Falk Workshop

Digestive Diseases: State of the Art and Daily Practice

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Abstracts of Invited Lectures

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DIGESTIVE DISEASES: STATE OF THE ART AND DAILY PRACTICE

Santiago de Chile (Chile)
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J. Brahm, Santiago (Chile)
J. Schölmerich, Regensburg (Germany)
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Cholestasis and complications of cirrhosis
Cholestatic liver diseases

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Cholestasis is defined as a disturbance of bile secretion which can result from a functional defect in bile formation at the level of hepatocytes or from impaired bile secretion/obstructed flow at the bile duct level. Retention of biliary constituents (particularly bile acids which are cytotoxic at higher concentrations) in cholestasis can lead to biliary fibrosis, cirrhosis and ultimately end-stage liver disease requiring liver transplantation. Recent progress has enhanced our understanding of the molecular pathogenesis of cholestatic liver diseases. Mutations in genes encoding for hepatobiliary transport systems can cause hereditary cholestatic syndromes (e.g., progressive familial intrahepatic cholestasis) and exposure to cholestatic agents (drugs, hormones, inflammatory cytokines) can lead to reduced expression and function of hepatic uptake and excretory systems in acquired forms of cholestasis (e.g. drug and sepsis-induced cholestasis). Moreover, hereditary transporter mutations may also predetermine the individual susceptibility to acquired cholestatic liver injury (e.g. drug-induced cholestasis, intrahepatic cholestasis of pregnancy). In addition to transporter changes which cause or maintain cholestasis, some alterations in transporter gene expression can be viewed as hepatoprotective mechanisms aimed at reducing intrahepatic accumulation of toxic biliary constituents such as bile acids and bilirubin. Such adaptive mechanisms include the induction of bile acid detoxification systems and recruitment of alternative export pumps for cholephiles at the basolateral membrane, finally leading to increased urinary elimination of bile acids and conjugated bilirubin. These molecular changes are frequently mediated by specific ligand (e.g., bile acid)-activated nuclear receptors. In addition to transcriptional changes, reduced transporter protein insertion to or increased retrieval from the cell membrane as well as other mechanisms such as altered cell polarity, disruption of cell-to-cell junctions and cytoskeletal changes may be involved in the pathogenesis of cholestasis. Understanding the detailed mechanisms regulating expression of transport systems and enzymes is essential for the development of novel therapeutic agents. Despite considerable progress over the past decade, the pathogenesis of immune-mediated cholangiopathies such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) still remains a mystery. Autoimmunity in PBC is directed against well-identified mitochondrially located autoantigens and appears to be the result of a combination of genetic and environmental influences.

