Untreatable Pain Resulting from Abdominal Cancer: New Hope from Biophysics?

Giuseppe Marineo

Delta Research & Development, Research Center for Medical Bioengineering, "Tor Vergata" University. Rome, Italy

ABSTRACT

Context Visceral pain characterizing pancreatic cancer is the most difficult symptom of the disease to control and can significantly impair the quality of life which remains and increase the demand for euthanasia.

Aim To investigate a possible new method based on biophysical principles (scrambler therapy) to be used in the effective treatment of drug-resistant oncological pain of the visceral/neuropathic type.

Setting Eleven terminal cancer patients (3 pancreas, 4 colon, 4 gastric) suffering from elevated drug resistant visceral pain.

Design The trial program was related to the first ten treatment sessions. Subsequently, each patient continued to receive treatment until death.

Main outcome measures Pain measures were performed using the visual analogue scale before and after each treatment session and accompanied by diary recordings of the duration of analgesia in the hours following each single application. Any variation in pain-killing drug consumption was also recorded.

Results All patients reacted positively to the treatment throughout the whole reference period. Pain intensity showed a significant decrease ($P<0.001$), accompanied by a gradual rise both in the pain threshold and the duration of analgesia. Nine (81.8%) of the patients suspended pain-killers within the first 5 applications, while the remaining two (18.2%) considerably reduced the dosage taken prior to scrambler therapy. No undesirable side effects were observed. Compliance was found to be optimal.

Conclusions The preliminary results obtained using scrambler therapy are extremely encouraging, both in terms of enhanced pain control after each treatment session and in view of the possible maintenance of effectiveness over time.

INTRODUCTION

The onset of pancreatic cancer pain is perceived as an essentially pure visceral pain which occurs via activation of mechanoceptors in response to intense stimuli. As the pathological conditions worsen and the tumor invades other structures, its characteristics develop and it takes on the features of visceral-somatic and visceral-neurogenic pain. The fibres that conduct visceral pain - Adelta fibres, conduction velocity (CV) 2.9-14.9 m/s, and C fibres, CV<2.9 m/s - are of the somatic and parasympathetic type. They differ from the nociceptive fibres of the somatic structures owing to their decreased innervation, mode of distribution and myelinic/amyelinic fibre ratio (1:4 in the superficial structures, 1:9 in the

visceral ones). These characteristics demand intense and prolonged stimuli in order to produce a sensation of pain. Furthermore, the reduced number of Adelta fibres means less control at the central level, which is reflected in an increase in vegetative reflexes (reduced arterial pressure, diffuse perspiration, slower cardiac frequency). When the visceral pain is deep, the pulses reach the upper nervous centres directly through the normal pain pathways. As a result of highly intense phenomena or the involvement of the serous surfaces of the viscera, the pain is often more superficial, at the level of the skin (process of parietalization of visceral pain). The superficial manifestation of visceral pain tends to mask the feeling of deep pain, and reduces the associated neurovegetative phenomena. The fibres of the algogenic sensitivity of the pancreas, through the celiac plexus, the splanchnic nerves and the communicating branches, reach the posterior spinal roots from the VI to the XI-XII thoracic segment. In cancer of the pancreas, the pain is caused by capsular distension or by infiltration of the splanchnic nerves, particularly in the advanced stage [1, 2]. Frequent failure in responding to drug treatment suggests using neurolesive options, in particular neurolithic celiac plexus blockage (NCPB), as an elective choice in the treatment of pancreatic cancer pain [3]. This option is not always feasible and may present risk factors linked to the mode of execution (paraplegia, monoparesis with loss of vescical and anal function, sexual dysfunctions) [4, 5, 6]. Even when the outcome is successful, the neurolesive technique, in any case, requires the prescription of painkillers, mainly opioids, and the effectiveness of the painkiller wears off in time [7, 8, 9]. This type of intense, devastating pain strongly undermines the patient's will to survive, often leading to a request for euthanasia. It also has a strong effect on the people caring for the patient and has important implications for health care management policies. These problems have been addressed in an analytical approach in which effective solutions were sought with the help of biophysics and bioengineering. During the basic research design phase leading up to the development of "scrambler therapy", one of the criteria selected as significant was that of non-invasiveness in order to respect the patient's dignity and quality of life as far as possible.

