Chapter 15
Botulinum Toxins for the Treatment of Cancer-Related, Postradiation, Postsurgical, and End of Life Pain

Abstract Botulinum neurotoxins exert an analgesic effect through a variety of mechanisms including inhibition of acetylcholine release from neuromuscular junction and release of pain mediators from peripheral nerve endings, dorsal root ganglia, and at the spinal sensory neuron level. Four open-label prospective studies have demonstrated effectiveness of ona-, abo-, and incobotulinum toxins in relieving pain at the site of radiation or surgery for cancer. Furthermore, single-case observations with onabotulinumtoxinA have shown that local intramuscular injection of this toxin can alleviate chronic and disabling local pain in advanced cancer and improve the quality of the end of life state among patients with terminal cancer.

Keywords Cancer • Cancer pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA (onaA) • AbobotulinumtoxinA (aboA) • IncobotulinumtoxinA (incoA) • Allodynia • Hyperalgesia

Introduction

Focal cancer therapy-related pain is induced by a variety of mechanisms. Approximately 25 % of the patients who undergo radiation or surgery for cancer develop pain at or close to the area of local radiation or surgery (Kanner and Foley 1981; Kehlet et al. 2006). List and Bilir (2004) attributed the postradiation pain observed in 15–30 % of patients with head and neck cancer to the development of fibrosis, scar, and keloid. Topical application of trolamine, calendula officinalis, hyaluronic acid, and lidocaine patch may provide transient relief (Fisher et al. 2000; Chargari et al. 2009; Kirova et al. 2011), but sustained relief is uncommon and was noted in only 25 % of patients who applied lidocaine patch to the allodynic region (Fleming and O'Connor 2009). Severe local pain after radiation and surgery may require potent systemic analgesic medications such as opioids which, although effective, often cause undesirable side effects. Among the multitude of side effects with these agents are nausea, somnolence, and constipation, each noted in more than 20 % of the patients (Cochrane review, Wiffen et al. 2014).

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Advanced cancer is associated with severe pain in 70–80 % of patients (Caraceni et al. 2012). The prevalence of severe pain in advanced cancer is similar to that of other chronic and advanced medical disorders (Harris 2014). For instance, the estimated prevalence of pain in chronic heart disease and chronic obstructive pulmonary disease has been reported as 44–77 % and 34–77 %, respectively (Solano et al. 2006; Borsook 2012). Palliative treatment of this form of pain is often difficult, and side effects of analgesic medications are poorly tolerated by debilitated patients.

This chapter will start with a discussion of therapy of postsurgical/postradiation pain in cancer patients, followed by application of botulinum neurotoxin (BoNT) therapy to chronic, severe end of life pain in cancer patients. To illustrate the intricacies of treatment with BoNTs in these settings, case reports are provided from the author's experience.

Botulinum Neurotoxin Therapy for Postsurgical/Postradiation Pain in Cancer Patients

The literature on this subject includes seven open-label (four prospective and three retrospective) studies (Table 15.1) as well as a few case reports (Fabregat et al. 2013). No blinded studies are available. The data collectively indicate that local injection of BoNTs into scarred/fibrotic or allodynic area significantly improves this form of pain in cancer patients.

Retrospective Studies

In the study of Van Daele et al. (2002), injection of onabotulinumtoxinA into the tight and painful sternocleidomastoid muscle relieved the pain and tightness in four of six patients. All patients had received radiotherapy for head and neck cancer. The injected dose was 20–25 units administered at 1 or 2 points into the sternocleidomastoid muscle.

Anecdotal case reports have also described marked reduction of postradiation pain after local BoNT-A injection. As an example, a 75-year-old gentleman with rectal cancer developed severe rectal pain and a large noncancerous rectal ulcer after local resection and radiation. Injection of onaA into the rectal wall at multiple sites reduced the pain dramatically and helped healing of the ulcer (De Micheli et al. 2003).