Diagnostic work-up includes a detailed history and physical examination, non-invasive radiologic tests (ultrasound, computerized tomography scan, and magnetic resonance cholangiography) for visualization of the biliary tree, and determination of autoantibodies (e.g. AMA for PBC). Liver biopsy may be necessary to evaluate small bile duct damage. Although jaundice is a hallmark of cholestasis, it is usually absent in adults with early stage chronic cholestatic liver disease such as PBC most of whom are entirely asymptomatic. If possible, therapy should address the cause of
cholestasis (e.g. relief of biliary obstruction, elimination of causative drugs, treatment of underlying infection/sepsis). However, for most chronic cholestatic liver diseases the cause of the disease is not known and treatment is mostly focused on limiting liver damage from accumulating cholephiles and supporting adaptive mechanisms. Ursodeoxycholic acid (UDCA) improves biochemical serum markers of cholestasis nearly regardless of cause and may delay disease progression in many cholestatic disorders. As such, UDCA is the mainstay for treatment of cholangiopathies such as PBC and PSC. PBC patients with biochemical response to UDCA have normal survival and the effectiveness of UDCA is highest when treatment is initiated at early stages. Patients with an incomplete biochemical response to UDCA may benefit from combination therapy with budesonide or fibrates. While UDCA also improves liver tests in patients with PSC, its effects on survival remain unclear. However, UDCA reduces the risk of colorectal dysplasia and malignancy from the frequently associated inflammatory bowel disease. Future research is needed to develop novel and more effective drugs for cholestatic diseases. norUDCA is a side chain-shortened C23 homologue of UDCA which possesses one less methylene group in its side chain, undergoes less conjugation with taurine or glycine than UDCA, but instead is secreted into bile mostly in unchanged form. The secreted norUDCA undergoes absorption by cholangiocytes, returns to the liver and is resecreted into bile. Such cholehepatic shunting leads to a bicarbonate-rich hypercholeresis and may also result in improved targeting to the liver. norUDCA (but not “conventional” UDCA) reverses sclerosing cholangitis in the Mdr2-/- cholangiopathy model within 4 weeks of treatment. Its possible therapeutic mechanisms include (i) amelioration of bile hydrophobicity by biliary enrichment with hydrophilic norUDCA and its metabolites, (ii) flushing of injured bile ducts by stimulation of bile flow and bicarbonate-rich choleresis, which dilutes toxic biliary content, (iii) induction of alternative bile acid detoxification (phase I and II enzymes) and elimination routes for bile acids, and (iv) direct anti-inflammatory and anti-fibrotic properties. These effects make norUDCA an attractive candidate drug for the treatment of cholangiopathies, in particular of sclerosing cholangitis. Nuclear receptors (e.g. bile acid receptor FXR) may also be promising therapeutic targets for cholestasis, hepatic fibrogenesis and inflammation. Many drugs already used to treat cholestasis and its complications such as pruritus (e.g., UDCA, rifampicin, fibrates) may act via activation of nuclear receptors. More specific and potent nuclear receptor ligands (e.g., FXR ligands) are currently being developed and tested in phase I/II trials. When medical treatment fails, liver transplantation is an option for end-stage cholestatic liver disease and provides excellent results in PBC and PSC.

Additional challenges in the management of cholestatic liver diseases include treatment of associated extrahepatic (autoimmune) diseases, osteoporosis, deficiency of fat soluble vitamins and pruritus. Portal hypertension can be an early event in chronic cholestatic liver disease, sometimes occurring before the development of cirrhosis. Patients with PSC carry a high risk for malignancy and should be regularly screened for cancer of the biliary tree (including gallbladder), pancreas and colorectum. Current pathogenetic concepts and therapeutic targets in pruritus include peripherally acting pruritogens, such as bile acids or endogenous opioids, and central mechanisms, including an increased central opioidergic tone and perturbations in the serotoninergic system. Apart from treatment of the underlying disease, pruritus can be managed by bile acid binding resins (cholestyramine), bile acid detoxifying enzyme-inducing agents (rifampicin) and opioid-serotonin antagonists. Liver transplantation may be indicated when severe pruritus is refractory
to medical treatment. Artificial extracorporeal liver support systems such as Molecular Adsorbents Recirculating System (MARS, a variant of albumin dialysis), and Prometheus (a device for fractionated plasma separation and adsorption) may also be efficient for treatment of pruritus through elimination of albumin-bound pruritogens such as bile acids. Several case reports and smaller case series have reported improvement of pruritus in adult and even pediatric patients with MARS and Prometheus treatment. Further controlled studies evaluating the efficacy of these systems in patients with cholestatic pruritus are needed.
Cirrhosis of the liver: Recent advances in the management of complications of portal hypertension

