Multiple aspects of a plasma cell dyscrasia

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CHAPTER 9

Summary, discussion and future perspective
Summary

Plasma cell dyscrasia and related diseases include a variety of disorders, all arising from monoclonal plasma cells in the bone marrow, but with variations in clinical presentation. Multiple Myeloma (MM) is the most frequently diagnosed plasma cell dyscrasia. Treatment is initiated when the CRAB criteria are met or when high-risk features are presented. Lytic bone lesions are an important source of morbidity in patients with MM. In recent years, bone lesions have been diagnosed more effectively with CT imaging and different nuclear tracers (radiopharmaceuticals). Treatment of MM has also improved substantially during the last decade. Much research has focused on optimization of diagnostic tests, treatment options and response monitoring.

Besides MM, several rare diseases are also linked to plasma cell dyscrasia which can be accompanied by severe clinical symptoms. Due to their rarity, they are frequently unrecognized and difficult to diagnose. Most frequently these diseases are treated with agents targeting the malignant plasma cells.

The aim of this thesis is to evaluate several aspects of malignant plasma cell disorders based on new imaging techniques and treatment regimens.

Chapter 2 provides a review of the various nuclear tracers that can be used to visualize MM activity in patients. Nuclear imaging techniques can be used not only for diagnostic purposes but also for response monitoring. Nuclear tracers have been developed to detect bone lesions, including the bone marrow and the extramedullary compartment. The properties of nuclear imaging enable the identification of specific cellular properties of the malignant plasma cells. For example, [18F]-FDG-PET recognizes the glucose metabolism and can be used not only as diagnostic test but also for treatment monitoring.

Chapter 3 describes the osseous involvement of MM defined with the use of whole body X-ray (WBX), [18F]-FDG-PET and somatostatin receptor scintigraphy (SRS). High expression of somatostatin receptors can be seen on malignant plasma cells. The use of WBX is limited by the fact that more than 30% of the trabecular bone must be lost before lesions can be visualized. The lesions also persist following chemotherapy, thereby limiting its usefulness during the treatment of relapsing disease. The purpose of the study presented in this chapter is to identify the most optimal technique for detecting skeleton lesions in patients with relapsing MM. The results indicate that SRS detects more lesions than WBX, but that [18F]-FDG-PET is more valuable than WBX and SRS.
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Chapter 4 reports on a study in which [18F]-FDG-PET and [18F]-Fluoroazomycin arabinoside ([18F]-FAZA) were used to demonstrate whether positive lesions on the [18F]-FDG-PET scan have a low oxygen content reflected by an increased uptake of [18F]-FAZA. In addition immunohistochemical stainings on bone marrow biopsies were performed to determine whether [18F]-FDG-PET uptake coincides with angiogenesis-related tumor hypoxia. The results showed that [18F]-FDG-PET can detect focal lesions, but increased hypoxia cannot be shown by [18F]-FAZA scans. Immunohistochemical stainings showed that increased HIF-2α expression in a high number of patients occurs in conjunction with an increase in MVD and elevated expression of VEGF, suggesting that the HIF signaling pathway was activated. Different expression patterns of HIF-1α and HIF-2α have been described, suggesting different roles for both factors. It has been proposed that HIF-1α increases directly in response to hypoxia, while HIF-2α is responsive during prolonged period of hypoxia. Furthermore, alternative pathways can be activated due to oncogene activation or mutations that trigger the expression of HIFs.

In Chapter 5 a study in relapsing MM patients with combination therapy of bortezomib, dexamethasone and low-dose oral cyclophosphamide as induction regimen followed by one year of maintenance therapy consisting of bortezomib and cyclophosphamide is described. Maintenance therapy might be an effective and tolerable manner to improve PFS. The study demonstrates that treatment with bortezomib, dexamethasone and low-dose cyclophosphamide is an effective and manageable regimen. Adding one year of maintenance therapy was feasible, with limited side effects and an increased response rate.