Stubblefield et al. (2008) also found BoNT-A injection helpful in relieving focal pain caused by radiation fibrosis. In this retrospective study of 23 patients, 30 % had painful trismus, and 43 % had trigeminal and cervical plexus neuralgia.

Voung et al. (2011) studied the effect of BoNT injection into the rectal wall immediately after high-dose-rate endorectal brachytherapy (HDREBT) in 15 patients with prostatic cancer. The patients who received 100 units of onaA into the rectal wall had a lower incidence of acute radiation prostatitis with significant reduction of bowel frequency and urgency ($P<0.05$) and lesser degrees of pain ($P=0.07$).

Table 15.1 Studies of BoNTs in post radiation/postsurgical pain of cancer patients

Study	Pts	Toxin type	Dose	Treatment	Location	PO	Results
Van Daele et al. (2002)	6 R	BoNT-A	20–25	Rad/chemo	Head and neck	Pain	Complete pain relief
							4 out of 6 patients
Wittekindt et al. (2006)	23 P	BoNT-A	60–120	Rad/surg	Head and neck	VAS at day 28	Only low dose was effective ($P<0.05$)!
			160–240				
Hartl et al. (2008)	19 P	onA/aboA	50/250	Chemo/rad	Head/neck	VAS and function, 4 weeks	VAS ($P=0.02$), function ($P=0.04$)
Stubblefield et al. (2008)	23 R	onaA	25–200	Rad/surg	Head/neck	Pain	Improved in 87 %
Mittal et al. (2012)	7 R	onaA	100	Rad/surg	Head/neck and breast	VAS, PGIC at week 4	VAS ($P<0.05$)
							PGIC: satisfactory
Bach et al. (2012)	9 P	aboA	100–400 (SCM)	Rad/surg	Head and neck	FDSNP at week 4	FDSNP ($P=0.01$)
			125–200 (PF)				Pain ($P=0.01$)
Rostami et al. (2014)	12 P	incoA	100 units	Rad/surg	Head and neck mastectomy	VAS at week 6	VAS, PGIC ($P<0.05$)

P prospective, *R* retrospective, *VAS* visual analog scale, *PGIP* patient global impression of pain, *FDSNP* functional disability scale for neck pain, *SCM* sternocleidomastoid, *PF* pectoralis flap

In another study (Bach et al. 2012) of nine patients with postsurgical contracture of sternocleidomastoid or pectoralis major muscle related to head and neck cancer, patients expressed pain relief after administration of aboA into sternocleidomastoid muscle (100–400 units) or the pectoralis muscle flap (125–200 units) with no side effects. Injections were administered at four to five locations into sternocleidomastoid muscle or into the pectoralis muscle flap.

Prospective Studies

Wittekindt et al. (2006) examined the efficacy of BoNT-A (type not specified) in 23 patients who reported neuropathic pain in the neck and shoulder following neck dissection for squamous cell carcinoma of upper "aerodigestive tract." BoNT-A was diluted by 1 or 2 cc preservative-free saline before administration. Patients were divided into low-dose (80–120 units) and high-dose (160–240 units) groups. Patients and physicians were blinded to the dose of injections. Injections were performed in 8–12 locations subcutaneously into targeted neck and shoulder regions. Patients' response to BoNT injection was measured by visual analog scale (VAS) at baseline prior to injections and at day 28 after injections. The mean baseline pain was 4.3 on VAS (0–10). The quality of life was evaluated by a questionnaire from the European Organization for Research and Treatment of Cancer (EORTC), specifically prepared for head and neck cancers, at the same time frames. At day 28, mean VAS score for the low-dose group changed from 4.3 to 3.6 ($P<0.05$), but the change for the high-dose group was not significant. Furthermore, the low-dose group also showed a trend for improvement of quality of life.