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Most complications that occur in patients with liver cirrhosis are due to an increased pressure in the venous portal system, a condition known as portal hypertension. These complications, among others include ascites, hyponatremia, gastrointestinal bleeding, hepatic encephalopathy, bacterial infections, and hepatorenal syndrome. The management and prevention of gastrointestinal bleeding due to esophageal varices has been well established for many years. By contrast, important advances in the field of management of renal complications of cirrhosis have not been made until very recently. The occurrence of hepatorenal syndrome in the setting of spontaneous bacterial peritonitis can now be markedly reduced by the administration of albumin together with the administration of antibiotics. This therapeutic approach has been shown to improve survival in these patients. On the other hand, recent studies have demonstrated that bacterial translocation from the intestinal lumen to the mesenteric lymph nodes is important in the development of circulatory abnormalities that exist in patients with advanced cirrhosis. The administration of prophylactic antibiotics, particularly quinolones, to patients with high risk of development of infection of ascitic fluid reduces the risk of development of spontaneous bacterial peritonitis, a severe complication of patients with cirrhosis. Moreover, long-term treatment with norfloxacin has been shown to reduce the frequency of hepatorenal syndrome and improve survival in patients with advanced cirrhosis. Investigations performed in recent years have demonstrated that the combined administration of vasoconstrictor drugs, particularly terlipressin, together with albumin improve renal function in 40–50% of patients with hepatorenal syndrome, a condition for which there was no effective therapy. This therapeutic approach may be particularly valuable for patients developing hepatorenal syndrome while awaiting transplantation. Finally, a new therapeutic approach for the management of hyponatremia in cirrhosis, which consists in the administration of drugs known as vaptans that selectively inhibit the V2 antidiuretic hormone receptors in the kidneys, is being evaluated. The short-term administration of vaptans to patients with cirrhosis and hyponatremia improves serum sodium concentration in the majority of patients. The long-term safety and efficacy of these drugs is currently under investigation. In summary, all these new methods of treatment or prevention of complications of portal hypertension will likely result in a decreased morbidity and mortality of patients with advanced cirrhosis.
Session III

Inflammatory bowel diseases
Ulcerative colitis and Crohn’s disease

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In the last decade much has been learned about the basis of inflammatory bowel disease as well as of diagnosis and treatment. This lecture can only discuss a few of the many possible aspects and will focus on the basis of therapy and therapy itself.

Genetic and epidemiologic studies have demonstrated that IBD is a group of distinct phenotypes based on different genotypes and environmental factors. Disease characteristics are rather different between referral center and population-based studies. The latter show that many patients with IBD have a very benign course – this applies to about 60% in ulcerative colitis and about 40% in different forms of Crohn’s disease. About 30% have the typical intermittent flares and remission phases while about 10% in ulcerative colitis and 20% in Crohn’s disease have chronic active and refractory disease leading to disturbed function of the intestinal tract. The different courses are probably due to different genetic susceptibility as demonstrated for the NOD2/CARD15 gene recently but environmental factors such as smoking have at least as much impact. Probably many more environmental factors have influences not only on the manifestation but also on the course of the disease – this needs to be clarified in the future.

Recent understanding of the susceptibility genes involved indicates a disturbed role of the innate immune system which as part of the intestinal barrier may play a predominant role. New approaches of treatment should target these defects.

Defects of the barrier are also manifest at the occurrence of antibodies to bacterial components in the serum of patients with IBD. In particular the ASCA, but many others have been found. Their clinical role, however, is still limited. Interestingly their frequency is also increased in relatives of IBD patients without disease manifestation. Further diagnostic progress comes from the development of magnetic resonance imaging, double balloon and wireless capsule endoscopy but time does not permit to discuss those. Of high importance is the fact that bacterial and viral superinfections can mimic flares of IBD but need different treatment and therefore need to be excluded before starting IBD therapy.

The goals of treatment in IBD thus far were induction of remission and maintenance without steroids. In the future the preservation of the main functions of the intestinal tract, i.e. absorption of nutrients in the small bowel, retention of water and electrolytes in the large bowel and controlled release of feces will be the aims. This implicates avoiding surgery and all structural damage. The long-term goal, healing of the disease, remains elusive at the moment.

Many different types of drugs can be used, most of them have immunosuppressive features. The basis in ulcerative colitis is the combined oral and rectal application of
5-ASA. This can also be used in Crohn's disease although it is somewhat less effective. Steroids are very effective in induction of remission in Crohn's disease more than in ulcerative colitis, the newer topical steroids such as budesonide play a major role in Crohn's disease. The need of steroids for the first flare seems to be predictive of a more severe long-term course. In patients resistant to or dependent on steroids azathioprine has been found effective. It can be used repeatedly and it induces so-called "mucosal healing" in quite a number of patients. In refractory ulcerative colitis cyclosporine and more recently infliximab play a role, the latter is more widely used in Crohn's disease. Additional inhibitors of tumor necrosis factor have been developed such as adalimumab and certolizumab, their effects are similar to infliximab, the application differs. Many other "biologics" have been developed and tested, thus far only natalizumab has been approved in the US but not in Europe.