Thrombose prophylaxis is generally given to MM patients who are treated with an IMID-containing regimen, but the efficacy of this approach in real life setting is not well defined. Chapter 6 reports on a retrospective analysis that was performed in an unselected patient population to determine real-life incidence of VTE in newly diagnosed MM patients treated with different anti-myeloma regimes, with and without thromboprophylaxis. The data showed that VTE risk during real-life MM treatment is unacceptably high at 15%, with similar rates in all first line treatment regimens with and without thromboprophylaxis.

The final part of this thesis highlights rare plasma cell dyscrasias. Chapter 7 describes a dataset of patients with plasmacytoma that was collected in a population-based registry in the northern region of the Netherlands. Progression to MM and prognostic features for progression to MM were scored, including analyzing angiogenesis parameters in the tumor. This population-based study demonstrates that solitary bone plasmacytoma patients are at high risk of developing MM following local radiotherapy. Except for localization, no other parameters could be defined for predicting progression to MM.
Chapter 8 describes the clinical presentation and treatment options of patients with scleromyxedema. This disease mimics systemic sclerosis with a wide range of systemic manifestations. The most intriguing finding is the presence of an M-protein; this is why scleromyxedema patients are frequently treated with regimens that are also used for MM patients. In this chapter, a patient is described who was treated with thalidomide and dexamethasone, followed by ASCT. After 7 years, the patient is still in complete remission, thus supporting the policy for early intensive treatment for this patient group.
Discussion, future perspectives and conclusions

In recent years, the diagnostic approach to multiple myeloma (MM) has shifted, with CT-imaging increasingly being used for the detection of lytic bone lesions. CT imaging has several advantages compared to whole body X-ray. It can be performed easily, more lesions are detected including extramedullary lesions and its use is not dependent on kidney function, as no intravenous contrast is required. A disadvantage, however, is that this imaging modality cannot be used to monitor disease activity, with old lesions remaining visible for a long time on CT scans.

Nuclear imaging is a unique whole-body imaging technique for visualizing and quantifying the molecular properties of disease activity. Nuclear imaging is particularly helpful for distinguishing between old and new lytic bone lesions in relapsed MM. This thesis describes several tracers that can be useful for detecting bone lesions in relapsed MM. [18F]-FDG-PET is the most commonly used metabolic tracer; it detects more new bone lesions than WBX, can be used to monitor disease activity, and can be of particular value in MM patients with limited disease specific-markers, such as M-protein or free light chains. Despite the diagnostic advantage of [18F]-FDG-PET in MM patients, 20% to 25% of the patients have a negative [18F]-FDG-PET scan despite the presence of symptomatic MM. This is likely due to the low tumor burden or lack of osseous involvement, with lesions remaining below the detection threshold of [18F]-FDG-PET. Large cohort studies have indicated that >3 focal lesions on the [18F]-FDG-PET is a poor prognostic marker, suggesting that a negative [18F]-FDG-PET scan may be a favorable prognostic marker. However, recent data have compared [18F]-FDG-PET and diffusion-weighted magnetic resonance imaging with background signal suppression (DWIBS). In 11% of the cases, DWIBS was positive but [18F]-FDG-PET was negative. Extensive research showed that expression of the gene encoding for Hexokinase-2 was significantly lower in PET “false” negative cases. This gene encodes the first step of glycolysis and may explain the negative [18F]-FDG-PET findings. Thus, caution should be observed when drawing conclusions based on a negative [18F]-FDG-PET scan. More sensitive or myeloma-specific tracers are required to provide better markers for myeloma activity.

