Radiotherapy

13

Sonja Krause, Jürgen Debus, and Dirk Neuhof

Contents

Abstract Solitary plasmocytoma occurring in bone (solitary plasmocytoma of the bone, SBP) or in soft tissue (extramedullary plasmocytoma, EP) can be treated effectively and with little toxicity by local radiotherapy. Ten-year local control rates of up to 90% can be achieved.

Patients with multiple myeloma often suffer from symptoms such as pain or neurological impairments that are amenable to palliative radiotherapy. In a palliative setting, short treatment schedules and lower radiation doses are used to reduce toxicity and duration of hospitalization.

In future, low-dose total body irradiation (TBI) may play a role in a potentially curative regimen with nonmyeloablative conditioning followed by allogenic peripheral blood stem cell transplantation.

13.1 Solitary Plasmocytoma

Solitary plasmocytoma are rare neoplasms originating from plasma cells in bone (solitary plasmocytoma of the bone, SBP) or in soft tissue (extramedullary plasmocytoma, EP). SBP comprise about 10% of plasma cell neoplasms and are mainly found in the axial skeleton (Holland et al. 1992), while EP are even more

S. Krause (✉)
Department of Radiation Oncology,
University of Heidelberg,
Im Neuenheimer Feld 400,
69120 Heidelberg, Germany
e-mail: sonja.krause@med.uni-heidelberg.de

T. Moehler and H. Goldschmidt (eds.), *Multiple Myeloma*,
Recent Results in Cancer Research 183, DOI: 10.1007/978-3-540-85772-3_13,
© Springer-Verlag Berlin Heidelberg 2011

rare (about 3%) with most manifestations in the head-and-neck region (Bachar et al. 2008). Patients typically present with symptoms caused by local tumor mass: pain and neurological deficits in the case of SBP; dysphagia, breathing problems, and epistaxis in the case of EP. Both SBP and EP can be treated effectively and with little toxicity by local radiotherapy (Kumar 2008; Michalaki et al. 2003).

13.1.1 Diagnostic Workup

Before starting local treatment of solitary plasmocytoma, thorough diagnostic workup is essential to rule out occult multiple myeloma, as patients having already progressed to multiple myeloma may require systemic treatment. Most authors define solitary plasmocytoma as one single, histologically confirmed lesion with normal bone marrow biopsy (<10% plasma cells), negative skeletal survey on plain film, normal blood count, normal serum calcium, and normal renal function (Tsang et al. 2001). The addition of whole-body MRI scans to diagnostic schedules may increase the sensitivity to detect multiple myeloma in up to 25% of patients initially considered to have solitary plasmocytoma (Wilder et al. 2002). In addition, MRI is helpful for definition of treatment volumes by clear delineation of soft tissue masses.

13.1.2 Radiotherapy of SBP

Concerning the definition of clinical target volumes of SBP, there is still ongoing debate whether the whole bone marrow of affected bones should be included. In the case of vertebral bodies, most authors recommend the inclusion of the affected bone and the two neighboring vertebral bodies (Tsang et al. 2001). If long bones are affected, some groups define clinical target volumes as radiographically visible mass surrounded by a 2–5 cm margin (Jyothirmayi et al. 1997; Ozsahin et al. 2006; Wilder et al. 2002) and achieve excellent local control rates. However, in a small retrospective series, Mayr et al. (1990) reported local relapse in three out of five patients with only partial bone irradiation compared to 100% local control in 12 patients with treatment of the whole bone. Unaffected regional lymph nodes were not included in the target volume. As to radiation doses, most authors recommend application of 40–50 Gy in 1.8–2.0 Gy fractions (Bolek et al. 1996; Holland et al. 1992; Kumar 2008) based on observations of Mendenhall et al. (1980) that doses >40 Gy resulted in local control rates of 94% compared to 69% after <40 Gy.

