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Overview of Personalized Medicine in GI Cancers

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Abstract

Cancer biomarkers may be used for prevention (identification of patients at high risk for cancer), estimating prognosis and/or response to conventional chemotherapies, or guide the use of specific targeted therapies. This overview provides examples in each category for gastrointestinal cancers and reviews current concepts in personalized medicine.

Keywords

Targeted therapy; Personalized medicine

Introduction

“Personalized medicine” is a broad term that encompasses multiple aspects of personalized medical management. In oncology, this all-embracing term may refer to the detection of various biomarkers for the purpose of prevention, prognosis, and/or treatment. Oncologists have traditionally relied on histopathologic descriptions and surrogates for the biological behavior of the tumor at clinical presentation, such as whether the malignancy tumor involves regional lymph nodes or spread to distant organs, to decide on a treatment plan. Our understanding of malignancies has now expanded to the molecular level, where signal transduction pathways and the alterations in the genes involved in these pathways have known biological consequences. Targeting the specific genes involved in a specific tumor has allowed clinicians to tailor available standard therapies or use targeted agents designed to inhibit a specific signaling pathway. This review is limited to the recent advances in gastrointestinal malignancies and the impact of “personalized medicine” on the manner in which we care for our patients. Since the management of breast cancer now routinely includes detection of biomarkers for prevention, prognosis, and treatment, some analogies can be made to illustrate specific aspects of personalized medicine.

Prevention

Surgeons have long been involved in the forefront of reducing the risk of solid tumor formation among patients with hereditary syndromes that increase their lifetime risk of

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cancer development by performing prophylactic surgical procedures. It is well known that among patients who are BRCA1 or BRCA2 mutation carriers, the lifetime risk of developing breast cancer is 56 and 87 %, respectively,¹ and prophylactic bilateral mastectomies are a reasonable option to reduce the risk of breast cancer in this high-risk group. Similarly, patients with hereditary colorectal cancer syndromes include familial adenomatous polyposis syndrome, characterized by germline mutations in the tumor suppressor adenomatous polyposis coli gene or hereditary nonpolyposis colorectal cancer caused by mutations in one of the DNA mismatch repair genes, may be offered elective prophylactic colectomies.² Approximately 10 % of gastric cancers are attributed to a germline mutation in the gene for E-cadherin (CDH1); such patients have an 87 % lifetime risk of hereditary diffuse gastric cancer. Recently, Yoon and colleagues³ reported on the results of prophylactic total gastrectomy for ten patients with a median age of 42 who tested positive for a CDH1 mutation. On histologic evaluation, nine patients had 77 foci of noninvasive cancer, and two patients had multiple foci of T1 invasive cancer. The ability to identify the specific genetic mutations for these highly penetrant hereditary syndromes represents a significant advance since early surgical intervention affords the highest cure rate.

Prognosis

Personalized medicine has been used as a guide to assess which patients are at high risk of future locoregional or distant recurrence. Traditionally, after surgical extirpation of a solid tumor, adjuvant chemotherapy is given to many “at risk” patients but only benefit a few. A panel of molecular biomarkers is now used to identify subpopulations of patients most likely to benefit from standard adjuvant chemotherapy. An example from breast cancer is the use of a 21-gene recurrence score assay (Oncotype Dx) for early stage, node-negative, hormone receptor-positive, and HER-2 negative breast cancers. A significant subset of these patients will receive sufficient therapeutic benefit from hormonal therapy alone, and the addition of chemotherapy contributes to morbidity without concomitant improvement in mortality. Use of this assay has been shown to change clinical management in 30–38 % of cases, mostly by demonstrating a low risk of recurrence and obviating the need for chemotherapy.^{4, 5}

Recently, two similar assays have been developed to categorize the risk of recurrence for stage II colon cancer patients, a group of patients who are generally not offered adjuvant chemotherapy. Nevertheless, up to 20 % of these patients will have recurrent colorectal cancer. ColoPrint uses a panel of 18 genes to help identify high-risk patients who may benefit from adjuvant chemotherapy.⁶ Oncotype has also developed a 12-gene recurrence score assay.⁷ A high-recurrence score suggests that despite having lymph node-negative colon cancer, this patient would benefit from conventional adjuvant chemotherapy. In the same study, the authors also developed an 11-gene “treatment score” which predicts the likelihood of benefit from adjuvant 5-fluorouracil/leucovorin for stage II and III colon cancer patients (prediction of response to chemotherapy). Interestingly, the genes used by ColoPrint and Oncotype that were associated with recurrence risk are completely different from each other. One reason may be that the assays are performed on frozen tumor tissue versus formalin-fixed paraffin-embedded tissue, respectively. Furthermore, the genes associated with chemotherapy benefit are not the same as the genes associated with recurrence. Currently, these assays are all being prospectively and independently validated in the ongoing Prospective Study for the Assessment of Recurrence Risk in Stage II Colorectal Patients using ColoPrint⁸ and the Quick and Simple and Reliable clinical trials.

