Clinical features of Ewing and chondrosarcoma

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Chapter 10

Summary

Ewing sarcoma and chondrosarcoma are two of the most common forms of primary malignant bone sarcoma, osteosarcoma being the third. They are rare forms of cancer with an incidence of less than a thousand new patients diagnosed with sarcoma in the Netherlands each year. For patients with surgical treatment options the diagnosis is good. However if they presents themselves with or develop metastatic disease the outcome is poor.

Ewing sarcoma affects mostly children and adolescents with a peak incidence at age 15. It is characterized by a chromosomal translocation involving the EWSR1 gene on chromosome 22 and an ETS transcription factor gene, with EWSR1- FLI1 being the most common fusion protein.

In the last decades the outcome for patients with Ewing sarcoma has not improved greatly. Conducting phase I/II studies is import in order to develop proof of principle for new treatment strategies. **Chapter 2** gives an overview of the peer reviewed studies enrolling Ewing sarcoma patients between 1990 and 2010. In this time period two phase I and six phase II were published which enrolled only Ewing sarcoma patients. No trials for Ewing sarcoma patient were published between 1990 and 1999 but we found an increasing number of early phase trials in the following years. The results of the trials were disappointing, 9.5% of all Ewing sarcoma patients enrolled achieved a complete response, 7.5% had a partial response and 3% stabile disease. More trials were performed which enrolled patients with all forms of sarcoma or solid tumours. The results of these trials are difficult to translate to patients with a specific form of cancer.

For patients with metastatic or relapsed Ewing sarcoma new treatment strategies are urgently needed. Two interesting targets for potential therapies are the insulin-like growth factor 1 receptor (IGF-1R) pathway and the poly ADP ribose polymerase (PARP). Current knowledge of these pathways are summarized in **chapter 3**. Activation of the IGF-1R pathway results in stimulation of cellular proliferation, cell motility and inhibition of apoptosis. The IGF signalling pathway has been implicated in malignant transformation and disease progression. Higher plasma concentrations of IGF1 are associated with increased cancer risk. It is interesting that the peak incidence of Ewing sarcoma correlates with the increased levels of the IGF ligands in puberty. Several clinical trials have been conducted to evaluate the efficacy of IGF-1R inhibition in Ewing sarcoma patients. The results of these trials were disappointing and further development was stopped. Possibly the wrong patient population was treated. Another option is to treat the patients with a dual IGF-1R and IR inhibitor, preventing possible of the cells in which they switch from IGF-1/IGF-1R

to IGF-2/IR-A signalling. A phase II trial with a dual inhibition antibody is currently being conducted and we eagerly await the results.

PARPs are a family of proteins which are activated upon DNA damage. If PARP is inactivated cells are more prone to go into apoptosis upon DNA damage. EWSR1-FLI1 positive Ewing sarcoma cell lines and xenografts were shown to be highly sensitive to PARP-1 inhibition. Since this discovery in 2012, the results of one clinical trial were published. Unfortunaly no complete or partial responses were seen. Preclinical work suggests that better results can be expected with combination treatment but this needs to be tested in clinical trials.

For patients who develop relapsed or refractory Ewing sarcoma several palliative chemotherapy treatment regimens are being used. In several sarcoma centers in Europe these patients are treated with the combination of etoposide and carboplatin or etoposide and cisplatin. There is no published literature on the effect of this combination treatment. A retrospective analysis of the survival data for these patients is reported in **chapter 4**. The data of 107 patients were collected, 61 were treated with carboplatin-etoposide and 46 with cisplatin-etoposide. The median overall survival is 23 months for both groups. Response rate in the carboplatin-etoposide treatment group was 51%, with a progression free survival of 14.5 months. In the cisplatin-etoposide group the response rate was 29% and a progression free survival of 6.3 months. Comparing the outcome data of this analysis to published data of other palliative treatment regimens, we conclude that it is a good additional treatment option in this patient population.

