Retrospective studies in mesenchymal tumours: clinical implications for the future

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English summary

This thesis consists of several retrospective studies in mesenchymal tumours. As mesenchymal tumours are rare, the use of all available data is essential for a rapid progress of scientific research without the need of large patient groups. Although retrospective studies have their limitations, these studies use the available patient data as much as possible. The results of the retrospective studies in this thesis will improve the design of future studies and daily patient care.

Soft tissue tumours

Desmoid-type fibromatosis

Chapter 2 studies the non-surgical treatment of desmoid-type fibromatosis, a disease with a highly variable natural behaviour. Based on pathology reports from PALGA, the Dutch nationwide pathology registry, this study shows that the incidence of non-surgical treatment has increased between 1993 to 2013 from 0.6% to 12.8%, but that surgery is still the primary treatment in most patients. The study shows a favourable outcome in patients with active surveillance or treated with radiotherapy or with systemic therapy. Because of the rarity of the non-surgical treatments and the variable natural behaviour of this disease, these results should be interpreted with care, but provide a base for further studying non-surgical treatments.

Chapter 3 focusses on a potential side effect of radiotherapy as one of the established treatment modalities in desmoid-type fibromatosis. Radiotherapy has shown an 80% control rate with an average dose of 56 Gy. This study reports six unique cases of radiation induced sarcoma from four different referral hospitals which indicates that these radiation induced sarcomas arising in desmoid–type fibromatosis are extremely rare. It was investigated whether these sarcomas occurring after radiotherapy originate from the desmoid-type fibromatosis or from the surrounding tissue. The results show that sarcomas occurring after radiation of desmoid-type fibromatosis can develop as a new primary sarcoma (not harbouring a CTNNB1 mutation, which was present in the desmoid-type fibromatosis) or as a malignant transformation of the desmoid-type fibromatosis (retaining the CTNNB1 mutation). We did not find an association between the type of CTNNB1 mutations and a higher risk of a radiotherapy induced sarcoma.

Gastro-intestinal stromal cell tumour

In **chapters 4 and 5** gastro-intestinal stromal cell tumours (GIST) are studied. GISTs are the most frequent mesenchymal tumours of the gastrointestinal tract. This rare tumour has a relatively favourable prognosis due to treatment with tyrosine kinase inhibitors, such as imatinib, sunitinib and regorafenib. The discovery of CD117 (KIT) and later DOG-1 as immunohistochemical markers for GIST enabled pathologists to distinguish GIST more easily as a separate entity and so it could also be studied as

separate entity for drug trials. The introduction of imatinib made it even more important to diagnose GIST correctly. A Dutch nationwide population based study on the incidence of GIST was published in 2005 and showed a reported incidence of 12.7 patients per million inhabitants. As incidence numbers are important for both health care planning and study design, **chapter 4** studied the development of the incidence of diagnosed GIST between 2003 and 2012, showing an increase from 12.2 to 17.7 patients per million inhabitants per year. Improvements in diagnostic procedures and increased awareness are probably at least partially the cause for this increase. A real increase in the incidence is also possible, but causal or risk factors for GIST are not known. This study also evaluates the adherence to the current ESMO (European Society for Medical Oncology) guidelines and shows that only a minority of patients had pathology revision in a reference centre and/or mutation analysis. Both increased for tumours with a higher risk of metastases. Due to the importance of a correct diagnosis of GIST for a good prognosis, it is important to adhere to these guidelines.

Chapter 5 reports our experience with imatinib-induced agranulocytosis in patients with metastatic GIST. In general imatinib has limited side effects and is well tolerated. Although neutropenia is rare, imatinib is the most effective drug in GIST and it is important to continue treatment if possible for the best overall outcome. In three Dutch GIST reference centres, four patients were identified. All four patients showed rapid and full recovery after the discontinuation of imatinib. Several treatment options for the prevention of a recurrence of this side effect are discussed such as dose reduction, cotreatment with prednisolone and granulocyte colony stimulating factor. The study suggests a possible management algorithm for imatinib induced agranulocytosis.

Soft tissue sarcomas

The next four chapters **(chapters 6, 7, 8 and 9)** discuss studies in soft tissue sarcoma. Soft tissue sarcomas are a group of rare tumours originating from connective tissue, such as muscles, adipose tissue, nerves and so on. **Chapter 6 and 7** are two retrospective European Organisation for Research and Treatment of Cancer (EORTC) database studies. **Chapter 6** describes the differences in survival between patients with locally advanced disease, patients with distant metastatic disease only and patients with both locally advanced disease and distant metastases. **Chapter 7** reports the survival after completing doxorubicin monotherapy as first line palliative treatment in soft tissue sarcomas and provides data on overall survival and progression-free survival in patients completing at least 6 cycles of doxorubicin treatment.