Basic Principles of Scrambler Therapy

The pain system, like the entire tegumentary system, is characterized by a high level of information content which forms its essence. Specific receptors, normally subdivided into two classes (mechanoceptors for mechanical stimuli and multimodal receptors for those that respond indifferently to all painful stimuli), are biological elements that are able to convert a chemical, physical or mechanical event into specific pain information. Many substances have the capacity to dynamically modulate the response to pain by sensitizing or desensitizing the receptors and the conduction/processing pathways during the ascending phase. The complex modifications activated by the nervous system in response to a painful stimulus are thus the focus of a wide variety of organic reactions also designed to re-establish conditions of homeostatic equilibrium which the pain information signals as being disturbed or in danger. In most cases, this equilibrium can be rapidly restored thanks to a series of reactions involving much of the biological system as a whole. In this case, pain information, its purpose achieved, returns to a silent state. However, there are situations in which this has not happened, either due to the impossibility of removing the cause of the biological damage or due to intrinsic damage to the pain system itself (neuropathies) as a result of damage due to compression of the nerve fibres. In such a context, the onset of very extensive, complex reactions may be observed, themselves capable of modifying the original information triggering the pain phenomenon (sensitization-autonomization), thus setting up an iterative process which, in the case of chronic pain, and of neuropathic and visceral pain in particular, tends to render all known therapeutic strategies gradually (or

completely) ineffective. The useful fact that emerges from all these scenarios is the central role of control exerted by information over the chemical-structural variations of the system. I mention *en passant* the fact that by information we mean the measurable and mathematical expressible component of a news item or rather the measurable elimination of the uncertainty of an arbitrary event. In this case, information is represented by the sequence of pulses generated by the activated nociceptor, pulses that "describe" the type of pain, attributing to it specific properties such as, for example, the intensity or the type of sensation experienced. Overall, this represents a good description of a cybernetic process, that is, one of communication (pain information) and regulation (chemical feedback to modify perception and adaptive reactions). It may thus be reasonably assumed that it is possible to control the lower levels of the complexity of the pain system (the chemical reactions regulating the coding of pain information and subsequent feedback) by manipulating the "information" variable alone at higher levels of complexity. An arbitrary system level must, in this case, be such as to be able to make up for the incomplete knowledge characterizing the role of the chemical molecules involved in the pain phenomenon, which may conveniently be represented by means of the “black box technique”. This involves using a model in which the input and the output are known but not the internal translation process taking place inside the "box". It must also take place at a stage at which information expression is sufficiently "visible" for it to be investigated analytically and be interpreted univocally. For it to be treated easily enough using comparatively inexpensive technology in order to develop the method, this information content has been defined and investigated at the level of complexity (emerging properties different from the individual variables interacting in this particular state of the system) expressed by the biopotentials generated by the receptors depending on the nociceptive stimulus. A brief parenthesis must be opened at this point. There is a general tendency to accept that the coding of nociceptive stimulus intensity as an equivalent pain sensation is expressed simply by an equivalent variation in the mean receptor discharge frequency, in other words a "frequency modulation". We also know that it is possible to excite a nerve fibre electrically by "synrchonizing" it with the frequency of our generator. Theoretically, therefore, if the generic coding by means of which a receptor transforms the stimulus to which it responds into information, a simple variable frequency generator would be sufficient to successfully simulate and evoke many different types of perception. However, we know that this is not true. In fact, frequency is only one of the aspects which adds information properties to the sequence of pain pulse, just as the same note on a musical instrument can be univocally identified by its frequency. However, we can all easily distinguish the same note played on a piano and on a saxophone or electronic instrument; the information for the same frequency is thus similar but different. We also know that a few musical notes, depending on the sequence linking them together, can form a large number of different sonorities. Those having a wide range of information content are decoded as music, melody, and as various sub-groups characterizing the genre; the others as noise, that is, the sequence of notes adds different significant properties to the "message" composed depending on how it is structured. A similar problem arose in the analytical study of the pain information. After having thus selected the arbitrary level of the system's complexity, a study was made of the biopotentials representing the pain information by means of their variations, expressed this time not only by the mean frequency but by their dynamic structure when placed in a sequence. In practice, the mean frequency was not considered as the mere product of biological tolerance or receptor stress but more realistically as an epiphenomenon of the "information procedure" triggered by the single pulse components generated by the receptor (which then go to make up the mean frequency),