It would be tempting – in analogy to patients with rheumatoid arthritis – to select initially those patients being at risk for structural damage and treat them initially in an aggressive way. Such an approach (top down strategy) has been tested in one trial which, however, did not show convincing evidence. This is probably due to the fact that patients could have the disease for more than two years and were included without prior selection of those at risk.

As expected immune suppression has its price. Infectious complications may occur and will occur, in particular, when different immune suppressants are combined. Thus, the option of surgery has not to be forgotten although it induces structural loss. It has been shown early that radical surgery is less effective than non-radical surgery in Crohn's disease while colectomy in ulcerative colitis cures the disease with the exception of the possible occurrence of pouchitis in those patients getting a pouch. Interestingly patients subjectively judge their life quality after pouch or permanent ileostoma rather good in more than 90%.

Finally, the new concepts of barrier defects lead to attempts to manipulate the luminal side using antibiotics or probiotics. This has been successful in maintaining remission in ulcerative colitis or in pouchitis, antibiotics have been shown effective in Crohn's disease. New approaches with ligands of the innate immune system, with endogenous usbstances such as bile acids and barrier lipids such as phosphatidylcholine show some promise but need to be tested in a more rigorous way.

In summary there are different subpopulations of IBD needing different approaches for diagnosis and in particular for treatment. Bacterial host interaction seems to be the key to understanding genetic and environmental influences on IBD. Standard treatments have nicely developed, we need to adjust them better to the individual needs. The future holds many interesting new approaches beyond the simple immunological paradigm. Microbiologics, nutrients, old factors such as lipids and bile acids should be appropriately tested. The future treatment will be based on understanding the homeostasis in the GI-tract and does not need to be expensive.
Session IV

Digestive cancer
Hepatocellular carcinoma

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The incidence of hepatocellular carcinoma (HCC) has increased worldwide and now it ranks within the major five cancer killers (1). Cirrhotic patients constitute the population at risk and in them this neoplasm represents the first cause of death (2). Because of this relevance all practice guidelines support surveillance plans based on ultrasound examination every 6 months (2). Diagnosis can be established by biopsy or by non-invasive criteria that have been prospectively validated (2, 3). Surveillance aims to diagnose the tumor at an early stage, when it might be curable by resection, liver transplantation or percutaneous treatment (2, 4).

Early diagnosis is attained in 30% of the patients and treatment allows 5-year survival rates above 50%. Patients with single tumors and well-preserved liver function are optimal candidates for resection, while liver transplantation benefits patients with more advanced cirrhosis with single lesion ≤ 5 cm or three nodules < 3 cm. Percutaneous ablation through ethanol injection or radiofrequency is highly useful for solitary tumors ≤ 3 cm and Child-Pugh A patients may exceed 50% survival at 5 years (2, 4).

Unfortunately, most of the patients are diagnosed at advanced stages when they only merit palliative therapies. Recent randomized controlled trials and meta-analysis indicate that chemoembolization improves survival of patients with asymptomatic disease and preserved liver function (5). Chemotherapy has marginal activity both when used as single agent and when combining different drugs. In addition, it is frequently associated with significant toxicity that impairs quality of life (2, 4). Hence, until very recently a major proportion of subjects was left without effective therapy. However, the advent of molecular targeted therapies has changed this scenario. A large, placebo controlled trial has shown that sorafenib is able to significantly improve the survival of patients with advanced HCC with a more than 30% reduction of the risk of death along time (6). These results have opened the path for further evaluation of these agents and ongoing trials will evaluate the efficacy of the combined therapy and sure the benefits for patients will be expanded. At the same time, the results with sorafenib have provided the background to test this agent at earlier phases of the disease: – as an adjuvant after resection or ablation aiming to reduce recurrence rate. – as a coadjuvant for chemoembolization aiming to enhance the initial treatment response and expand its duration.

The enclosed figure summarises the staging and treatment strategy that is followed at the BCLC group. In brief, patients are divided in major strata according to tumor stage and degree of liver function impairment. Patients at an early stage are considered for treatments that may provide long term cure, while patients diagnosed at intermediate or advanced stage are considered for chemoembolization and sorafenib, respectively. In the near future, results of ongoing investigations will sure
refine this decision making strategy. Data available until now and the development of major methodology guidelines have paved the way for large scale investigations, both in molecular profiling and in clinical management. Hopefully, in few years we will see how HCC has evolved from a malignancy with grim prognosis to a disease with several treatment options providing a long term survival, thus paralleling the evolution observed in other cancers.

