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and the authors conclude with the opinion that abatacept therapy in RA will represent the primary clinical application of co-stimulation blockade with the potential to demonstrate a role in the treatment of a broad range of immunological disorders.

The myelodysplastic syndromes (MDS) constitute a group of acquired disorders of the bone marrow caused by defective clonal stem cells. Together with chronic lymphocytic leukemia, they represent the most frequently occurring hematological malignancy, with an incidence of 15 to 50 new cases/100 000/year. MDS are characterized by advancing bone marrow failure, increased risk of life-threatening infection, and myeloid cell abnormalities. Although the natural history of MDS is variable, approximately 30% of cases transform into acute myeloblastic leukemia and there are high rates of morbidity and mortality secondary most commonly to bleeding and infection. MDS present as a variety of sub-types, the number of which is dependent upon the classification system: the French American British (FAB) system identifies five morphological sub-groups with prognostic importance; the World Health Organization system includes seven sub-groups; and the International Prognostic Scoring System identifies those patients at enhanced risk of transformation. Allogenic stem cell transplantation represents the only curative therapy but is only suitable in a minority of cases, the remainder of patients being managed conservatively through combinations of infection prophylaxis, blood and platelet transfusions, and growth factors such as erythropoietin and granulocyte-colony stimulating factor. Emerging candidate therapies include the methyltransferase inhibitors (MTI) such as azacytidine, a chemically synthesized nucleoside analogue that has the potential to reverse gene methylation and is currently the only drug in this class with US Food and Drug Administration approval for use in all subtypes of MDS. Raj and Mufti outline and review the role of and clinical evidence for azacytidine in MDS. They begin with an introduction to classification procedure and the role of epigenetics in assessing disease progression and risk. They then move onto a discussion of the rationale for azacytidine in MDS, and its chemical structure and pharmacokinetics. An analysis of the three successive cancer and Leukemia Group B (CALGB) studies includes discussion of the Phase III randomized controlled

trial that demonstrated azacytidine's effectiveness relative to the best model of supportive care. The authors also summarize the clinical response, relapses and toxicity, the drug's mechanism of action in MDS, and duration of therapy. They conclude with a brief discussion of other MTI's in MDS, the role of combination therapy, and future directions in the management of this group of hematological conditions.

Psoriatic arthritis (PsA) is a progressive, unpleasant and potentially debilitating inflammatory arthritis characterized by joint pain and swelling, fatigue and moderate-to-severe skin lesions. The condition can result in severe joint erosion and attendant significant reduction in functional capacity and quality of life. It is frequently misdiagnosed and, together with a lack of disease classification guidelines and consensus-led diagnostic criteria, this hampers accurate estimates of prevalence and incidence. Although the etiological and pathophysiological factors that contribute to development of PsA remain to be fully elucidated, the condition seems to arise from a complex interaction between genes, environment, and the immune system. In particular, developing insights into the fundamental immunological mechanisms of the disease highlighted the role of TNF- α in mediating the pathogenesis of PsA and led to the development of a number of anti-TNF- α drugs for PsA therapy. Philip Mease reviews the role of infliximab, a chimeric, human-mouse IgG1 monoclonal antibody, in the treatment of PsA. He discusses its clinical presentation and sub-types together with the etiology and pathophysiology of the condition before moving onto current treatment approaches. He outlines the traditional role of the non-steroidal anti-inflammatory drugs (NSAIDs) and DMARDs and notes that both classes of drugs are hampered by inadequate control, failure to halt disease progression and poor compliance rates due to side-effects and lack of efficacy. His discussion of infliximab includes thorough discussions of the IMPACT and IMPACT II trials and the subsequent multi-centre, randomized, double-blind, placebo-controlled Phase III studies, SPIRIT in the US and EXPRESS in Europe. The author concludes with a consideration of other TNF- α agents and the newer T-cell-directed agents for PsA treatment.