In another prospective study (Hartl et al. 2008), the efficacy of onabotulinumtoxinA (onaA) and abobotulinumtoxinA (aboA) was assessed in 19 patients with nasopharyngeal and oropharyngeal cancer who developed severe spasm of masseter muscles and trismus, on the average, 5.6 years after radiotherapy for cancer. Eleven patients had received chemotherapy in addition to radiation. The location of cancers was in the nasopharynx ($n=3$), oropharynx ($n=9$), oral cavity ($n=2$), oral cavity and nasopharynx ($n=1$), larynx ($n=3$), and parotid gland ($n=1$). Each masseter muscle was injected at two points, either with onaA (50 units) or aboA (250 units). At 4 weeks postinjection, pain, spasms, and functional score (measured in a 20 subset questionnaire) all improved significantly compared to baseline ($P=0.002$, $P=0.004$, $P=0.04$, respectively). No difference was noted between onaA and aboA.

Yale Ongoing Prospective Study

We are currently studying the effect of incobotulinumtoxinA (incoA) on moderate to severe focal pain (VAS >5) at the site of cancer resection or cancer radiation. Patients had had radiation and surgery for breast or head and neck cancer. Efficacy

of treatment is measured by VAS, patient global impression of change (PGIC), and Quality of Life Scale for pain at 4, 6, 8, 10, and 12 weeks postinjection. The primary outcome is two grades or more improvement in VAS with additional patient satisfaction expressed in PGIC at 4 weeks. The secondary outcome is improvement of quality of life at 6 weeks. A total of up to 100 units of incobotulinumtoxinA, diluted in 1 cc of saline, was injected into the area of local pain indicated by the patient. The injections were both subcutaneous and intramuscular. The target number of the study is 20 patients. The preliminary results (Rostami et al. 2014) of this open-label prospective study are presented below. To date, 12 patients were enrolled in the study, and 10 patients completed the assessments. Two patients died during the study from complications of cancer and were removed from the final analysis. Of the remaining ten who completed the study, eight patients demonstrated significant reduction of pain and improvement of both quality of life and patient impression of change 6 weeks postinjection. The mean VAS of 7.4 at baseline was lowered to 3.8 at week 6 ($P < 0.05$). These positive results agree with our previous retrospective report of seven cancer patients with local postradiation/postsurgical pain (Mittal et al. 2012). In these seven patients, intramuscular injection of 80–160 units of onabotulinumtoxinA (onaA) reduced the local pain at 4 weeks postinjection. Both types of BoNT-A (inco and ona) seemed to be equally effective against pain. None of the patients developed any side effects in either of the prospective or the retrospective study.

The following cases are presented from the authors experience with BoNT therapy for postradiation/postsurgical pain in cancer patients.

Case 1: Carcinoma of the Base of the Tongue Associated with Painful Upper Neck Spasms and Burning Pain Interfering with Speaking and Swallowing

A 47-year-old, right-handed gentleman was referred to the Yale Neurotoxin Treatment Clinic for evaluation of right upper neck pain and difficulty in swallowing and speaking of 5 years duration. Six years ago, he was found to have a tumor at the base of the tongue and cervical lymphadenopathy on the right side. He underwent resection of the tumor with removal of lymph nodes and neck muscles on the right side. The tumor was a squamous cell carcinoma. Shortly after resection, he received radiotherapy to the base of the tongue and right side of the neck. A few months later, he experienced tingling and pulling of the base of the tongue which gradually evolved into painful spasms and burning sensation below the angle of the right jaw interfering with speaking and eating. Treatment with a variety of analgesic drugs was only minimally helpful.

General medical and neurological examinations were normal except for loss of muscles on the right side of the neck and mild weakness of the tongue. A vertical surgical scar was visible on the right side of the neck extending from lower neck to the lower edge of the mandible. Several areas of induration and keloid formation

