The Biology of Cancer

P. Nenclares, KJ Harrington

Medicine 2020; 48(2): 67-72.

Abstract

Cancer is a genetic disease. Most common cancers are caused by acquired mutations in somatic cells. In contrast, specific germline mutations account for rare hereditary cancer syndromes. In general, cancer-associated genes can be divided into two groups: oncogenes and tumour suppressor genes (TSGs). Oncogenes undergo activation and are phenotypically dominant, while TSGs undergo inactivation and are phenotypically recessive. Oncogenic activation can occur by: specific point mutations within the gene sequence; amplification of the number of copies of the gene; or translocation of DNA to sites where transcription is more active or where a new fusion gene is formed that encodes a protein with enhanced biological activity. TSGs are inactivated by mutations that destroy the function of the protein encoded by the gene, or by silencing of the gene's promoter. The biological behaviour of cancer can be considered in terms of eight specific hallmarks and two additional so-called enabling characteristics. Improved understanding of the mechanistic basis of these processes has revolutionized diagnosis, treatment and prognostication

Keywords: Angiogenesis, Apoptosis, Cancer, Growth factor, Hallmarks, Immune evasion, Intratumoural heterogeneity, Invasion, Metastasis, MRCP, Oncogene, Telomerase, Tumour suppressor gene, Warburg effect.

Breast cancer

Sharat Chopra, Eleri Lloyd Davies

Medicine 2020; 48(2): 67-152.

Abstract

Breast cancer is the most common cancer affecting women, with a recent estimate of lifetime risk of 1 in 8. In 2016 the number of women with breast cancer in the UK had risen to 54,600, accounting for 15% of new cancer cases; the highest rise was in 50–90-year-olds, with a peak in >90-year-olds. This is probably attributable to lifestyle factors such as diet, alcohol consumption, lack of exercise and late pregnancies. Because of advances in earlier diagnosis and major treatment, survival rates have gradually improved over the last 20 years, 80% of patients with early breast cancer now surviving 10 years after diagnosis. Recent advances in surgical management include oncoplastic techniques for breast conservation and advances in breast reconstruction after mastectomy. The management of the disease-positive axilla is another hot topic in management. Most patients with breast cancer are offered either neoadjuvant or adjuvant treatment in the form of radiotherapy, hormones, chemotherapy and biological agents, aiming to reduce recurrence and improve overall survival. Novel developments include the use of biological markers to predict outcome and response to chemotherapy, and newer combination immunotherapy agents, which can improve survival in the metastatic setting. This overview discusses the up-to-date management of breast cancer and recent developments.

Keywords: Adjuvant therapy, biological markers, breast cancer, MRCP, neoadjuvant treatment, oncoplastic, pertuzumab, sentinel node biopsy, trastuzumab.

Opportunistic Bacterial, Viral and Fungal Infections of the Lung

Ricardo J José, Jimstan N Periselneris, Jeremy S Brown

Medicine 2020; 48(6): 366-72.

Abstract

Opportunistic infections are a major cause of morbidity and mortality in severely immunocompromised patients, such as those given chemotherapy or biological therapies, and those with haematological malignancy, aplastic anaemia or HIV infection, or recipients of solid organ or stem cell transplants. The type and degree of immune defect dictates the profile of potential opportunistic pathogens; T-cell-mediated defects increase the risk of viral (cytomegalovirus, respiratory viruses) and *Pneumocystis jirovecii* infections, whereas neutrophil defects are associated with bacterial pneumonia and invasive aspergillosis. However, patients often have combinations of immune defects, and a wide range of other opportunistic infections can cause pneumonia. Importantly, conventional non-opportunistic pathogens are frequently encountered in immunocompromised hosts and should not be overlooked The radiological pattern of disease (best assessed by computed tomography) and speed of onset help identify the likely pathogen(s); this can then be supported by targeted investigation including early use of bronchoscopy in selected patients. Rapid and expert clinical assessment can identify the most likely pathogens, allowing timely appropriate therapy.

Keywords: *Aspergillus, Cryptococcus,* fungi, immunocompromised host, MRCP, *Nocardia,* opportunistic infections, pneumonia, viruses.

Nonalcoholic Fatty Liver Disease: What Does the Primary Care Physician Need to Know?

Jeffrey Budd, Kenneth Cusi

The American Journal of Medicine 2020; 133(5): 536-43.

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States and is soon to be the leading cause of liver transplantation. Patients at the greatest risk are those with obesity and type 2 diabetes mellitus. In 2019 the American Diabetes Association guidelines called, for the first time, for clinicians to screen for steatohepatitis and fibrosis all patients with type 2 diabetes and liver steatosis or abnormal plasma aminotransferases. This requires primary care physicians to be aware of key aspects related to the diagnosis and treatment of NAFLD, as well as to when to refer to a specialist. Unfortunately, there is still significant medical inertia as clinicians remain unaware of its high morbidity/mortality. Early diagnosis in the primary care setting is critical to prevent progression to end-stage liver disease. Patients with NAFLD are also at a higher risk of developing type 2 diabetes mellitus and cardiovascular disease. Despite general perception to the contrary, weight loss by lifestyle intervention or bariatric surgery and several pharmacological treatments (eg, vitamin E in nondiabetics,

pioglitazone or glucagon-like peptide 1 receptor agonists in patients with or without diabetes) can often be successful to reverse steatohepatitis and prevent disease progression.

Intermittent Fasting: A Heart Healthy Dietary Pattern?

Tiffany A. Dong, Pratik B. Sandesara, Devinder S. Dhindsa, Anurag Mehta, Laura C. Arneson, Allen L. Dollar, Pam R. Taub, Laurence S. Sperling

The American Journal of Medicine 2020; 133(8): 901-7.