All studies reported excellent local control of SBP with 10-year local control rates of up to 90% (Liebross et al. 1998; Wilder et al. 2002). Tumor remission after radiotherapy was achieved after 3–5 months (Jyothirmayi et al. 1997). Interestingly, persistence of tumor mass after therapy had no influence on survival rates (Bolek et al. 1996). Local failure inside or outside the radiation field rarely occurred, and very few patients developed solitary lesions in other locations (Frassica et al. 1989). However, overall survival was diminished severely by a high rate of progression to multiple myeloma: About half the patients developed multiple myeloma after 1–3 years (Bolek et al. 1996; Holland et al. 1992) resulting in 5-year overall survival ranging from 32% (Bolek et al. 1996) to 74% (Frassica et al. 1989). Most studies observed a 10-year disease-free survival of about 25% (Frassica et al. 1989; Ozsahin et al. 2006). Given the high probability of systemic disease development, a small prospective study by Aviles et al. (1996) achieved much lower progression rates of 12% in patients treated with radiotherapy followed by administration of low-dose prednisone/melphalan over 3 years compared to 54% progression to myeloma in patients treated with radiotherapy alone. However, the question of adjuvant chemotherapy remains to be addressed by larger prospective studies.

13.1.3 Radiotherapy of EP

For radiation therapy of EP, especially in the head-and-neck region, most authors followed guidelines for squamous cell carcinoma in that location for definition of target volumes and radiation doses. Most groups applied doses of 40–60 Gy in 1.8–2.0 Gy fractions (Creach et al. 2009; Michalaki et al. 2003). Tournier-Rangeard et al. (2006) found a much better local control with doses to the target volume >45 Gy than with <45 Gy (100% vs. 50% 5-year local control rate) and even recommended a 10 Gy boost in case of bulky disease if toxicity is tolerable. For EP of nasal cavity or paranasal sinuses, three portal fields were used (one anterior and two lateral wedged fields), EP of nasopharynx, oropharynx, or hypopharynx were usually treated with two laterally opposing fields (Chao et al. 2005; Liebross et al. 1999). In recent years, more complex techniques have evolved that provide a better protection of uninvolved tissues with a high susceptibility to radiation such as the parotid or submandibular gland: Intensity-modulated radiotherapy (IMRT) with up to nine or more photon beams allows the formation of individually shaped treatment volumes.

Concerning the question whether unaffected cervical lymph nodes should be treated (elective neck irradiation, ENI), discussion is still ongoing. Some authors observed recurrences in cervical nodes in up to 30% of patients with untreated cervical lymph nodes and thus recommended ENI, at least for high-risk locations such as oral cavity, naso- and oropharynx and larynx and for bulky tumors (Chao et al. 2005; Liebross et al. 1999; Mayr et al. 1990; Tournier-Rangeard et al. 2006). Others finding recurrence rates in local lymph nodes of <4% advised against the application of ENI in order to reduce long-term toxicity (Chao et al. 2005; Jyothirmayi et al. 1997; Susnerwala et al. 1997).

EP can be controlled locally by radiotherapy in a similarly effective fashion as SBP: 5-year local control rates 72–100% were reported for EP (Liebross et al. 1999; Tournier-Rangeard et al. 2006). However, most studies observed a better overall survival for EP patients of 76% after 5 years (Bachar et al. 2008; Ozsahin et al. 2006) and 54–72% after 10 years (Chao et al. 2005; Ozsahin et al. 2006). Ten-year disease-free survival rates ranged from 55% to 75% (Chao et al. 2005; Ozsahin et al. 2006; Tournier-Rangeard et al. 2006). Concerning progression to multiple myeloma, EP patients seemed to have lower conversion rates of 10–32% after 10 years compared to SBP patients (Bachar et al. 2008; Bolek et al. 1996; Kumar 2008; Liebross et al. 1999).