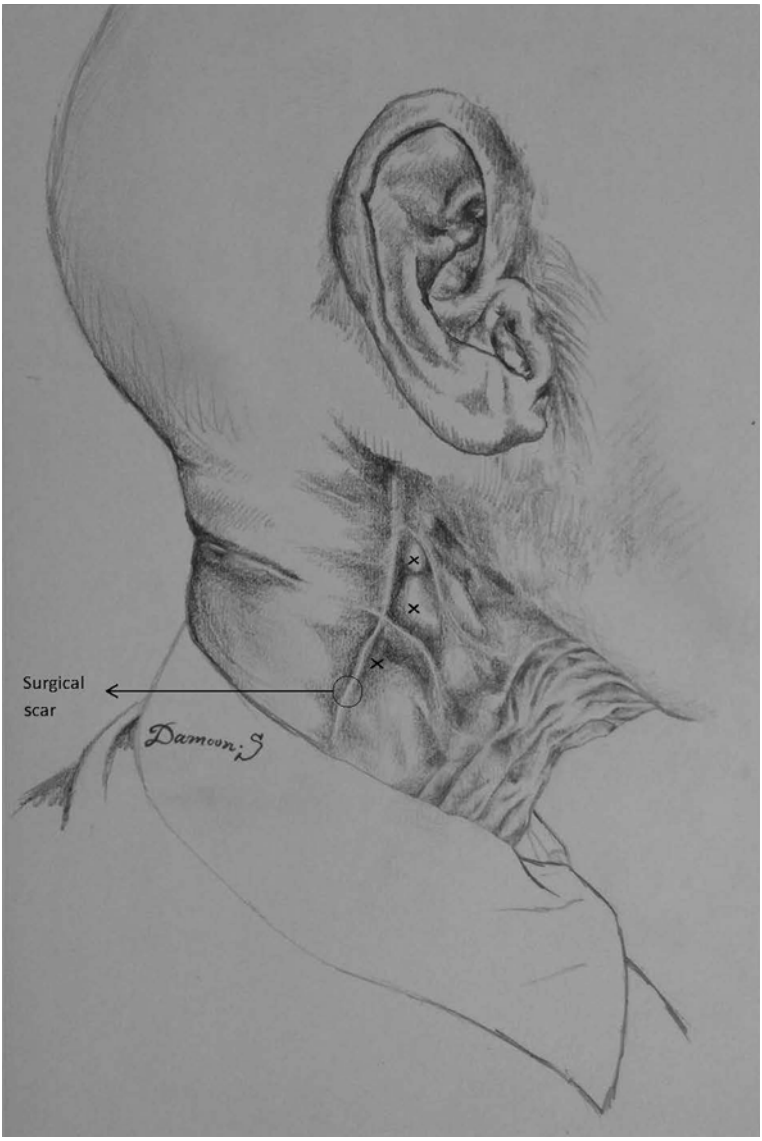

Fig. 15.1 Patient 15-1. onaA injection sites in the right side of the neck into areas of keloid, induration, and fibrosis. (Created by Damoun Safarhour, published with permission of © Bahman Jabbari 2014. All rights reserved.)

were present, the hardest and most painful being located anterior and slightly below the angle of the right jaw (Fig. 15.1).

Twenty units of onabotulinumtoxinA was injected into each of the three areas of indurated, scar tissue on the right side of the neck (Fig. 15.1). The dilution was 100 units/cc. A 0.75 in.-long, 27.5 gauge needle was used for injections. After a week,

patient reported total cessation of muscle spasms and burning pain as well as marked improvement of his swallowing and speech. He reported no side effects. The pain and discomfort returned after 6 months. Over the next 7 years, the patient continued to receive onaA injections into the same cervical regions, for the past 4 years with a slightly higher dose of onaA (30, 30, and 20 units). The injections have remained efficacious over 7 years when employed at 6 month intervals.