Abstract

Dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet, have been shown to improve cardiac health. Intermittent fasting is another type of popular dietary pattern that is based on timed periods of fasting. Two different regimens are alternative day fasting and time-restricted eating. Although there are no large, randomized control trials examining the relationship between intermittent fasting and cardiovascular outcomes, current human studies that suggest this diet could reduce the risk for cardiovascular disease with improvement in weight control, hypertension, dyslipidemia, and diabetes. Intermittent fasting may exert its effects through multiple pathways, including reducing oxidative stress, optimization of circadian rhythms, and ketogenesis. This review evaluates current literature regarding the potential cardiovascular benefits of intermittent fasting and proposes directions for future research.

Initial Clinical Experience with ^{90}Y-FAPI-46 Radioligand Therapy for Advanced-Stage Solid Tumors: A Case Series of 9 Patients

Justin Ferdinandus, Pedro Fragoso Costa, Lukas Kessler, Manuel Weber, Nader Hirmas, Karina Kostbade, Sebastian Bauer, Martin Schuler, Marit Ahrens, Hans-Ulrich Schildhaus, Christoph Rischpler, Hong Grafe, Jens T. Siveke, Ken Herrmann, Wolfgang P. Fendler and Rainer Hamacher

Journal of Nuclear Medicine May 1, 2022; 63 (5): 727-34.

Abstract

Fibroblast activation protein (FAP) is overexpressed in several solid tumors and therefore represents an attractive target for radiotheranostic applications. Recent investigations demonstrated rapid and high uptake of small-molecule inhibitors of FAP (^{68}Ga-FAPI-46) for PET imaging. Here, we report our initial experience of the feasibility and safety of ^{90}Y-FAPI-46 for radioligand therapy of extensively pretreated patients with solid tumors.

Methods: Patients were considered for ^{90}Y-FAPI-46 therapy if they showed both an exhaustion of all approved therapies based on multidisciplinary tumor board decision, and high FAP expression, defined as SUV_{max} greater than or equal to 10 in more than 50% of all lesions. If tolerated, ^{90}Y-FAPI-46 bremsstrahlung scintigraphy was performed after therapy to confirm systemic distribution and focal tumor uptake, and ^{90}Y-FAPI-46 PET scans were performed at multiple time points to determine absorbed dose. Blood-based dosimetry was used to determine bone marrow absorbed dose. Adverse events were graded using Common Terminology Criteria for Adverse Events (version 5.0).

Results: Nine patients either with metastatic soft-tissue or bone sarcoma (*n* = 6) or with pancreatic cancer (*n* = 3) were treated between June 2020 and March 2021. Patients received a median of 3.8 GBq (interquartile range [IQR], 3.25–5.40 GBq) for the first cycle, and 3 patients received subsequent cycles with a median of 7.4 GBq (IQR, 7.3–7.5 GBq). Posttreatment ^{90}Y-FAPI-46 bremsstrahlung scintigraphy demonstrated sufficient ^{90}Y-FAPI-46 uptake in tumor lesions in 7 of 9 patients (78%). Mean absorbed dose was 0.52 Gy/GBq (IQR, 0.41–0.65 Gy/GBq) in the kidney, 0.04 Gy/GBq (IQR, 0.03–0.06 Gy/GBq) in bone marrow, and less than 0.26 Gy/GBq in the lung and liver. Measured tumor lesions received up to 2.28 Gy/GBq (median, 1.28 Gy/GBq). New laboratory G3 or G4 toxicities were noted in 4 patients (44%, *n* = 2 patients with thrombocytopenia only, *n* = 2 patients with new onset of thrombocytopenia and anemia). Other G3 or G4 laboratory-based adverse events occurred in 2 patients or fewer. No acute toxicities attributed to ^{90}Y-FAPI-46 were note. Radiographic disease control was noted in 4 patients (50%).
Conclusion: FAP-targeted radioligand therapy with ^{90}Y-FAPI-46 was well tolerated, with a low rate of attributable adverse events. Low radiation doses to at-risk organs suggest feasibility of repeat cycles of ^{90}Y-FAPI-46. We observed signs of tumor response, but further studies are warranted to determine efficacy and the toxicity profile in a larger cohort.

Morbidity in Patients with Permanent Hypoparathyroidism after Total Thyroidectomy

Anders Bergenfelz, Erik Nordenström, Martin Almquist
Surgery 2020; 167 (1): 124-8.

Abstract
Background: Permanent hypoparathyroidism is common after thyroidectomy. The present study evaluated the risk for morbidity in patients operated with total thyroidectomy with and without permanent hypoparathyroidism.
Methods: Data was retrieved from the Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery and cross-linked with the Swedish National Prescription Registry for Pharmaceuticals, the National Data Inpatient Registry, and Causes of Death Registry. Patients with benign thyroid disease were included. Permanent hypoparathyroidism was defined as treatment with active vitamin D for more than 6 months after thyroidectomy. Analyzed morbidity was evaluated by multivariable Cox's regression analysis and presented as hazard ratio and 95% confidence interval.
Results: There were 4,828 patients. The mean (standard deviation) follow-up was 4.5 (2.4) years. Some 239 (5.0 %) patients were medicated for permanent hypoparathyroidism. Patients with permanent hypoparathyroidism had an increased risk for renal insufficiency, hazard ratio 4.88 (2.00–11.95), and an increased risk for any malignancy, hazard ratio 2.15 (1.08–4.27). Patients with permanent hypoparathyroidism and known cardiovascular disease at the time of thyroidectomy had an increased risk for cardiovascular events during follow-up, hazard ratio 1.88 (1.02–3.47).
Conclusion: Patients with permanent hypoparathyroidism after total thyroidectomy have an increased risk of long-term morbidity. These results are a cause of great concern.