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Human chromaffin cell graft into the CSF for cancer pain management: a prospective phase II clinical study

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Abstract

A number of pre-clinical studies have demonstrated the value of adrenal medullary allografts in the management of chronic pain. The present longitudinal survey studied 15 patients transplanted for intractable cancer pain after failure of systemic opioids due to the persistence of undesirable side-effects. Before inclusion, all the patients had their pain controlled by daily intrathecal (I-Th) morphine administration. The main evaluation criteria of analgesic activity of the chromaffin cell allograft was the complementary requirement of analgesics and in particular the consumption of I-Th morphine required to maintain effective pain control. Out of the 12 patients who profited from enhanced analgesia with long-term follow-up (average 4.5 months), five no longer required the I-Th morphine (with prolonged interruption of systemic opioids as well), two durably decreased I-Th morphine intake and five were stabilized until the end of their follow-up. Durable decline and stabilization were interpreted as indicative of analgesic activity by comparison with the usual dose escalation observed during disease progression. In most cases, we noted a relationship between analgesic responses and CSF met-enkephalin levels. The results of this phase II open study demonstrate the feasibility and the safety of this approach using chromaffin cell grafts for long-term relief of intractable cancer pain. However, while analgesic efficacy was indicated by the reduction or stabilization in complementary opioid intake, these observations will need to be confirmed in a controlled trial in a larger series of patients.

Keywords: Cancer pain; Chromaffin cell; Allograft; Intrathecal morphine; Met-enkephalin

1. Introduction

It is estimated that about 90% of the chronic pain stemming from progression of malignant tumours can be effectively controlled using the WHO three-step analgesic-ladder approach (Zech et al., 1995). However, some patients develop intolerable side-effects and resistance to adjuvant treatments. In addition, the use of systemic routes of administration (e.g. oral, transdermal) may be hampered by the increases in daily doses of opioid; this pseudo-tolerance stems from the progressive increase in noxious stimulation during the course of the disease.

In selected patients with intractable cancer pain, these iatrogenic problems may be overcome by intrathecal (I-Th) spinal or intra-cerebro-ventricular administration of morphine and/or bupivacaine. Direct administration of morphine into the CSF, designed to act directly on opioid receptors in the posterior horns of the spinal cord or the brain stem, can induce powerful analgesic activity at very low doses and with limited side-effects at a stage where systemic administration is no longer tolerated (Wang, 1977; Lazorthes et al., 1980, 1995a,b; Leavens et al., 1982; Tung et al., 1982; Penn and Paice, 1987; Onofrio and Yaksh, 1990; Follett et al., 1992).

However, this alternative route has several drawbacks, including cost, the need for specialized maintenance and possible mechanical complications of the implantable delivery systems, and the risk of bacterial contamination when the injection is repeated at requisite intervals from an access port (Lazorthes et al., 1985; Sallerin-Caute et al., 1998;

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Mercadante, 1999). Cell therapy thus offers promise in such cases.

The chromaffin cells localized in the medullary portion of the adrenal glands were selected as they produce and release high levels of opioid peptides and catecholamines (Livett et al., 1981; Wilson et al., 1982; Coupland, 1989) as well as other neuropeptides (somatostatin, neurotrophic factors) in culture.

These neuroactive endogenous substances have been shown to reduce, independently and perhaps synergistically, pain sensitivity after injection into the lumbar spinal CSF of normal rats (Yaksh and Reddy, 1981; Wilcox et al., 1987; Drasner and Fields, 1988; Sherman et al., 1988). Pre-clinical studies have shown that adrenal medullary tissue or isolated chromaffin cell transplants into the spinal subarachnoid space induce a powerful and long-lasting analgesia without neurotoxicity in acute or chronic pain models (Sagen et al., 1986a,b; Sagen and Pappas, 1987; Wang and Sagen, 1994; Siegan and Sagen, 1997). In addition, there is no apparent decrease in the analgesia induced by these allografts over 6 months, and symptoms of arthritic or neuropathic pain do not recur following transplantation (Hama and Sagen, 1993, 1994).