13.1.4 Treatment Toxicity

Very little data can be found in literature addressing treatment toxicity, probably because of small patient numbers and a variety of different locations. Creach et al. (2009) described toxicity in 18 patients treated for EP in the head-and-neck region (10 patients received an additional irradiation of cervical lymph nodes): 10 of 18 patients reported xerostomia, 5 complained of nose bleedings. Other side effects were nasal obstruction, larynx edema, dysfunction of the lacrimal canal, hypothyreosis, problems related to the paranasal sinuses and Lhermitte's sign, each occuring in one patient. In this small group of patients, two developed a secondary malignoma: one patient suffered from a myxoid fibrous histiocytoma in the radiation field 6.5 years after radiotherapy, another developed a malignant brain tumor after 6.9 years. The reason for this unusually high rate of secondary malginoma remains unclear.

13.2 Palliative Treatment of Multiple Myeloma

In spite of considerable progress in the treatment of multiple myeloma, the disease still is not curable. Thus, effective palliation is an

important issue in treatment concepts. Local radiotherapy is used in the palliative treatment of the most frequent symptoms of multiple myeloma: Reduction of pain due to osseous or soft tissue masses, prevention or additive treatment of bone fractures, and reduction of neurological symptoms due to spinal compression.

13.2.1 Pain Control

Local pain caused by irritation of spinal nerves or spinal cord is often the first and the most common symptom in patients with multiple myeloma, occurring in 55–90% of patients (Plasswilm and Belka 2004; Mose et al. 2000). Local radiotherapy has been an important part in the palliative treatment of painful spinal masses for a long time: A study published in 1975 (Mill 1975) reported the palliation of pain by local radiotherapy in 81% of 65 patients presenting with multiple myeloma. Over time, many groups achieved similar results (Rostom 1988; Yaneva et al. 2006). A complete elimination of pain could not be achieved in all patients, but most profited from radiotherapy by a reduction of their symptoms. Mose et al. (2000) reported complete elimination of pain in 34.4% of 71 treated volumes and partial analgesia in 50.7%.

The irradiated volume usually contained the whole affected bone, in the case of vertebral manifestations including the neighboring vertebral bodies, in order to prevent spreading via the dorsal venous vascular plexus connecting neighboring vertebral bodies (Wilkowski et al. 2002). However, Catell et al. (1998) have shown that in the case of long bones, effective pain reduction is possible by irradiation of only part of the respective bone. Planning should be based on CT scans for better evaluation of pasaosseous soft tissue masses (Wilkowski et al. 2002). Various techniques are applied for irradiation: In most cases, photon beams are used for treatment of bone lesions in a single-field or multi-field technique. Electron beams (with the maximum radiation dose occurring near the body surface) are used for treating superficial lesions (e.g., treatment of the rib cage or sternum).

Wilkowski et al. (2002) reported significant pain reduction by radiation doses as small as 10–15 Gy, but most groups applied higher doses of 25–30 Gy in 10–15 fractions (Bosch and Frias 1988; Leigh et al. 1993). However, hypofractionated irradiation (e.g., 1×8 Gy, 4×4 Gy, 4×5 Gy) was shown to relieve pain in a similarly effective manner (Falkmer et al. 2003).

Pain reduction was in some cases already perceived during radiation therapy but usually started 2–3 weeks after therapy (Plasswilm and Belka 2004). The analgetic effect was described as long-lasting, with relapse rates of 6% after a median of 16 months (Leigh et al. 1993).

A predictive factor for good clinical response was a high Karnofsky performance score of 80–90% (Mose et al. 2000). In addition, the simultaneous application of chemotherapy seemed to enhance the analgetic effect of radiotherapy. Mose et al. could induce pain reduction in 96.3% of patients receiving simultaneous chemotherapy and radiotherapy but only in 77.5% of patients treated with radiotherapy alone. Adamietz and Bottcher (1994) reported local response in 80% of patients under radiochemotherapy compared to 39.6% of patients under radiotherapy alone.

In summary, local radiotherapy has been shown to be an effective tool for pain control in multiple myeloma. However, it had no effect on survival rates (Mose et al. 2000; Yaneva et al. 2006).

