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Gemcitabine-based therapy for leiomyosarcomas? For All?

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Current treatment options for recurrent or advanced leiomyosarcoma (LMS) of the uterus or other organs are limited. Although approximately 60% of women with uterine LMS present with disease limited to the uterus, cure rates range only from 20% to 60%. Patients with advanced-stage LMS and patients with recurrence after initial resection have a poor prognosis. Except for rare cases of resectable, isolated pulmonary metastases, such patients are not considered curable. In addition, few chemotherapy agents have been identified with activity against LMS. Single agents that demonstrate moderate activity in LMS include ifosfamide (response rate, 17%), intravenous etoposide (11%), doxorubicin (25%), trabectidin (10%), and gemcitabine (7%). Combination chemotherapy regimens with activity in previously untreated patients include hydroxyurea, dacarbazine and etoposide (overall response rate, 18%), doxorubicin plus ifosfamide (response rate, 30%), gemcitabine plus docetaxel (response rate, 16−53%). The duration of response is short, from 6 to 14 months. More recently, topotecan or vinorelbine have been tested, but without success. Finally, doxorubicin and ifosfamide, either alone or in combination, have served as the backbone for metastatic sarcoma therapy for over 15 years. With the limited number of drugs available for LMS, there has been an ongoing search for new agents, be they cytotoxic or cytostatic. Gemcitabine, with its novel mode of action and already proven activity in several other solid tumours, has been evaluated in an open non-randomised multicentre phase II trial published in 2002. The drug, given at the above described dosage and schedule, is not very effective in with advanced STS. However, its activity in histological subtypes of STS cannot be excluded. Other phase II studies have been conducted in soft tissue and bone sarcomas. These have generally involved gemcitabine, such as the U.S. Food and Drug Administration – approved bolus schedule, and have shown only low response rates. Collectively, uterine leiomyosarcoma is clearly more sensitive to gemcitabine than other histological types, even leiomyosarcomas from other sites, and other histological types may occasionally respond to treatment. Other phase II trials testing gemcitabine in association with docetaxel have shown that the combination is highly active in patients with LMS, with an overall response rate of 53%. Similarly, post-resection gemcitabine-docetaxel treatments for stages I−IV high-grade uterine leiomyosarcomas have yielded 2-year progression-free survival rates that appear superior to historical rates. A comparison of all trials including both uterine and other leiomyosarcomas, with careful stratification for known prognostic factors, would potentially be useful to determine if gemcitabine (alone or in combination) ensures efficient treatment of all leimyosarcomas. In this presentation, we review the data regarding drug pharmacology and all available clinical trails (phase II & III studies) as a rationale for the use of gemcitabine alone or in combination. The studies reviewed concern specific subtypes like LMS (uterine or non uterine) possibly most sensitive to gemcitabine than other subtypes. Other compounds, such as trabectidin or anti-angiogenic agents evaluated in phase II studies, are presented with the objective to delineate the possible place of each drug in the treatment of LMS.

References

Hensley et al., 2009; Hensley et al., 2008; Hensley et al., 2008; Hensley et al., 2002; Look et al., 2004; Bay et al., 2006; Maki, 2007; Svancarova et al., 2002; Leu et al., 2004; Amant et al., 2009.

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Tyrosine-kinase inhibitors in very rare sarcoma subtypes

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Recent progress in the understanding of the biology of soft tissue sarcomas and locally aggressive connective tissue tumors have enabled the identification of distinct molecular and pathological entities: six molecular subgroups of connective tissue tumors may be distinguished: (1) sarcoma with specific translocations generating fusion gene whose protein products modulate transcription or may act as growth factors (e.g. EWS/Fli1 in Ewing sarcomas, PDGF-col1a1 in DFSP); (2) sarcomas with mutated activated kinases (KIT in GIST); (3) sarcomas with deletion of tumor suppressor genes such as NF1 sarcomas, or rhabdoid tumors (INI1); (4) Sarcomas with simple genetic alterations (mdm2/cdk4 amplification in WD/DD liposarcomas; (5) Sarcomas with gross genetic alterations (e.g. leiomyosarcomas); (6) Tumors with alterations of the intercellular adhesion pathways (aggressive fibromatosis with APC deletion or b catenin mutations). This classification is rapidly evolving. The identification of the “driver” mutation in some of these diseases paved the way for the selection of efficient targeted therapies. One of the most demonstrating examples is the identification of KIT and PDGFRA kinase mutations in GIST which led to the development of imatinib, sunitinib nilotinib or agent promoting kinase destruction (IPI504). Other examples are currently avaialble. Imatinib is active in DFSP, a PDGF driven tumor and in pigmented villonodular synovitis (PVNS), an M-CSF driven tumor with. Within the 1st molecular subgroup of tumors, in Ewing sarcoma, whose fusion gene product regulates IGFBP3, anti-IGF1R Ab yielded responses in now several phase I and II trials. Treatment of giant cell tumor of the bone with denosumab is an other example of this successful approach. The understanding of the driver molecular alterations of these tumors paved the way for the development of targeted treatment inhibiting driver mutations. In this presentation, we will describe several examples of successful treatment designed through a rationally based approach in these rare tumiors.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
Innovations in early clinical trials

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Phase 0 clinical trials: facts and promise

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Despite some recent improvements, there is still a significant attrition rate in cancer drug development. Several proposals to perform more efficient early clinical trials have been proposed. One approach is exploratory IND (ExpIND) and a subsequent phase 0 trial. One of the main caveats that have been raised regarding this kind of trials is the lack of therapeutic intent.

In this session we will describe what defines a Phase 0 trial, what types of Phase 0 trials have been proposed, and how they could aid in the design and potential success of subsequent larger phase I to II trials. For this, we will discuss the results of the first Phase I trial in Oncology (with ABT-888) into the context of the development of Poly(ADP-ribose) polymerase (PARP) inhibitors.

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Use of biologics in drug development

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Over the past several years significant advances have been made in our understanding of a growing number of critical pathways involved in human cancer. These advances have led to the development of novel therapies that are being collectively known as molecularly targeted in order to highlight their specificity and their interference with key molecular events responsible for the malignant phenotype. Examples of approved targeted agents include agents directed against the human epidermal growth factor receptor 1 (EGFR) such as gefitinib, erlotinib and cetuximab, against the human epidermal growth factor receptor 2 (HER2) such as trastuzumab and lapatinib and the anti-VEGF bevacizumab. The clinical development of these agents will require a new set of skills and a greater degree of complexity when compared to conventionally developed chemotherapeutic agents. In recent years, we have witnessed growing interest in the methodology of clinical trials with these molecular-targeted agents and alternative endpoints have been proposed. They include the identification of a ‘target effect’, the measurement of ‘surrogates’ for biological activity, safety issues, selection of the patient population most likely to benefit, early evaluation of activity for potentially useful drugs when significant tumor shrinkage cannot be demonstrated and early readouts of clinical benefit.

In conclusion, many important questions regarding the methodology of clinical research with target-based agents remain open and need to be defined by research in the near future.