Skin and soft tissue infections (SSTIs) are one of the most frequent sites of bacterial infection and concomitantly,

in the US, rate as one of the most common reasons for both institution of antibiotic therapy and admission to hospital. Complicated SSTIs (cSSTIs) are by definition more inherently serious. They represent a significant clinical challenge, not only as they frequently present with associated bacteremia and sepsis but also because the underlying pathologies that predispose to their development – such as host immunosuppression, surgery, diabetes mellitus, and peripheral vascular disease – may mean they are less sensitive to standard antibiotic therapy and require in-patient surgical intervention and parenterally administered drug regimens. Management of cSSTIs is further complicated by the range of bacterial pathogens and constantly evolving resistance to available antibiotics. Meropenem is a broad-spectrum antibiotic of the carbapenem class that demonstrates excellent therapeutic activity across a range of pathogens commonly associated with cSSTIs. In the first of two reviews of the treatment of cSSTIs, Douglas Fish presents a comprehensive review of meropenem and its use in these conditions. He begins with an overview of the clinical characteristics of cSSTIs, their associated bacterial etiology and the considerations underpinning appropriate therapeutic interventions. The author provides a thorough review of meropenem including a consideration of its antibacterial activity and pharmacokinetics and pharmacodynamics before moving onto a discussion of the clinical data in which he provides an in-depth critique of the largest and most recent study. In discussing its role in cSSTIs, he highlights its excellent activity against the bacteria most commonly associated with these conditions; proven clinical efficacy; low toxicity; competitive wholesale pricing; and possible advantages relative to other available therapeutic agents; and concludes with a personal recommendation regarding an appropriate dosing regimen.

In the second review of antibiotic therapy in the treatment of SSTIs, David Guay addresses the role of moxifloxacin, one of the newer members of the fluoroquinolone class of antimicrobials. He comprehensively reviews the *in vitro* antimicrobial activity of moxifloxacin and underscores the fact that it demonstrates significantly greater *in vitro* activity against potential Gram-positive and Gram-negative aerobic pathogens in SSTIs, relative to earlier quinolones such as ciprofloxacin. From a pharmacokinetic perspective, moxifloxacin demonstrates good penetration of muscle, subcutaneous adipose tissue, and inflammatory blister fluid and the author provides a table of comparative pharmacokinetic parameters in healthy adult volunteers. The

results of clinical trials are presented in light of the limitations intrinsic to their interpretation: the problems inherent in designing trials of SSTIs that are both rigorous and reproducible; the majority of studies were underpowered to avoid Type II statistical errors; and the consequent lack of generalization of results. In addition, the author addresses issues of safety and potential drug–drug interactions. Of these, the sole pharmacodynamic interaction with potential clinical relevance is the additive electrophysiological effects of moxifloxacin when combined with other drugs with the ability to prolong the QT_c interval. However, a lack of rigorous epidemiological and multi-dose studies at present precludes an assessment of the clinical relevance of this potential effect.

Pancreatic cancer is a highly aggressive malignancy that is, for the most part, chemo-refractory and has a five-year survival rate of approximately 2%; most patients present with unresectable disease and survive for less than one year after diagnosis. Gemcitabine monotherapy was adopted worldwide as a standard of care in the therapy of advanced pancreatic cancer following a randomized controlled trial in which it showed significantly enhanced clinical benefit and a modest increase in median survival relative to 5-fluorouracil. However, continuing poor prognosis coupled with conflicting data from trials of combination therapy clearly indicate the need to continue the search for new and more effective therapeutic strategies. The last ten years have seen a considerable accrual of knowledge in the molecular pathogenesis of pancreatic cancer and the identification and development of novel potential therapies has arisen from our enhanced understanding of the tumor/stroma/host axis and the interface with genetics and epigenetics. Anomalies in signal transduction via the epidermal growth factor receptor (EGFR) exert influence at several key stages of tumor development including proliferation, susceptibility to apoptosis, invasion, angiogenesis, and metastasis. Exploitation of this pathway is showing promise in the treatment of advanced pancreatic cancer, primarily through the use of monoclonal antibodies against the extracellular domain and small molecule tyrosine kinase inhibitors (TKIs) that compete at the ATP binding site of the tyrosine kinase domain.

Erlotinib is a quinazoline-based small molecule TKI with high selectivity against the EGFR. Naureen Starling and colleagues introduce the role of EGFR signaling in pancreatic cancer and give an overview of the pre-clinical evaluation of erlotinib in which they discuss the elucidation of the pharmacology and preliminary pharmacokinetics of

erlotinib through early phase studies. Combination therapy offers considerable benefit in the management of cancer through the modulation of resistance, synergistic effects of combined drugs, and attendant potential for an enhanced effectiveness. The authors review the clinical development of erlotinib/gemcitabine combination therapy for the management of pancreatic cancer. They discuss the results of the National Canadian Institute of Cancer international, multi-centre, randomised, placebo-controlled Phase III trial and the conflicting data from the TRIBUTE and TALENT studies, noting that the latter studies' failure to select for potential responders to EGFR TKIs attenuated erlotinib's therapeutic effect. Two ongoing studies, TARGET and SWOG, are mentioned briefly together with potential erlotinib-associated toxicity and the importance of careful evidence-based patient selection. The authors conclude with the observation that recent findings, although small, represent important progress and, notwithstanding pharmacoeconomic and quality of life considerations, form the basis for future multi-targeted approaches to a disease that is both aggressive and difficult to treat.