Case 2: Intense Left Cervical Pain Following Laryngectomy and Neck Dissections for Squamous Cell Carcinoma of the Pyriform Sinus

A 48-year-old man underwent laser supraglottic laryngectomy with bilateral neck dissections for squamous cell carcinoma of the left pyriform sinus. This was followed by courses of chemotherapy and radiation. Two years later, patient developed intense left cervical pain and left shoulder pain beginning with spasms of the left sternocleidomastoid (SCM) muscle. The pain was described as deep and aching, but at times sharp and jabbing. A variety of medications including fentanyl 25 mcg/h patch and hydromorphone 2 mg tablets, given as needed, provided no significant pain relief. He was then injected with a total dose of 200 units of onabotulinumtoxinA into the left cervical and shoulder muscles: left SCM, left trapezius, left splenius, and left levator scapulae muscles at several points, 15–20 units per site (Fig. 15.2). After a week, he reported marked reduction of pain (from VAS 8 to 1); on PGIC, he expressed the outcome as "very satisfactory." The response continued over a period of 3 years with repeat injections performed every 4 months. The patient did not report any side effects.

Case 3: Severe Spasms of Masseter Muscles 6 Months After Resection and Radiation of a Left Tonsillar Cancer

A 54-year-old male with a history of left-sided tonsillar cancer had undergone surgical resection and radiation therapy. Six months later, he noted painful spasm of the right masseter and pain during eating or jaw opening. This eventually spread to the left masseter and to the upper neck regions. The pain became excruciating during jaw opening, eating, and chewing. Baclofen, 20 mg daily, combined with a variety of analgesics offered little help. At Yale Botulinum Neurotoxin Clinic, he was injected with onaA into the masseter muscles bilaterally. Each masseter received 60 units of onaA, divided at two sites (30 unit per site). The total dose for both masseters was 120 units. Patient reported significant reduction of his pain after 10 days. The pain intensity score of 9 in VAS recorded at baseline changed to 1 at 4 weeks. He reported no side effects and in PGIC reported the change as "very satisfactory." Pain returned, though less intense, after 3 months. Repeat injections every 3 months thereafter had the same beneficial effect. Patient still visits Yale Neurotoxin

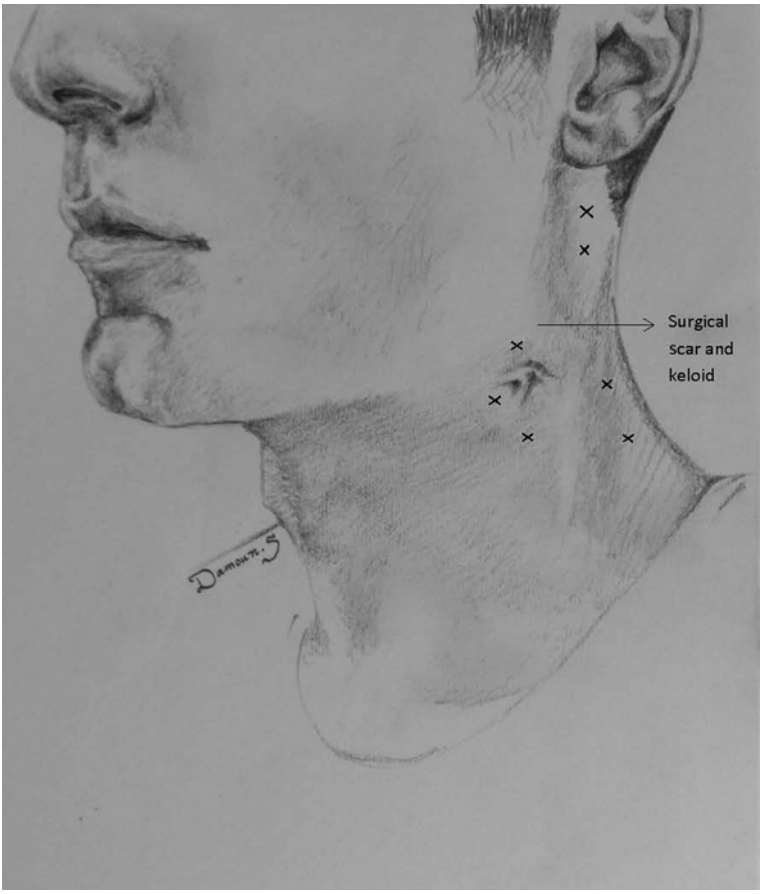

Fig. 15.2 Patient 15-2. onaA injection sites in the left side of the neck and shoulder into the sternocleidomastoid, levator scapulae, splenius, and trapezius muscles. (Created by Damoun Safarhour, published with kind permission of Bahman Jabbari 2014. All rights reserved.)