References:


Barcelona staging and treatment strategy

Stage 0
PST 0, Child-Pugh A

Stage A - C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Stage D
Okuda 3, PST >2, Child-Pugh C

Very early stage (0)
Single < 2cm. Carcinoma in situ

Early stage (A)
Single or 3 nodules < 3cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Advanced stage (C)
Portal invasion, N1, M1, PS 1-2

Terminal stage (D)

Normal

Single
Portal pressure/ bilirubin

Increased

3 nodules ≤3cm

No
Associated diseases

Yes

No

Yes

Resection
Liver Transplantation (CLT / LDLT)
PEI/RF
Chemoembolization
Sorafenib

Curative Treatments
50% - 75% at 5 years

Randomized controlled trials
40% - 50% at 3 yr vs 10% at 3yr

Symptomatic treatment

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Colorectal cancers arise through the adenoma – carcinoma sequence in which adenomas develop from normal intestinal epithelium and then transform into invasive cancers. Colorectal cancers are much commoner in elderly patients. Patients who have had a colorectal cancer resected are at high risk of recurrence in the remaining bowel. Other risk factors for colorectal cancer include dietary factors in which fibre is protective and fat and red meat increases risk. Obesity and a sedentary life-style increase risk as well. The strength of these risk factors is heavily influenced by the genetic make-up of the patient. Long-standing inflammatory bowel disease (IBD) is also a risk factor though the number of IBD patients developing colorectal cancer is falling, partly because of colonic surveillance and partly because of more effective control on colonic inflammation, particularly with 5-aminosalicylic acid. The inherited genetic syndromes Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC) are well known but account for less than 5% of cancers.

The most effective way to prevent the development of colorectal cancer is by colonoscopy and clearance of adenomas by polypectomy. In general, adenomas and early cancers do not cause symptoms and patients did not seek medical attention until an invasive cancer has developed. For this reason a systematic approach for the screening of patients at risk of adenoma has been adopted in most western countries. The methods used for screening vary from country to country. In most countries screening is a two stage process in which patients at very low risk of cancer are eliminated from screening process with a simple test such as a guaiac faecal occult blood test. In the second stage the remaining patients who have a significant risk of adenoma or carcinoma undergo, in most countries, colonoscopy and polypectomy.

In addition, in most countries two types of surveillance is undertaken; post-polypectomy surveillance and surveillance after resection of colorectal cancer. Development of subsequent advanced adenomas is more likely if the initial adenoma is greater than 1 cm in diameter or there are more than 3 in number or have they have villous architecture or high grade dysplasia on histological examination. A number of detailed protocols have been proposed for the follow-up of patients with adenomas. The majority recommend repeat colonoscopy after 5 years for patients with low risk adenomas and after 3 years for patients with adenomas great than 1cm in diameter or with high risk histology. Incomplete removal of adenomas is a major difficulty and for this reason many authorities recommend repeat colonoscopy 2 to 6 months after removal of large sessile polyps. Most authorities agree that after resection of colorectal cancer colonoscopy should be undertaken after 1 year and then 3–5 years later.
The mainstay of treatment for colorectal cancer remains colectomy. However there have been important advances in chemotherapy for metastatic disease. For decades, treatment has relied on Fluoropyrimidines such as 5-Fluorouracil which gives a median survival of 10–12 months. Addition of either Irinotecan or Oxaliplatin increases survival to 14–16 months, while addition of both drugs to 5-FU given by continuous infusion increases survival to 20 months. Targeted therapy with the angiogenesis inhibitor Bevacizumab (Avastin) or the Epidermal Growth Factor Inhibitors Cetuximab and Panitumumab as additions to conventional chemotherapy can also extend survival to 20 months. Currently, the great cost of these new drugs present a major challenge to all Health Care Systems which remains unresolved. Nonetheless drug treatment of colorectal cancer is improving significantly in a step by step fashion in way similar to the improvements of therapies for Lymphomas and Leukaemias seen in the 1970s and 80s.

References:

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