Alternative tracers that can target other cell biological properties of the malignant plasma cells are currently available. Studies with 11C-Methionine (11C-MET) has shown that this imaging technique can detect more bone lesions compared with [18F]-FDG-PET, particularly when a low number of aberrant plasma cells are present in the bone marrow. Based on these properties, 11C-MET seems a promising tracer for detecting active bone lesions in patients with a negative [18F]-FDG-PET scan. However, there are constraints on the widespread use of 11C-MET due to its relatively short half-life of approximately 20 minutes, which necessitates production by an on-site cyclotron.
A more interesting approach is the use of more specific tracers targeting myeloma. Plasma cells have very high CD38 expression. Daratumumab, a monoclonal antibody against CD38, is now widely used in studies for treating MM. It would be interesting to see whether scanning with radiolabeled anti-CD38 can provide better and more myeloma-specific imaging than [18F]-FDG-PET, particularly in FDG-negative cases. A disadvantage may be that CD38 is still not fully myeloma-specific. For example, several white blood cells, including CD4\(^{+}\), CD8\(^{+}\), B-lymphocytes and natural killer cells, express CD38 at relatively low levels which may result in false positives. Another potential treatment option involves radio-immunotherapy using therapeutic radioactive labeled (e.g. Lutetium-177) anti-CD38. One concern is that excessively high radioactivity exposure of the adjacent bone marrow may also affect other hematopoietic cells. Further research with radiolabelled anti-CD38 and radio/immunotherapy is needed to address these questions.

This thesis describes the use of somatostatin receptor scintigraphy (SRS) SPECT and compares it to [18F]-FDG-PET. SRS-SPECT was inferior to [18F]-FDG-PET for detecting focal bone lesions. However, SRS-SPECT is limited by the moderate resolution of SPECT compared with PET. New [68Ga]-labeled somatostatin receptor based PET compounds are currently available that provide better imaging techniques for these receptors. Studies in the diagnostic work-up for neuroendocrine tumors (NET) with somatostatin labeled PET compounds have shown that [68Ga]-DOTA-TOC/-TATE/-NOC/-lanreotide PET/CT has superior resolution and thus better sensitivity than conventional SRS-SPECT, replacing SRS-SPECT for staging NET by PET/CT. As somatostatin receptors are highly expressed on malignant plasma cells, [68Ga]-DOTA subtypes are potentially diagnostically useful in MM.

MRI is frequently used in the diagnostic process of MM, particular for the spine and pelvis. MRI has a high sensitivity for visualizing focal and, more specifically, diffuse plasma cell infiltration of the bone marrow.

The role of novel MRI sequences is another area for further study. Diffusion weighted imaging (DWI) and delayed contrast enhancement (DCE) seem to improve the diagnostic properties of MRI in MM patients. Furthermore, nuclear imaging techniques can be combined with the MRI, for example FDG-PET/MRI, which combines metabolic information with anatomical information from the MRI. [18F]-FDG-PET/CT has been compared to FDG-PET/MRI in MM patients. Lesions detected with [18F]-FDG-PET/CT were also detected by FDG-PET/MRI, but whether this provides better diagnostic and prognostic value requires further evaluation. Response monitoring with MRI is difficult, but is improved when combined with PET. PET/MRI systems are not yet widely available, and further investigation and optimization of PET/MRI protocols is needed.
New quantification methods using [18F]-FDG-PET are currently available. Total lesion glycolysis (TLG) and metabolic tumor volume (MTV) can be calculated using [18F]-FDG-PET and may be more accurate than conventional SUV measurements for predicting overall tumor burden of focal lesions in MM. Initial data for TLG and MTV in MM are available. TLG and MTV were strongly associated with overall survival (OS) and progression-free survival (PFS), making them interesting prognostic markers\(^2\). International guidelines need to be developed to standardize TLG and MTV calculation in order to use these data in clinical research and trial settings.

Due to the continued development of novel agents, treatment response in MM continues to improve. Monitoring treatment response has also improved over the years. Detection of minimal residual disease (MRD) in the bone marrow is possible, for example using multiparametric flow cytometry immunophenotyping or next-generation sequencing. However, plasma cell infiltration of the bone marrow in multiple myeloma can be patchy, thus increasing the risk of a false negative MRD assessment. Nuclear imaging can be used to evaluate and monitor response to treatment by detecting metabolic activity over the whole body. Data on response evaluation after treatment, both autologous stem cell transplantation (ASCT) and chemotherapy only, show that a negative [18F]-FDG PET/CT scan is associated with prolonged time-to-progression compared to patients with a positive [18F]-FDG PET/CT for ASCT-eligible and ASCT-ineligible patients\(^3\).