13.2.2 Recalcification

Osseous instability, particularly of vertebral bodies, is another challenge in palliative treat-

ment of multiple myeloma. The pathologically upregulated osteoclastic activity in multiple myeloma patients can be compensated for some time by increased osteoblast function, but in later disease stages, this compensation fails, and osteolytic lesions threaten spinal stability (Hjertner et al. 2006).

Local radiotherapy should be started as soon as possible after diagnosis of an unstable osteolytic lesion, as it has been shown that radiologically unstable lesions without actual fracturation of the bone responded much better to radiotherapy than already fractured bones (Liebross et al. 1998, 1999). Mose et al. could induce recalcification in 47.4% of irradiated bones. In a small series published by Lecouvet et al. (1997), fractures occurred in 5% of irradiated vertebrae compared to 20% of nonirradiated vertebrae. In addition, manifestation rates of new focal lesions could be reduced by spinal radiotherapy.

A comparatively small group of patients (about 10%) present with neurological impairments due to spinal compression. The most common causes for spinal compression are vertebral fractures, however, some patients suffer from weakness of limbs or inability to walk caused by extradural extension of plasmocytoma of an adjacent vertebra or extradural compression without bone disease. The therapeutic approach recommended by most authors is local radiotherapy, preferably after local decompression by laminectomy. Although life expectancy of patients with malignant spinal compression is limited and therefore short-course radiotherapeutic schedules (e.g., 1×8 Gy, 5×4 Gy) seem a sensible option, it has been shown that long-course schedules (e.g., 10×3 Gy) result in much better improvement of motor function. Rades et al. (2006) reported an improvement of motor function in 52% of patients with neurological impairments. Of 70 nonambulatory patients, 47% even regained the ability to walk.

13.3 Total Body Irradiation (TBI)

Autologous transplantation of peripheral blood stem cells after myeloablative conditioning has been shown to improve long-term survival but cannot achieve long-term cure. Until recently, the standard conditioning regimen comprised total body irradiation (TBI) with a radiation dose of 8 Gy followed by chemotherapy. This concept was changed by the publication of the Intergroupe Francophone du Myélome 9502 trial (Moreau et al. 2002): The authors observed equal event-free survival in patients conditioned with 8 Gy TBI plus melphalan 140 mg/m^2 compared to patients treated with melphalan 200 mg/m^2. However, toxicity was lower and 45-month survival slightly favorable in the latter group. Thus, TBI lost importance in a potentially curative setting.

In recent years, a new role for TBI in pretransplantation conditioning seems to emerge: Several studies described a potentially curative regimen with nonmyeloablative conditioning with 2 Gy TBI in one single fraction alone or combined with fludarabine followed by allogenic peripheral blood stem cell transplantation (PBST) and immunosuppressive treatment. In this concept, TBI causes a transient immunosuppression and helps to induce a graft-versus-myeloma effect with tolerable graft-versus-host disease (Gerull et al. 2005; Bruno et al. 2009; Georges et al. 2007).

The target volume for TBI are all tumor cells and all lymphatic tissues, so the whole body including the skin must be treated. This requires large radiation fields of up to 210×70 cm, compared to the radiation fields of 40×40 cm in 1 m distance from focus that conventional linear accelerators usually provide. Radiation Oncology departments developed different techniques for covering such large treatment volumes. One approach is to increase the distance between focus and patients by treating the patient sitting on a special chair and applying laterally opposing fields with a focus distance of 3.5 m.

References

Adamietz IA, Bottcher HD (1994) Estimation of radiotherapy effect in multiple myeloma. Int J Radiat Oncol Biol Phys 29:221

Aviles A, Huerta-Guzman J, Delgado S, Fernandez A, Diaz-Maqueo JC (1996) Improved outcome in solitary bone plasmocytomata with combined therapy. Hematol Oncol 14:111–117

Bachar G, Goldstein D, Brown D, Tsang R, Lockwood G, Perez-Ordonez B, Irish J (2008) Solitary extramedullary plasmocytoma of the head and neck–long-term outcome analysis of 68 cases. Head Neck 30:1012–1019