Pain is a frequent outcome of cancer and its treatment. Its prevalence and severity are in part dependent upon the disease stage and the site of primary tumor and metastases, with prevalence rates estimated at 30% amongst those patients who are being actively treated for metastatic spread and 60% to 90% of patients with advanced disease. However, in spite of the existence of incremental, validated, consensus-based guidelines for analgesia, pain control in cancer is frequently sub-optimally managed. This appears to be a result of a number of factors including concerns regarding tolerance, side effects, and out-of-date knowledge amongst both health professionals and patients. Opiates represent the preferred treatment strategy for palliation of severe pain amongst cancer patients and their use is guided by the World Health Organization three-step analgesia ladder, a flexible framework developed to assist in the appropriate application of analgesic drugs. Mandala and colleagues address the question of how to optimize the use of opiates in the palliation of cancer pain by focusing on four separate aspects of therapy. Firstly, they consider how best to implement the use of opioids and make two suggestions: (1) the necessity of appropriate assessment by an inter-disciplinary team who can deliver a holistic approach to pain control; and (2) the introduction of straightforward protocols or guidelines to further assist in management of symptoms. Secondly, they consider approaches to optimize the use of morphine, which in spite

of being the most widely used and cost-effective opioid, is limited by poor systemic availability of the orally administered drug that results in inter-individual variability in the dose-response. The authors discuss thoroughly the dose-titration approach to administration and give a brief overview of the role of spinal morphine. Thirdly, they address the major clinical challenge of management of side effects (including gastrointestinal and central nervous system) and suggest a four-step approach including dose reduction, toxicity management, opioid rotation, and alternative routes of administration. Lastly, they consider the role of other potent opioids including methadone, oxycodone, and transdermal fentanyl.

The increase in antibiotic resistant strains of microorganisms worldwide continues to be a major concern that highlights the necessity for the development of new and more effective treatments. While the contribution of multi-resistant Gram-positive pathogens continue to be a major problem in the hospital setting, the growing tendency towards progressive shortening of hospitalization has led to community-acquired infections involving Gram-positive cocci becoming more common. It is therefore of note that Roberto Manfredi has provided a comprehensive review of the role of multi-antibiotic resistant Gram-positive pathogens in both the hospital and community setting. The review considers current guidelines for the management of these infections, particularly in compromised individuals. Their effective management is hampered by the spectrum of available antimicrobial compounds being significantly impaired in selection and clinical efficacy by the spread of methicillin-resistant and more recently glycopeptide-resistant Gram-positive microbial strains. In this regard the potential contribution of linezolid a novel oxazolidinone derivative is described in terms of microbiological properties, clinical indications and effectiveness together with tolerability, safety issues and pharmacoeconomic assessments. Other important issues are also discussed including the usefulness of linezolid in pediatric populations, the presence of Gram-negative pathogens necessitating the use of combination therapy and the degree to which linezolid-resistance pathogens may in time prove problematic.

Restless leg syndrome (RLS), also known as Ekbom's syndrome, is a prevalent sensorimotor and sleep disorder characterized by sensations of discomfort deep within the legs that can only be relieved by repetitive leg movements. The pathogenesis of RLS, is probably a function of the interaction between a lack of systemic or brain iron and

inadequate subcortical dopaminergic neurotransmission. The condition has been clearly defined since the mid-1940s; however, in spite of this it remains poorly recognized and is notable for its frequent misdiagnosis and inadequate treatment. Cotter and O'Keefe examine the factors that contribute to the condition being so frequently overlooked (and that can result in a delay of over a decade for an accurate diagnosis); outline contemporary approaches to its pathogenesis and treatment; and enumerate the benefits to the patient of adequate diagnosis and management. In laying

the groundwork for our understanding of RLS, the authors elaborate upon the current diagnostic criteria, including essential criteria and supportive and associated clinical features; address a number of myths and misconceptions underlying the condition; and discuss why a diagnosis of RLS should be considered important and managed accordingly. They also present a succinct discussion of the therapeutic regimens available for the management of both primary and secondary RLS and conclude with a brief summary of treatment options.