Treatment Clinic every 3 months (6 years follow-up). The dose for the past 2 years has been reduced to 50 units per masseter.

Comments

Botulinum neurotoxins can influence and reduce pain via a variety of mechanisms (Hallett 2000). These include inhibition of pain mediator (CGRP, SP, glutamate) release from nerve endings and dorsal root ganglia and at the spinal level. Reduction of local inflammation, inhibition of sodium and purinergic channels (ATP), and decrease discharge of sympathetic neurons are among other factors contributing to the analgesic effects of BoNTs. These effects collectively subdue peripheral and

ultimately central sensitization and lead to a powerful analgesic effect (see Chap. 2 of this book for more details).

Results of the four aforementioned, prospective studies (open label) with BoNTs for treatment of postradiation/postsurgical pain among cancer patients are encouraging. This form of pain is hard to treat, and introduction of a novel therapeutic modality with a safe and low side effect profile is welcome given the fragility of the patients and their higher propensity for developing side effects with potent conventional analgesic medications. These preliminary results demonstrate a few points of clinical significance:

- In at least half of our patients, the analgesic response to BoNT lasted 6 months rather than the usual 3 months duration of relief noted in treatment of movement disorders.
- The available information demonstrates that onaA, incoA, and aboA all can alleviate postradiation/postsurgical pain in patients with cancer.

Controlled and blinded studies are necessary to substantiate the validity of these data, although blinded studies are difficult to perform in cancer patients with disabling pain.

Botulinum Neurotoxin Treatment of End of Life Cancer Pain

The mechanism of focal pain in advanced cancer and end of the life cancer pain is multifactorial. In a majority of patients, pain has a peripheral origin and results from direct invasion of neural tissue by cancer or reactive issue post surgical or radiation therapy. Centrally, it can result from activation of pain mechanisms by a central nervous system cancer that may cause either a neuropathic pain or painful muscle spasms (Fu et al. 2013). Examples are provided below from the author's experience:

Case 1: Severe Jaw Pain and Trismus Due to the Direct Invasion of Masseter Muscle and Jaw Bone by a Non-small Cell Cancer of the Lung

A 69-year-old female with stage IV non-small cell carcinoma of the lungs with metastasis to bone (femur and petrous bone) and brain underwent multiple courses of chemotherapy and radiation therapy. Three months after completion of radiotherapy, she complained of jaw stiffness, inability to open the mouth fully, and right masseter pain when attempting to open the mouth. Over a few weeks, the problem reached a point that she refrained from eating. Her medications, oxycodone (10 mg, twice daily) and fentanyl (25 mcg patch every 72 h), provided temporary pain relief but did not alleviate the trismus. An MRI showed enlargement of right masseter due to neoplastic involvement (Fig. 15.3).

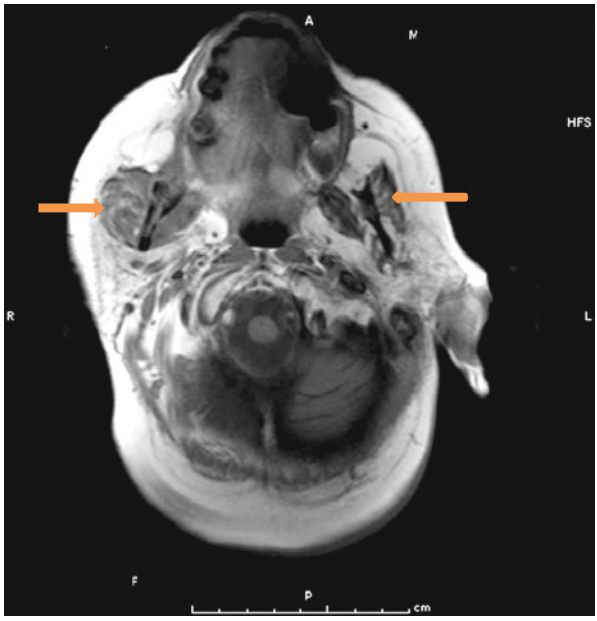

Fig. 15.3 Patient 15-3. Magnetic resonance imaging with special base view showing the right masseter enlargement presumably from cancerous involvement (*arrows*)