Treatment

Unlike conventional chemotherapeutic regimens which are broadly cytotoxic against proliferating cells, molecular-targeted therapies are “rationally designed” therapies directed at specific cancer-associated signaling pathways. The prototypical drug that exemplifies this concept in the breast cancer arena is the use of tamoxifen, an estrogen receptor antagonist or, more recently, selective estrogen receptor modulators, on patients whose tumors test positive for the presence of estrogen and/or progesterone receptors. Only patients who have tumors with hormone receptors benefit, while tumors lacking receptor expression will not receive clinical benefit from the targeted therapy.

An example of targeted molecular therapy is the drug imatinib (Gleevec) for the adjuvant treatment of primary gastrointestinal stromal tumors (GIST). Imatinib inhibits KIT or PDGFRA, receptor tyrosine kinases that are mutated in over 80 % of GISTs. In a phase III clinical trial, DeMatteo and colleagues⁹ showed that among KIT-positive tumors, the recurrence rate of patients treated with 1 year of adjuvant imatinib after surgical resection was 8 % compared to the placebo group which had a recurrence rate of 20 % at a median follow-up of 19.7 months. Unfortunately, acquisition of secondary mutations in KIT or PDGFRA¹⁰ is not uncommon, highlighting the fact that single-agent targeted therapies are rarely curative.

Recently, for advanced (metastatic and/or unresectable) pancreatic neuroendocrine tumors (PNET), the tyrosine kinase inhibitor sunitinib and the inhibitor of mammalian target of rapamycin (mTOR), everolimus, have been shown independently to improve progression-free survival compared to placebo. Preclinical in vitro and in vivo studies have demonstrated that PNET express multiple growth factor receptor tyrosine kinases, such as vascular endothelial growth factor receptor and insulin-like growth factor-1 (IGFR-1) which mediate PNET angiogenesis and cellular proliferation, respectively. Sunitinib targets the multiple receptor tyrosine kinases present on tumor cells as well as stromal cells such as endothelial cells in the tumor micro-environment. Everolimus targets the mTOR signaling pathway stimulated by autocrine activation of IGFR-1 in the tumor cells. Phase III clinical trials have now shown that treatment with either sunitinib [¹¹] or everolimus [¹²] compared to placebo delays time to progression from approximately 5 to 11 months.

Cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR) by inhibiting the binding of its cognate ligands EGF or transforming growth factor α , has been shown to improve progression-free and overall survival in patients with advanced colorectal cancer.¹³ EGFR activation initiates many signal transduction cascades, such as the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K)/Akt (protein kinase B) signaling pathway which promote cellular proliferation and survival. Multiple studies have revealed that in many cases, primary resistance to cetuximab is attributable to mutations in molecules involved in these downstream signaling pathways, such as KRAS, BRAF, or PIK3A, obviating the need to activate EGFR by its ligand at the cell surface. Approximately 40 % of patient tumors have activating KRAS mutations, and among such patients, the median overall survival on cetuximab was 4.5 months, similar to patients receiving best supportive care (4.6-month median overall survival). In contrast, patients with wild-type KRAS tumors had a median overall survival of 9.5 months on cetuximab, compared with 4.8 months with best support care.¹⁴ Mutations in KRAS and BRAF, another important kinase in the MAPK pathway found in up to 10 % of colorectal cancers, are mutually exclusive.¹⁵ Thus, mutations in the BRAF gene may also account for failure of anti-EGFR treatment.¹⁶ The existence of multiple activating mutations in colorectal cancer confirms that colorectal cancer is a heterogeneous disease, and therefore, optimal use of targeted therapies is best in specifically

defined subpopulations of patients, and may also require combinations of available targeted therapies.

Limitations/Challenges

Personalized medicine is the realization of applying our knowledge of cancer biology from genome science to clinical practice. Although the technologies to perform bio-marker discovery are available, their use in the clinical management of patients is limited by (1) the pace with which we can validate the utility of the biomarker in prospective clinical trials and (2) the ability to elucidate the molecular and biochemical basis for the biomarker's importance in cancer progression.

Conclusions

The emerging use of cancer biomarkers may lead to a new era where one day physicians no longer recommend treatment predicated on population-based statistics, but rather on the specific characteristics of an individual patient and their tumor. Targeting a single molecule is unlikely to result in a profound response or durable remission among cancer patients, but the detection and targeting of several key molecules within relevant signaling systems, combined with other modalities such as surgery, will best optimize the care of the cancer patient in this new era.

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