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Glivec for GISTS

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Gastrointestinal Stromal Tumours (GISTS) are rare tumours of the gastrointestinal tract, with a differing level of agressiveness, but always malignant which recur either locoregionally or develop livermetastases. No effective systemic treatment has hitherto been available. GISTS are characterised by an immunohistochemical assay positive for cell surface expression of KIT (CD117). STI 571 (Glivec®) in a small molecule, orally bioavailable drug, that inhibits BCR-ABL leading to responses in CML patients and has also been shown to inhibit KIT.

Two studies have hitherto been reported, a dose finding European study in 36 GIST patients (1) and a randomized phase II study in 84 patients (2).

In the phase I study the maximal tolerated dose appeared 800 mg. Only 4 of the 36 patients progressed in the first 28 weeks. Clinical improvement was observed in 24 of 27 pts (89%). Toxicity mostly mild observed included peripheral edema (52%), fatigue (50%), skin rash (41%), periorbital edema (41%), nausea and vomiting (30%), diarrhea (17%) and anorexia (17%), occurring mostly in the first 8 weeks and later fading away.

In the phase II study at 400 mg a PR of 50% (22/44), SD 28% (12/44) and PD 22% (10/44) and at 800 mg: PR 70% (28/40), SD 25% (10/40) and PD 5% (2/40) were observed.

PET scanning on day 8 in the European study and selected data of the American study herald a clinical response later as will be demonstrated at this meeting by Stroobants et al. An update of the clinical data will be given.

References

[1] van Oosterom et al, ASCO Proc. 20, abst. 2, 2001.
[2] Blanke et al., ASCO Proc. 20, abst. 1, 2001

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Induction of differentiation in liposarcomas via PPARgamma-developing a rational therapeutic strategy

Abstract not received.

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The new Melanoma staging system

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A completely revised staging system for melanoma has been approved by the American Joint Committee on Cancer as well as the UICC TNM Committee, the WHO Melanoma Program and the EORTC Melanoma Committee. Major revisions of the new melanoma staging system include: 1) melanoma thickness and ulceration but not level of invasion to be used in the T category (except for T1 melanomas); 2) the number of metastatic lymph nodes and the delineation of clinically occult (i.e.: "microscopic") vs. clinically apparent (i.e.: "macroscopic") nodal metastases to be used in the N category; 3) the site of distant metastases and the presence of elevated serum lactic dehydrogenase (LDH) to be used in the M category; 4) an upstaging of all patients with Stage I, II, and III disease when a primary melanoma is ulcerated. The ability to stage patients more accurately with sentinel node technology was demonstrated by the 20 to 29% differences in 10-year survival for patients with the same TNM criteria who had clinical vs. pathological staging of their lymph nodes. To validate the staging system, thirteen cancer centers and cancer cooperative groups contributed staging and prospective survival data for 17,600 melanoma patients with complete clinical, pathologic and follow-up information. In a multivariate analysis of 13,581 patients with localized melanoma, the two most powerful independent characteristics of the primary melanoma were tumor thickness and ulceration. For 1201 patients with lymph node metastases, the three most significant factors were: 1) the number of metastatic nodes 2) the tumor burden at the time of staging (i.e.: microscopic vs. macroscopic)); and 3) the presence or absence of ulceration of the primary melanoma. Among 1158 Stage IV patients, survival differences were significantly greater for skin, subcutaneous or distant lymph node metastases compared to lung metastases ($p=0.003$) or other visceral sites of metastases ($p<0.0001$). The new staging system, along with a validating multivariate analysis of 17,600 melanoma patients should now form the basis for statistical design and analysis of future melanoma clinical trials that will help determine future standards of care.

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Is there evidence based consensus on adjuvant therapy in stage II–III melanoma?

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Interferons are cytokines with various modulating effects on the inflammatory response. These pleiotropic effects may depend on the concentrations of IFN and include direct and indirect antitumor activities as well as recently recognized anti-angiogenic activity at relatively low doses of IFNalpha. For such a wide range of biologic activities it has been widely recognized that the dose for optimal biologic activity may differ greatly from the maximally tolerated dose. This leads to a difficult position to develop a strategy in clinical development in the absence of clear surrogate endpoints to identify active doses of IFN. It has resulted in a great number of empirical trials, each with its own hypothesis on dose and dose schedule, evaluating a wide range of doses of IFN in a wide range of clinical stages: from melanoma stage II, stage III and mixed stage II–III trials. With all this heterogeneity it comes as no surprise that the outcome of these trials has varied in all stages and has varied almost as widely as the dose range employed. It is remarkable that under these conditions IFN has, for lack of prove of clinical activity, has not been approved for treatment of patients with stage IV melanoma. In spite of this high dose interferon therapy has been approved in the adjuvant setting for high-risk melanoma both in the USA and in Europe, whilst low dose interferon therapy has been approved in Europe but rejected in the USA in the adjuvant setting for intermediate risk melanoma. All this reflects inconsistency in the outcome of trials, reflecting some, but a modest effect of IFN in the adjuvant setting.

Outcomes have been debated vividly but as of yet have not allowed for definitive conclusions on the efficacy or inefficacy of IFN in the management of malignant melanoma as no convincing data have been accumulted on its impact on overall survival in spite of a relatively consistent impact of relapse free survival.

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CD95(APO-1/Fas)-mediated apoptosis: regulation of life and death

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CD95, a member of the tumor necrosis factor (TNF) receptor superfamily induces apoptosis upon receptor oligomerization. The receptor and its ligand are important for apoptosis of peripheral T cells, for downregulation of an immune response and most likely, at least in part, also for peripheral T cell tolerance. In Aids, apoptosis mediated by this system might contribute to the depletion of T helper lymphocytes. Likewise, in diseases in which liver cells are destroyed the CD95 system might play a major role.

In a search to identify the intracellular signalling pathway of CD95 several molecules coupling to oligomerized CD95 were immunoprecipitated from apoptosis-sensitive human leukemic T cell and lymphoblastoid B cell lines. The following binding molecules were only associated with aggregated and not with monomeric CD95: phosphorylated FADD (MORT1) and caspase 8. Thus, caspase 8 was identified as the most CD95 receptor proximal protease which starts the cascade of protease reactions important for CD95-mediated apoptosis. Association of FADD and caspase 8 with CD95 was not observed with C-terminally truncated non-signalling CD95. FADD and FLICE did also not associate with a CD95 cytoplasmic tail carrying the lprcg amino acid replacement. FADD and caspase 8 form a death-inducing signalling complex (DISC) with the CD95 receptor and are, thus, the first CD95 associating proteins of a signalling cascade mediating apoptosis.The function of the DISC is discussed in detail, particularly with respect to its role in sensitivity and resistance to apoptosis.

The CD95 death system plays a role in destruction of liver tissue. In hepatitis cytotoxic T lymphocytes might use the CD95 system to kill infected hepatocytes. In M. Wilson copper overload leads to upregulation of the CD95 ligand that may finally contribute to acute liver failure. In HCC from patients treated with chemotherapeutic drugs the CD95 receptor and ligand are upregulated and may contribute to apoptosis of the tumor or, dependent on the drug sensitivity of the tumor, to the status of the tumor as an immunoprivileged site.