Injection of onabotulinumtoxinA (50 units) into the right masseter and 20 units into the right temporalis decreased the right masseter pain and improved jaw opening for 6 weeks. Subsequent injections of a larger dose of onaA into the right masseter (70 units) with additional injection into the left masseter (30 units) improved her quality of life (pain relief, less eating difficulty) over the next 18 months before her demise from complications of cancer.

Case 2: Disabling, Deep Neck and Shoulder Pain Due to an Extensive Pontomedullary Astrocytoma

A 29-year-old male with a grade 3 pontine astrocytoma (Fig. 15.4) experienced painful spasms of the neck and shoulder muscles 6 months following radiation therapy. Tizanidine, 2 mg three times a day, had minimal effects, and nonsteroidal anti-inflammatory analgesics were not helpful. Abnormal neurological findings included a left sixth and seventh nerve paresis, left side spasticity, and gait ataxia.

Administration of onabotulinumtoxinA into the neck and shoulder muscles resulted in significant pain relief. The following muscles were injected: left and right splenius capitis (40 units each), left and right trapezius (40 units each), left and right levator scapulae (40 units each), and left and right sternocleidomastoid (20 units each). The total dose was 280 units. Each muscle received two injections, except for the sternocleidomastoid muscle (one injection, upper part). Injections were repeated every 3 months for 2 years until the patient passed away from complications of cancer. Each injection relieved pain for 2.5 months.

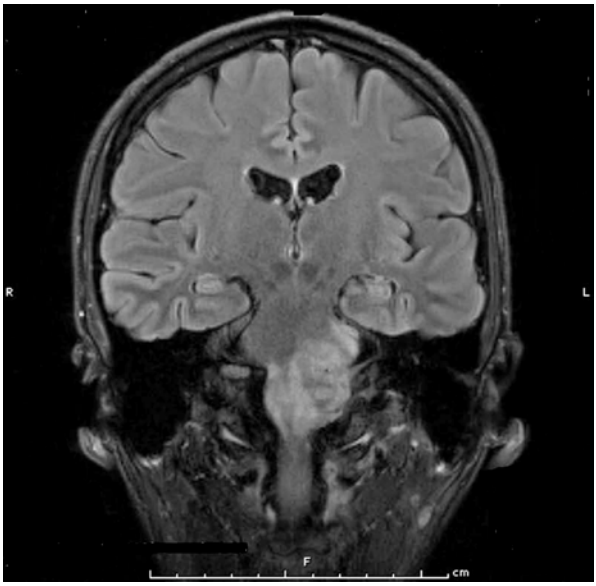

Fig. 15.4 Patient 14-5. Brain MRI showing a large pontomedullary mass

Case 3: Disabling, Painful and Dystonic Upper Limb Contractions After Gamma Knife Surgery for Recurrent Frontoparietal Brain Tumor

A 79-year-old gentleman was referred to the Yale Botulinum Neurotoxin Treatment Clinic for evaluation of painful muscle contractions affecting the left shoulder and left arm muscles. Patient had had recurrent meningiomas in the right posterior frontal region for the past several years which had resulted in focal motor seizures of the left side. These seizures were treated with a variety of medications, most recently with a combination of Depakote (750 mg daily) and Klonopin (2 mg daily). The recent abnormal movements, however, had begun 3 months ago shortly following a Gamma Knife surgical excision of a recurrent right posterior frontal lobe tumor. The movements were different from those associated with his seizures in that they occurred as episodic "very painful" contractions of the left upper limb muscles associated with "wandering movements" of that limb. These painful contractions failed to respond to non-opioid analgesics and to 10 mg three times daily of baclofen.