The analgesia induced by chromaffin cell grafts probably stems, at least in part, from the catecholamines and opioid peptides released into the host CSF, since it is reversed or attenuated by opiate and adrenergic antagonists. In addition, catecholamines and met-enkephalin levels in the CSF are raised following chromaffin cell allografts, compared to 'sham' animals implanted with fragments of muscle (Sagen and Kemmler, 1989; Sagen et al., 1991).

The results of these pre-clinical studies suggested that chromaffin cell allografts provide a local endogenous source of opioid peptides and catecholamines. They would act as 'living biological pumps', releasing sufficient amounts of these substances do diminish the chronic pain durably, but without the development of tolerance (Wang and Sagen, 1994, 1995).

The initial clinical results of this innovative concept have been somewhat contradictory.

- A first trial on two patients concluded that this method did not represent a useful alternative (Vaquero et al., 1988, 1989).
- Other preliminary clinical studies have claimed long-lasting analgesia in correlation with the release of met-enkephalin and catecholamines in the CSF (Sagen et al., 1993; Winnie et al., 1993; Lazorthes et al., 1994, 1995a,b, 1996). Cell therapy for pain control has yet to be validated in a large series of patients (Foley and Yaksh, 1993).

The primary objective of this pilot clinical study (phase II open) was to determine the feasibility of this innovative approach and to verify its long-term safety. The secondary aim was to record the conditions for analgesic activity of adrenal medullary allografts, as indicated by a stabilization, reduction or complete cessation of complementary (systemic and intrathecal) analgesic intake in these progressive and terminal conditions. The 15 patients in this open, single centre and prospective clinical study were recruited between June 1993 and January 1998. The protocol complied with statutory ethical practices in France, and was approved in December 1992 by the Consultative Committee for the Protection of Persons in Biomedical Research (CCPPRB) and by the Ethical Committee of our Institution.

2. Patients and methods

2.1. Patient population (Table 1)

The patients were recruited and selected in the Multidisciplinary Pain Center at Toulouse University Hospital. The clinical study included 15 adult patients (10 men and five women) from 39 to 83 years, with severe pain lasting from 3 to 60 months (mean 15 months) and related to regional extension ($n = 14$) or bone metastasis ($n = 1$) of a visceral cancer at advanced and inoperable stages (rectum (5), lung (4), colon (2), urethra (1), parotid (1), breast (1), uterus (1)). The topography of the intractable pain was localized to lombo-sacral metameres in most patients ($n = 8$), thoracic metameres in four patients, the lower cervical area in one case (patient 13), the cervico-facial area in another case (patient 12), and one case (patient 2) presented diffuse painful bone metastases.

In 14 cases out of 15, the pain physiopathology was attributed to excess noxious stimulation secondary to regional invasion of the malignant tumour ($n = 13$) or to diffuse bone metastases ($n = 1$). One case (patient 13) presented with pain of mixed mechanisms (Pancoast–Tobias syndrome), in which the neuropathic component secondarily dominated the clinical picture due to progressive deafferentation of the distal end of the upper limb.

2.2. Inclusion criteria

All the patients presented irreducible pain related to clearly established, non-resectable cancerous lesions. The pathophysiological mechanism of the intractable pain was nociceptive and in relation to a loco-regional and/or metastatic extension of the cancer. All the selected patients were adults at terminal stages of their disease with a life expectancy of a few months.

The chronic pain was expected to respond to morphine via oral and/or transdermal routes. The failure of systemic opioids was related to the persistence of undesirable side-effects rather than to tolerance despite the usual dose escalation. For this reason, we had to employ an alternative I-Th route of administration. All the included patients had their pain controlled (pain score between 0 and 2) by daily I-Th morphine administration using a lumbar access port