Epigenetic changes were found to play an important role on the onset and development of cancer. Gene expression is being influenced by these changes, without altering the nucleotide sequence of the DNA. Gene transcription is being regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) by modification of chromatin, which plays an important role in wrapping of DNA. Up-regulation of HDAC's are associated with silencing of tumour suppressor genes and oncogenesis. Several preclinical studies suggest that HDAC inhibition may be a new treatment option for Ewing sarcoma. For example, it was found that expression of EWSR1-FLI1 results in an upregulation of HDAC and hereby inactivation of the p53 pathway. In **chapter 5** a case of a patient with metastatic Ewing sarcoma who was treated with a HDAC inhibitor is described. The patient had progressive disease prior to start of the treatment and was treated with panobinostat monotherapy three times a week. After 20 days of treatment a low thrombocyte count was found and a switch was made to three times a week every other week. Two monthly CT-scans showed stabile disease for a duration of eighteen months. Clinical trials conducted for other solid tumours showed that combination treatment with chemotherapy may improve the results further. New clinical trials should be conducted to search for synergistic combinations of panobinostat and chemotherapy.

Chondrosarcoma is a more heterogeneous group of tumours that have in common the production of chondroid matrix. It affects mostly adults over 40 years of age. Chondrosarcoma consist of different subtypes, conventional being the most common and mesenchymal, dedifferentiated a clear cell the more rare forms.

Chondrosarcoma is a very rare disease and metastatic or unresectable disease is even more uncommon. Because of this conducting early phase clinical trials for patients diagnosed with chondrosarcoma is very difficult. Chapter 6 gives an overview of clinical trials and retrospective studies published between 2000 and 2013. A total of 31 studies enrolling 1 or more chondrosarcoma patients were identified, 11 phase I, 11 phase II and 8 retrospective studies. No phase III trials enrolling chondrosarcoma patients were published. For a long time chondrosarcoma was thought to be insensitive to chemotherapy and radiotherapy. However, several retrospective studies show that this is not correct and these patients may have a survival benefit. New trials need to be conducted in which drugs are tested with a sound biological rational.

For patients with advanced unresectable chondrosarcoma the predicted survival and benefit of treatment for this survival remains unclear. In chapter 7 data from two large sarcoma centers in Europe treating these patients was collected retrospectively. All patients diagnosed with unresectable central chondrosarcoma in either the Rizzoli Institute in Bologna Italy or Leiden University Medical Centre in Leiden the Netherlands between 1-1-1980 and 31-12-2011 were selected. A total of 171 patients were enrolled in this study. Overall survival for all patients was 48% at 1 year, 24% at 2 years, 12% at 3 years, 6% at 4 years and 2% at 5 years. Patients with only local unresectable disease had a significant better overall survival compared to patients with metastatic disease. The overall survival was significant better for patients who received systemic treatment versus the patients who received no treatment. This is in line with the changing opinion and published preclinical and clinical trials that chondrosarcoma patients due benefit from systemic treatment.

From previous studies it became clear that for patients diagnosed with chondrosarcoma histological subtype is a prognostic marker for overall survival. However, all patients are treated with the same regimens. Chapter 8 gives an overview of patients with unresectable chondrosarcoma, the different treatment regimens used and the outcome data. Retrospectively, the data was collected from patients treated in four sarcoma centers between 1980 and 2016. The data of 112 patients was collected, 50 (45%) with conventional, 25 (22%) mesenchymal, 34 (30%) dedifferentiated and 3 (3%) clear cell chondrosarcoma. No complete responses according to RECIST criteria were seen after the first treatment line. Seven patients had a partial response, one patient diagnosed with conventional, four with mesenchymal and two dedifferentiated chondrosarcoma patients. All these patients

were treated with a chemotherapy based regimen. The mean progression free survival and overall survival were respectively 11 and 87 months for patients diagnosed with conventional chondrosarcoma, 16 and 62 months for mesenchymal, 15 and 32 months for dedifferentiated and 10 and 16 months for clear cell chondrosarcoma. In line with previous studies the patients from our cohort with conventional or mesenchymal chondrosarcoma subtype had a better outcome than patients with dedifferentiated chondrosarcoma. The same treatment regimens gave different outcomes for the four subtypes, indicating that they should not be considered the same disease and should not be treated equally.