On examination, the patient had a mild left hemiparesis. Several episodes of involuntary movements of the right upper limbs were noted during examination. These were characterized by dystonic posturing of the limb with elbow extension, elbow flexion, arm adduction, and wrist flexion and extension. The affected arm also, at times, wandered around aimlessly. These dystonic muscle contractions and postures were painful, unnerved the patient during the day and interfered with his sleep. A magnetic resonance imaging showed areas of edema in the white matter deeper than the posterior frontal mass lesion, possibly related to radiation necrosis from the Gamma Knife procedure (Fig. 15.5).

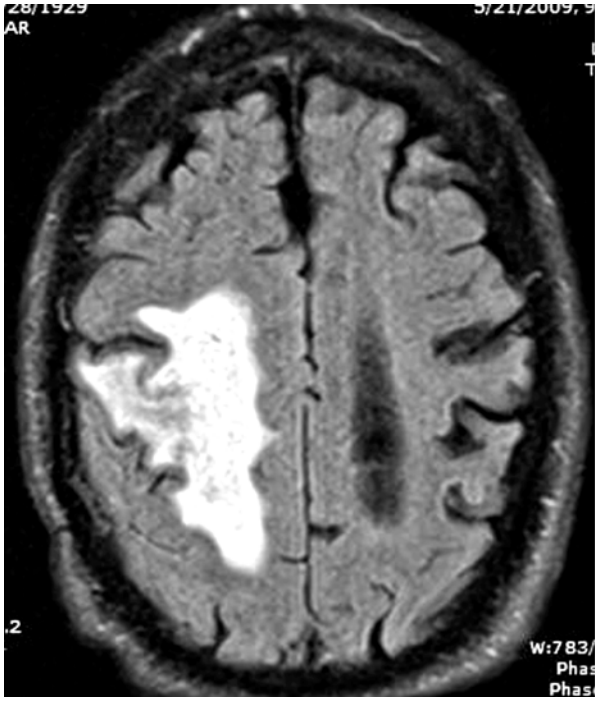

Fig. 15.5 Patient 15-5. T1-weighted brain MRI shows the right frontal mass and edema

Over the next 2 years, the patient was treated with intramuscular injections of onabotulinumtoxinA into the left upper limb and shoulder muscles: biceps (100 units), triceps (100 units), pectoralis (100 units), deltoid (40 units), trapezius (60 units), flexor carpi ulnaris (60 units), and flexor carpi radialis (40 units) for a total of 500 units per session. This treatment reduced the frequency of patient's painful episodic dystonia by 80 % as well as lowering the intensity of each episode by 50–70 %. BoNT therapy was repeated every 3–4 months. Patient and his wife repeatedly commented on the improvement of his quality of life. The patient died from complications of his brain tumor 2 years after initiation of BoNT therapy.

Comment

Although no blinded and prospective studies are available on the role of BoNT therapy for pain in advanced cancer, the aforementioned observations illustrate that BoNT therapy provides an avenue for treatment for end of life cancer pain which is effective and has a low side effect profile. The infrequency of treatment (every 3–4 months) is an advantage for patients who are too sick to take or remember tasking additional daily medications. Each of the three patients presented above enjoyed a significant improvement of the quality of their final months of life. In case of patient 1, BoNT therapy enabled the patient to eat and with less pain. Patient 2 experienced considerably less neck and shoulder pain. Patient 3 had less daily pain, better rest, and better sleep.

Conclusion

Preliminary data demonstrate that local injection of botulinum neurotoxins (ona, abo, and inco) can significantly reduce the local pain experienced by cancer patients after surgery and radiation therapy. The BoNTs seem to have an analgesic effect both in neuropathic pain and pain resulting from muscle spasms. Onabotulinumtoxin A, in a limited number of patients, has improved the end of life quality for cancer patients through its analgesic effect.

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