Future Perspectives of the Sentinel Node Concept: Implications for Clinical Trials
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In human solid cancers, lymph node status is the most important prognostic indicator of clinical outcome. Recent developments in the sentinel lymph node (SLN) concept and technology have resulted in the application of this revolutionary procedure to define the first draining node or SLN to which the cancer will metastasize. Selective sentinel lymphadenectomy (SSL) should be considered a standard of care for staging patients with primary invasive melanoma 1 mm or greater. It is essential that multidisciplinary teams should master the techniques of preoperative lymphoscintigraphy, intraoperative lymphatic mapping, and pathologic evaluation of the SLNs. The prognostic of micrometastasis in SLNs remains to be defined. Whether a complete lymph node dissection should be done following a positive SLN will be addressed by the ongoing multicenter selective sentinel lymphadenectomy trial (MSLT II). There is evidence that significant immunosuppression may be present in the SLNs. CCL21 in the regional lymph node regulates the recruitment of T cells, NK cells and dendritic cells. Recent studies have shown that tumor cells can bear chemokine receptors and may facilitate tumor metastasis. The critical issue to be defined is the role of the SLN in the process of lymphatic metastasis. Clinical trials using immune adjuvants such as GM-CSF may be developed to reverse immunosuppression in the SLNs with resultant expectation to eliminate micrometastasis in the SLNs.

Sorafenib, a Pluripotent Molecule
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One of the major targets under investigation for anticancer targeted therapies is the Ras mediated pathway which plays a central role in a variety of signal transduction processes. Downstream of Ras, the Raf serine/threonine kinases have emerged as the principal effectors of Ras in the mitogen-activated protein kinase (MAPK) pathway. This pathway has been the focus of considerable attention recently because of disappointing effects of therapy directed at Ras, particularly with the farnesyltransferase inhibitors. The Raf family consists of three genes A-raf, B-raf and C-raf. B-raf mutations have emerged as an important therapeutic target in melanoma particularly because b-raf mutations have been demonstrated in 60%–70% of melanomas and an even higher frequency of as much as 80% in benign nevi. The major mutation in B-raf, previously known as V599E now known as V600E, is caused by a thymidine to adenine transversion at nucleotide position 1796 in exon 11 or 15. Sorafenib is a small molecule Raf inhibitor previously known as BAY 43-9006 and is furthest along in clinical development in this class of drugs. It is a bi-aryl urea and potently inhibits activation of the MAPK pathway and ERK phosphorylation in human cancer cell lines. It is also a potent inhibitor of various receptor targeted kinases that are involved in tumor progression and angiogenesis including VEGFR-2, VEGFR-3 and platelet-derived growth factor. Phase I studies established a dose of 400 mg administered orally twice a day as the recommended phase II dose based upon dose related toxicities of diarrhea, skin rash, fatigue, hypertension and a hand-foot syndrome. Development of sorafenib has been unique in that because of the likelihood that this agent would produce stable disease and improvement in time-to-progression as opposed to a response, the principal trial design selected was a randomized discontinuation design. The major disease to have benefited in those early studies was renal cell carcinoma. This drug is now approved for that indication. Phase I studies were also done in combination with carboplatin and paclitaxel which demonstrated unexpectedly high activity in metastatic melanoma. Based upon this Flaherty and colleagues performed a phase II evaluation of sorafenib with carboplatin and paclitaxel in patients with metastatic melanoma and have shown results that appear to be promising with an overall 30% response rate and a median time-to-progression of 8.8 months. Based upon this randomized clinical trials are underway both in the first line and second line setting for patients with metastatic melanoma testing the combination of carboplatin and paclitaxel with sorafenib or with placebo in an effort to improve survival and time to progression.