In the future, MRD screening may be useful for determining the duration of maintenance treatment after ASCT, or after chemotherapy for ASCT-ineligible patients. Maintenance treatment may result in side effects and is costly. Identifying which patients may benefit from maintenance treatment is an important step towards better personalized medicine. A randomized study in which MM patients are randomized to short-term or long-term maintenance treatment stratified by MRD status may provide valuable insights. If MRD positive patients show more benefit from maintenance than MRD negative patients, it will underline the need of nuclear imaging techniques for treatment monitoring.

In some patients, the disease is not systemic, but consists of a solitary lesion of monoclonal plasma cells called a plasmacytoma. The current treatment strategy for a solitary plasmacytoma is local radiotherapy (RT) with 40Gy. This appears to be the best treatment for extramedullary plasmacytoma (EMP), as only a small percentage of patients with an EMP will progress to MM. On the other hand, solitary plasmacytomas of the bone (SBP) have a very high rate of progression to MM, as described in this thesis. Therefore these patients may benefit from systemic treatment. Recent studies suggest that patients with a SBP and a very small, but monoclonal plasma cell population in the bone marrow are at high risk for
progression to MM. It would be of interest to evaluate whether this group would benefit from adding systemic treatment to local radiotherapy, such as treatment with Daratumumab, bortezomib and dexamethasone for 6-12 months following RT. This may prolong the PFS to MM, or perhaps cure patients of their plasma cell neoplasms.

Venous thrombotic events (VTE) are one of the main complications of MM and its treatment. This thesis reports on the real-life incidence of VTE in newly diagnosed MM patients in the northern region of the Netherlands. The real-life incidence of VTE exceeds the incidence described in patients enrolled in studies. Guidelines should emphasize this fact, and thromboprophylaxis should be considered more frequently, not only during use of immunomodulating drugs, but also tailored to patient and treatment-specific characteristics. Furthermore, direct-acting oral anticoagulants (DOAC) are currently being used for prevention and treatment of VTE. DOAC are more convenient; they can be taken orally every day and without the need for blood monitoring. Therapeutic use of DOAC during induction treatment for MM might prevent VTE more effectively than prophylactic use of LMWH. However, studies are needed to conform this.

Finally, this thesis focuses on rare diseases related to the plasma cell. Scleromyxedema has a very low incidence, but recognizing and relating it to the plasma cell is very important, since treatment based on the underlying plasma cell neoplasm results in very good patient outcome. The same holds true for POEMS syndrome. POEMS is an acronym for polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein (M-protein) and skin changes. This very debilitating disease responds strongly to targeted plasma cell therapy. We retrospectively studied the treatment results in 27 patients diagnosed with POEMS in the Netherlands. Mean age was 51 years, 67% was male and median follow-up was 32 months. Induction treatment with lenalidomide/dexamethasone was used in 56% of patients and was effective in 73%. In total, 17 patients received ASCT as primary (48%) or secondary (15%) therapy. No disease relapse or mortality was seen after ASCT. However, in three patients ineligible for ASCT developed a relapse of POEMS syndrome. Based on these findings and the previous studies, we concluded that upfront treatment of POEMS syndrome patients should include ASCT. Recognizing POEMS disease and performing the full diagnostic workup in these patients are crucial steps for correct treatment selection and response monitoring. Considering the very low incidence of this disease and the diagnostic workup and follow up, treatment should be concentrated in a limited number of centers with expertise in myeloma treatment. This would improve outcomes, enable sharing of expertise and provide more opportunities for studies and for generating observational datasets.
Chapter 9

References


Summary, discussion and future perspective