Bolek TW, Marcus RB, Mendenhall NP (1996) Solitary plasmocytoma of bone and soft tissue. Int J Radiat Oncol Biol Phys 36:329–333

Bosch A, Frias Z (1988) Radiotherapy in the treatment of multiple myeloma. Int J Radiat Oncol Biol Phys 15:1363–1369

Bruno B, Rotta M, Patriarca F, Mattei D, Allione B, Carnevale-Schianca F, Sorasio R, Rambaldi A, Casini M, Parma M, Bavaro P, Onida F, Busca A, Castagna L, Benedetti E, Iori AP, Giaccone L, Palumbo A, Corradini P, Fanin R, Maloney D, Storb R, Baldi I, Ricardi U, Boccadoro M (2009) Non-myeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo. Blood 113:3375–3382

Catell D, Kogen Z, Donahue B, Steinfeld A (1998) Multiple myeloma of an extremity: must the entire bone be treated? Int J Radiat Oncol Biol Phys 40:117–119

Chao MW, Gibbs P, Wirth A, Quong G, Guiney MJ, Liew KH (2005) Radiotherapy in the management of solitary extramedullary plasmocytoma. Intern Med J 35:211–215

Creach KM, Foote RL, Neben-Wittich MA, Kyle RA (2009) Radiotherapy for extramedullary plasmocytoma of the head and neck. Int J Radiat Oncol Biol Phys 73:789–794

Falkmer U, Jarhult J, Wersall P, Cavallin-Stahl E (2003) A systematic overview of radiation therapy effects in skeletal metastases. Acta Oncol 42:620–633

Frassica DA, Frassica FJ, Schray MF, Sim FH, Kyle RA (1989) Solitary plasmocytoma of bone: Mayo clinic experience. Int J Radiat Oncol Biol Phys 16:43–48

Georges GE, Maris MB, Maloney DG, Sandmaier BM, Sorror ML, Shizuru JA, Lange T, Agura ED, Bruno B, McSweeney PA, Pulsipher MA, Chauncey TR, Mielcarek M, Storer BE, Storb R (2007) Nonmyeloablative unrelated donor hematopoietic cell transplantation to treat patients with poor-risk, relapsed, or refractory multiple myeloma. Biol Blood Marrow Transplant 13: 423–432

Gerull S, Goerner M, Benner A, Hegenbart U, Klein U, Schaefer H, Goldschmidt H, Ho AD (2005) Long-term outcome of nonmyeloablative allogeneic transplantation in patients with high-risk multiple myeloma. Bone Marrow Transplant 36:963–969

Hjertner O, Standal T, Borset M, Sundan A, Waage A (2006) Bone disease in multiple myeloma. Med Oncol 23:431–441

Holland J, Trenkner DA, Wasserman TH, Fineberg B (1992) Plasmocytoma. Treatment results and conversion to myeloma. Cancer 69:1513–1517

Jyothirmayi R, Gangadharan VP, Nair MK, Rajan B (1997) Radiotherapy in the treatment of solitary plasmocytoma. Br J Radiol 70:511–516

Kumar S (2008) Solitary plasmocytoma: is radiation therapy sufficient? Am J Hematol 83:695–696

Lecouvet F, Richard F, Vande BB, Malghem J, Maldague B, Jamart J, Ferrant A, Michaux JL (1997) Long-term effects of localized spinal radiation therapy on vertebral fractures and focal lesions appearance in patients with multiple myeloma. Br J Haematol 96:743–745

Leigh BR, Kurtts TA, Mack CF, Matzner MB, Shimm DS (1993) Radiation therapy for the palliation of multiple myeloma. Int J Radiat Oncol Biol Phys 25:801–804

Liebross RH, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R (1998) Solitary bone plasmocytoma: outcome and prognostic factors following radiotherapy. Int J Radiat Oncol Biol Phys 41: 1063–1067

Liebross RH, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R (1999) Clinical course of solitary extramedullary plasmocytoma. Radiother Oncol 52:245–249

