radiosensitizers, enhancing the efficacy of radiation as well as providing some potential for adjuvant systemic effect. Prospective trials support the addition of concomitant therapy for glioblastoma, and advanced head and neck, non-small-cell lung, esophageal, anal, bladder, pancreatic, gastric, and cervical cancers. Based on randomized trials, adding chemotherapy to definitive radiation has become standard of care.[6] What is striking about these findings is the similarity of benefit across tumor and treatment types. In all of these tumors, one may achieve an absolute survival benefit of around 10%.[6] Likewise, all of the trials show some increase in local control as well as generally distant disease control, but with some increase in toxicity with combination therapy. Although the benefits are real, they are modest and often decrease with patient age as toxicity increases.

Postoperative radiation in the adjuvant setting

Radiation therapy after the resection of solid tumors is commonly used when there is a significant risk of local recurrence. Radiation generally does what it always does – markedly decreases the risk of locoregional relapse – but there is often debate about its impact on OS. It is accepted as most critical in head and neck cancer in which local control is key, and as having a small survival benefit in breast cancer (be it after lumpectomy or mastectomy), but that is not clearly the case for other common solid tumors such as soft-tissue sarcoma, and esophageal, gastric, pancreatic, non-small-cell lung, pros-

tate, and rectal cancers.[7] For those tumors, randomized trials have not consistently demonstrated that radiation after complete resection yields an OS benefit.

A node is a node is a node

Lymphatic metastases to regional lymph nodes are common for almost all solid tumors. And for these tumors, nodal involvement has the same significance – evidence of lymphatic metastasis is associated with a higher risk of hematogenous metastases, systemic failure, and death. The greater the extent of nodal metastases, the poorer the prognosis will be. So the more nodes involved and the greater the volume of nodal involvement (from detectable by only polymerase chain reaction to immunohistochemistry, to micrometastasis, macrometastasis, and bulky disease with extracapsular extension), the higher the probability of recurrence.[8]

Although prophylactic lymph node dissections decrease the risk of regional recurrence and provide prognostic information, most data for melanoma, and breast, esophageal, thyroid, lung, pancreatic, gastric, and urologic cancers do not show a statistically significant OS benefit.[8]

Survival and removal of the primary cancer in metastatic disease

Resection of the primary tumor may be recommended for palliation in a number of metastatic malignancies. However, there is some debate as to whether such resections provide additional benefit in OS for renal cell carcinoma, gastrointestinal stromal tumor, and breast, gastric, colorectal, and thyroid cancers.[9] Prospective, randomized data in the interferon era supported this approach for renal cancer. Data from retrospective studies have indicated improved survival for some tumors, but patient selection for the studies makes it difficult to interpret the data despite investigators' attempts to adjust for patient characteristics.

Removing the primary tumor could benefit the patient by reducing total body tumor bulk and/or the rate of subsequent metastases from the primary, or possibly by changing trophic or conditioning factors associated with the primary site. Although the removal of the primary tumor remains controversial, (and has not been supported in prospective randomized trials in breast cancer) it would seem to make the most sense in patients with large primaries and lesser metastatic disease burdens.

Adding anti-VEGF therapy to chemotherapy for metastatic disease

Bevacizumab is a humanized anti-VEGF monoclonal antibody that is widely used in the treatment of a range of cancers. Phase 3 trial results have demonstrated its benefit in improving progression-free and sometimes overall survival in many tumor types, which has led to its approval by the US Food and Drug Administration for the treatment of glioblastoma multiforme, renal carcinoma, and colorectal, non-small-cell lung, ovarian, cervical and breast cancers – although for breast cancer, the approval was transient.[10] Findings from other trials have not shown improvement in OS for pancreatic, gastric, and prostate cancers. However, even when one looks at the negative trials, the same overall trends are apparent in terms of improved response rate, progression-free survival, and OS, which suggests a very similar effect in solid tumors.[10]

Metastatectomy for cure

Although surgery for metastatic disease is generally palliative, it can be curative in selected cases. Metastatectomy is most commonly done for colorectal cancer (typically to the liver or lung), lung cancer (to the brain), and sarcomas (to the lungs). It has also played a role in melanoma and hypernephroma, diseases that might be more prone to an oligometastatic pattern. In all, careful patient selection and staging will lead to optimal outcomes. For all of these cancers, features favoring a higher probability of long-term survival are similar: single versus multiple metastases, long versus short disease-free interval, longer doubling time, and earlier initial stage of the primary disease. And in all of these, there is a relatively similar outcome with 20%-30% of patients remaining disease free at 5 years.

Incidentalomas: not just endocrine tumors

We have developed a tremendous capacity for overdiagnosis and overtreatment. A common oncologic consultation is how aggressively to pursue an incidentally detected abnormality that may or may not be cancer. Better and greater use of body imaging has led to the detection of small, asymptomatic precancerous or cancerous lesions that for most patients would likely not have clinical relevance. Pituitary microadenomas and adrenal adenomas are quite common in the general population, but are rarely malignant or of consequence. Thyroid nodules are common, but with a greater potential to be malignant. Screening for prostate-specific antigen levels in men has led to the diagnosis of prostate cancer of uncertain clinical relevance and significant overtreatment with unclear benefit on OS. Perhaps 30% of "cancers" detected on routine mammography now are ductal carcinoma in situ, and the need for treatment of all these is being increasingly questioned. As CT scanning for lung cancer screening gains traction, the detection of ground glass opacities and adenocarcinoma in situ increases. Abdominal imaging frequently detects cystic pancreatic lesions of uncertain significance as well as small renal tumors.[11]

Again, the debates are similar with detection of lesions and cancers in a range of sites. The hope is that molecular signatures may provide the answer as to what we should pursue and what we can just watch, but for now it is not clear when the overtreatment of many patients warrants

the benefits to a few when one considers the consequences and costs of treatment.

When to stop disease-remitting therapies

Perhaps the most difficult discussion we have with our patients, but one that ultimately occurs for all the incurable diseases we treat, is when to stop aggressive treatments.[12] In general, as patients go from first-, to second-, to third- line therapies and beyond, the probability of response declines, the duration of response becomes shorter, and the patient's quality of life becomes worse with progression of disease and often cumulative toxicities from prior therapies. Yet we now can offer an increasing number of lines of therapies in a variety of malignancies as new agents become available. Often, therapy is stopped for declining performance status rather than exhaustion of therapeutic options. As with many of the issues already noted here, this discussion may be similar in lymphomas, myeloma, leukemia, and the broad range of solid tumors.

Conclusions

I have tried to provide some observations and approaches from what I have learned as a generalist. We have spent enormous effort subdividing diseases over the course of the past several decades of oncologic research, but there remain perhaps as many similarities among the different cancers as there are differences. For oncologists who do not practice across an array of tumor types, this might be less apparent. However, the framework for the discussion with the patient and the controversies in the literature can be similar regarding when to start therapy, how to sequence therapy, whether to take a break from therapy or continue maintenance, when to use adjuvant radiation therapy or chemotherapy, whether prophylactic lymphadenectomy improves survival, whether to resect a primary in the setting of metastatic disease, whether to resect metastatic disease for cure and when to stop disease remitting treatments. Certainly more could be enumerated.

This is not to say that all these diseases are the same. All of the advances we have made and all the recommendations we make to our patients have come from studying individual diseases and treatments. Indeed, the future of oncology is to further tailor therapy to each patient's individual disease and situation. But for those of us who are still trying to treat many different types of cancer and keep up with the volume and complexity of advances, recognizing common patterns can help make sense of what can seem like an overwhelming amount of data.

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