Antiangiogenic Strategies: Current Trials
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Antiangiogenic cancer therapy has been frequently perceived as "magic bullet", capable to eventually cure any type of cancer. This unrealistic perception was largely based on overwhelming preclinical experiences with first generation antiangiogenic agents. Realistically, however, the goal of antiangiogenic cancer therapy is to inhibit the tumor's capacity to grow beyond considerable size. Hence, angiogenesis inhibitors are primarily expected to halt tumor progression and to induce disease stabilization. While sole inhibition of vascular endothelial growth factor (VEGF)-driven angiogenesis failed to increase survival in most advanced cancer patients, targeting VEGF in combination with standard chemotherapies has finally proved successful in prolonging overall survival of different types of metastatic cancer compared with standard chemotherapy alone. While simultaneous targeting of both vascular and cancer cells was mainly achieved by combining anti-VEGF monoclonal antibody bevacizumab with standard cytotoxic therapies, multitargeted small molecule tyrosine kinase inhibitors (TKIs) alone may increase survival of cancer patients, as they can affect pathways involved in both endothelial and cancer cell survival and/or growth. A variety of different clinical trials have been recently imitated in advanced melanoma patients that evaluate the impact of targeted antiangiogenic therapy by using bevacizumab and multitargeted TKIs (e.g., sorafenib, AZD2171), either alone or in combination with cytotoxic chemotherapy. The opportunities and obstacles of combinatorial growth factor- and growth factor receptor-targeted antiangiogenic approaches for malignant melanoma will be herein discussed with particular reference to selected ongoing clinical trials. In this regard, the development of broadspectrum TKIs constitutes a crucial strategy to delay or minimize resistance to antiangiogenic agents, as antiangiogenic TKIs may exert distinct complementary mechanisms of action that target also signaling of angiogenic molecules other than VEGF and affect both endothelial cells and other proangiogenic cell populations. Angiogenesis inhibitors are likely to change cancer therapies in the next decade; however, future standard treatment of cancers can be anticipated to still rely on the combinational use of conventional cytotoxic and/or cancer-directed targeted therapies.
Thymosin-Alpha: A New Immunomodulator
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Thymosin alpha-1 (Talpha1) is a 28-amino acid polypeptide, produced syntheti-
cally but originally isolated from thymosin fraction 5, a bovine thymus extract
containing a number of immunologically active peptides. It has multiple biological
activities primarily directed towards immune response enhancement; in vitro
studies have shown that Talpha1 can influence T-cell maturation and differentia-
tion, stimulate production of Th1 cytokines such as IFNalpha and IL-2, and activate
natural killer cell-mediated cytotoxicity. Talpha1 has been evaluated for its
immunomodulatory activities and related therapeutic potential in infectious
diseases and cancer. As a biologic response modifier, Talpha1 is clinically used
in combination with IFNalpha for patients with chronic hepatitis virus B and C
infection showing significant virological and biochemical response rates and being
well tolerated. It is believed to be useful to prevent liver cirrhosis and
hepatocarcinoma related to chronic viral hepatitis. In clinical trials, the addition
of Talpha1 to combination chemoimmunotherapy regimens has resulted in
significant improvement in response and survival times in different cancers such
as lung cancer, melanoma, leukemia, squamous cell carcinoma, colon cancer.
Finally, Talpha1 has also been shown to be helpful for reducing the adverse effects,
mainly hematological toxicity, of cytotoxic drug therapy in neoplastic patients.

Selective Electrochemical Tumour Ablation (SECTA) with Intralesional
Bleomycin
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To date, there is no recommended standard therapy for recurrent and inoperable
tumours of skin and soft tissue. While surgery, cryotherapy, radiotherapy, systemic
or intratumoral immunomodulating chemotherapy, are commonly used, management of skin
and soft tissue tumours can be a major challenge, particularly in cases of rapidly
progressive disease, and multiple recurrences. Intralesional therapy modalities
typically lack severe side effects and can be desirable alternatives. The therapeutic
efficacy of several intralesionally administered cytostatic agents and cytokines, such
as bleomycin, cisplatin, interferon-alfa, fotemustine, interferon-beta, GM-CSF and
IL-2 has been investigated with varying outcomes. SECTA delivers promising and
outstanding results. SECTA is a novel treatment, using pulsed electrical currents,
which enable the delivery of large molecules such as bleomycin into cells. The
efficacy and feasibility of this new treatment option has been reported for head and
neck tumours, various types of skin cancer, notably in malignant melanoma.
Depending on localisation and general health of patients, treatments were
administered on an outpatient basis or they were hospitalization for 1-3 days;
patients tolerated treatment well and objective response rates appear higher than
with other therapies, including intralesional bleomycin alone. To substantiate
SECTA in combination with intralesionally administered bleomycin, a prospective,
multicenter pre-marketing clinical trial for the treatment of cutaneous cancer is
currently being conducted at 19 centres throughout Europe. SECTA is an effective,
outpatient based, well-tolerated and minimally therapeutic option for patients
presenting with cutaneous and soft tissue tumours.