Mayr NA, Wen BC, Hussey DH, Burns CP, Staples JJ, Doornbos JF, Vigliotti AP (1990) The role of radiation therapy in the treatment of solitary plasmocytomas. Radiother Oncol 17:293–303

Mendenhall CM, Thar TL, Million RR (1980) Solitary plasmocytoma of bone and soft tissue. Int J Radiat Oncol Biol Phys 6:1497–1501

Michalaki VJ, Hall J, Henk JM, Nutting CM, Harrington KJ (2003) Definitive radiotherapy for extramedullary plasmocytomas of the head and neck. Br J Radiol 76:738–741

Mill WB (1975) Radiation therapy in multiple myeloma. Radiology 115:175–178

Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, Sotto JJ, Guilhot F, Marit G, Doyen C, Jaubert J, Fuzibet JG, Francois S, Benboubker L, Monconduit M, Voillat L, Macro M, Berthou C, Dorvaux V, Pignon B, Rio B, Matthes T, Casassus P, Caillot D, Najman N, Grosbois B, Bataille R, Harousseau JL (2002) Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood 99:731–735

Mose S, Pfitzner D, Rahn A, Nierhoff C, Schiemann M, Bottcher HD (2000) Role of radiotherapy in the treatment of multiple myeloma. Strahlenther Onkol 176:506–512

Ozsahin M, Tsang RW, Poortmans P, Belkacemi Y, Bolla M, Dincbas FO, Landmann C, Castelain B, Buijsen J, Curschmann J, Kadish SP, Kowalczyk A, Anacak Y, Hammer J, Nguyen TD, Studer G, Cooper R, Sengoz M, Scandolaro L, Zouhair A (2006) Outcomes and patterns of failure in solitary plasmocytoma: a multicenter Rare Cancer Network study of 258 patients. Int J Radiat Oncol Biol Phys 64:210–217

Plasswilm L, Belka C (2004) Strahlentherapie beim Myelom. Der Onkologe 8:858–863

Rades D, Hoskin PJ, Stalpers LJ, Schulte R, Poortmans P, Veninga T, Dahm-Daphi J, Obralic N, Wildfang I, Bahrehmand R, Engenhart-Cabilic R, Schild SE (2006) Short-course radiotherapy is not optimal for spinal cord compression due to myeloma. Int J Radiat Oncol Biol Phys 64:1452–1457

Rostom AY (1988) A review of the place of radiotherapy in myeloma with emphasis on whole body irradiation. Hematol Oncol 6:193–198

Susnerwala SS, Shanks JH, Banerjee SS, Scarffe JH, Farrington WT, Slevin NJ (1997) Extramedullary plasmocytoma of the head and neck region: clinicopathological correlation in 25 cases. Br J Cancer 75:921–927

Tournier-Rangeard L, Lapeyre M, Graff-Caillaud P, Mege A, Dolivet G, Toussaint B, Charra-Brunaud C, Hoffstetter S, Marchal C, Peiffert D (2006) Radiotherapy for solitary extramedullary plasmocytoma in the head-and-neck region: a dose greater than 45 Gy to the target volume improves the local control. Int J Radiat Oncol Biol Phys 64:1013–1017

Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, Stewart AK (2001) Solitary plasmocytoma treated with radiotherapy: impact of tumor size on outcome. Int J Radiat Oncol Biol Phys 50:113–120

Wilder RB, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R (2002) Persistence of myeloma protein for more than one year after radiotherapy is an adverse prognostic factor in solitary plasmocytoma of bone. Cancer 94:1532–1537

Wilkowski R, Schymura B, Busch M, Zimmermann F (2002) Strahlentherapie. In: Bartl R (ed) Manual Multiples Myelom – Empfehlungen zur Diagnostik, Therapie und Nachsorge. Zuckschwerdt, München, pp S138–S142

Yaneva MP, Goranova-Marinova V, Goranov S (2006) Palliative radiotherapy in patients with multiple myeloma. J BUON 11:43–48