Because of the rarity of soft tissue sarcomas these tumours are often studied as one group, despite differences in prognosis for different histologic subtype and other prognostic factors. **Chapter 6** shows an important difference in overall survival, progression free survival and overall response rate between patients with only locally advanced disease versus patients with only distant metastatic disease versus patients

with both locally advanced and distant metastatic disease. Prognostic factors, such as time since initial diagnosis, localization of primary tumour, histologic subtype and performance status, had a different impact between the different disease stage groups. Prospective validation of these results is necessary.

To improve prognosis of patients with soft tissue sarcoma new treatment strategies are studied, such as maintenance treatment after first line doxorubicin. **Chapter 7** describes the overall survival and progression free survival of patients completing 6 cycles of doxorubicin without progression. This data is essential when designing these maintenance studies. The study shows that only approximately 36.6% of all patients treated with first-line doxorubicin qualify for maintenance treatment. The progression free survival of 8.7 months and the overall survival of 20.1 months after randomisation is much longer than the commonly reported progression free survival and overall survival, but this is due to the selection of responding patients. However, this increased survival for these patients should be accounted for in maintenance trials.

One of the new drugs in the treatment of soft tissue sarcoma is pazopanib, a tyrosine kinase inhibitor, that has shown a 3 months increase of progression free survival compared to placebo. **Chapters 8 and 9** report adverse events of pazopanib: hepatic toxicity and pneumothorax. Hepatic toxicity is one of the major adverse events causing treatment discontinuation. **Chapter 8** describes a patient with an endometrial stromal sarcoma and liver function test abnormalities**.** In this patient the dose was reduced in several steps to 200 mg every second day (usual dose 800 mg/day). In this dose, treatment was still effective with a time on treatment of 9 months. This report suggests that dose reduction lower than the recommended minimal dose of 400 mg per day can be safe and effective in patients with hepatic toxicity. This study also reports a remarkable long progression free survival in a patient with endometrial stromal cell sarcoma treated with pazopanib.

Pneumothorax as side effect of pazopanib is studied in **chapter 9.** It reports the development of a spontaneous pneumothorax in six patients treated with pazopanib for a soft tissue sarcoma. The incidence of spontaneous pneumothorax as side effect in patients treated for soft tissue sarcoma was estimated to be 14% in our centre. Literature suggests this side effect to be sarcoma specific as it is not reported in other cancers. In all patients reported in this study pleural or subpleural metastases were present and some of these showed necrosis, which could be the cause of the occurrence of the pneumothorax. The treatment of the pneumothorax was difficult, probably because pazopanib inhibits VEGFR 1, 2 and 3 (Vascular Endothelial Growth Factor Receptor).

The results of **chapter 8 and 9** are important as these chapters report new side effects or new treatments for side effects of a relatively new drug.

Bone tumours

The last part of the thesis focuses on two rare bone tumours: giant cell tumours of bone (GCT-B) and osteosarcoma.

Giant cell tumour of bone

GCT-B is an intermediate, locally aggressive tumour causing a lot of morbidity. Denosumab, a monoclonal antibody against RANKL (receptor of nuclear factor kappa-B ligand), was recently introduced as treatment for GCT-B. Until now, the incidence of GCT-B is not exactly known. **Chapter 10** reports the results of a study on the incidence of GCT-B in the Netherlands based on the Dutch nationwide pathology registry, PALGA. The incidence is approximately 1.7 patients per million inhabitants in the Netherlands. The median age of patients was 35 years (range 9-77) and the tumours were most commonly localized in the femur (35%) and tibia (18%). The incidence of local recurrence was 0.40 patients per million inhabitants per year. The incidence we report is higher than previously reported in literature, probably due to the use of PALGA, which covers all Dutch pathology reports and is archiving these automatically. The data of this study help to plan care for these patients and to plan future research.

Osteosarcoma

Although osteosarcoma is the most common malignant bone tumour, it is still very rare. First line treatment with doxorubicin and cisplatin with or without methotrexate is well defined, but second line treatment is not well-established. Several regimens are used. In the Leiden University Medical Center ifosfamide is currently used as a second line treatment, but literature lacks data on overall and progression free survival. **Chapter 11** reports the results of ifosfamide monotherapy in the Leiden University Medical Center. Sixty-two patients treated with ifosfamide monotherapy were identified in the Leiden University Medical Center treated with an intended dose of 5 g/m^2 or 9 g/m^2. This study shows an improvement in overall survival for patients treated with 9 g/m^2 compared to 5 g/m^2 in univariate analysis (10.9 versus 6.7 months resp.), but not in multi-variate analysis. Progression free survival was not significantly different, but showed a trend towards a better PFS for the intended dose of 9 g/m^2 compared to 5 g/m^2 (3.8 vs 2.1 months resp.). One of the other important results of this study is the prognostic impact of WHO performance status, i.e. a better performance status is associated with a better survival. This study can be used as benchmark for future studies, when comparing new treatment options in phase II studies.

Discussion and future perspectives

Chapter 12 summarizes the evidence generated in the retrospective studies reported in this thesis and discusses the results of the separate studies against the background of the other studies of this thesis and the current literature. It also describes future perspectives for sarcoma research and daily patient care.