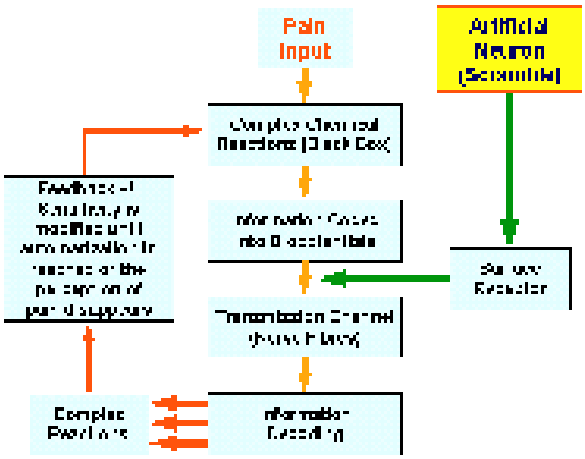

Figure 1. Simplified model of scrambler therapy.

together with the sequential relationship among them. The research procedure adopted therefore allowed a comparatively complex system model to be constructed which could be defined in purely conceptual rather than experimental terms, in which the biological variables were translated into cybernetic variables, extrapolating the role and the modality of the pain information regardless of the biochemical aspects and its etiopathogenesis, using systems theory and information theory to rationalize the research procedures. The hypothesis of operating by blocking nervous transmission was immediately rejected although it is actually one of the more commonly adopted solutions. By its very nature, the nervous system reacts to and processes information. Theoretically, the absence of information can only increase the entropy (information disorder) [10] of the channel involved, and very probably will produce adaptive reactions increasing the sensitivity to the painful stimulus. The approach actually adopted to respect the initial theoretical criteria (use of information as the active principle) was to replace the "pain" information with artificial "non-pain" information, in full respect of the information theory, to which the reader is referred to for further information. Essentially, an artificial neuron was developed that behaves as a "pain scramble", that is, as a system capable of interfering with pain signal transmission by "mixing" another signal into the transmission channel (the nerve fibres) for the purpose of masking the original information by modifying its content (from pain to non pain), although still allowing it to be recognized as "self" by the nervous system. The process is outlined in Figure 1.

Note should be taken of the many similarities but also of the important differences as compared to traditional scrambler techniques, used mainly to "protect" confidential information from possible interception during the transmission, with conversion back to the original signal on reception. In our specific case, the ultimate aim is obviously different, and there are additional conditions and aims to be respected in view of the particular type of application involved. In this sense, it is significant that the information produced by the "mixing" is not just any kind of information but has the property of being recognized, as far as possible, as "self" and as non-pain. Otherwise, the system would be totally ineffective. These conditions were obtained by simulating sequences of biopotentials artificially generated by digital synthesis and having the following characteristics.

Compatibility with the Transmitting and Receiving Channel

Construction of a set of wave forms (basic coding) which, when assembled in real time by means of suitable control algorithms, can simulate as exactly as possible the geometric trend specific to endogenous biopotentials.

Compatibility of the Information Content

Dynamic generation using artificial neurons of "packets" (strings) of information recognized as "non pain", the content of which is varied over time by means of suitable algorithms used to recognize the simulated signal as "self" and to reduce the adaptation of the perception as a function of the noise, and the amplitude of which is such that it may be decoded as the dominant stimulus by means of the over-modulation of the endogenous biopotentials. The latter

Figure 2. Prototype scrambler therapy ST5.

condition has given rise to the theoretical expectation of a favorable readaptation of algogenic sensitivity. It is hypothesized that the learning mechanism of the pain system, now "remodelled" to suit the non-pain scrambler information as a result of the well known adaptive properties that lead to a sensitization to intense and frequent pain stimuli, results in a gradual raising of the subjective pain threshold.

Global Optimization of the Simulation with the Characteristics of the Biological System

Increased compatibility of the simulated signal with the nervous system with the inclusion of the noise figure of the nervous transmission network in the principal information during simulation of the stochastic fluctuation.

MATERIALS AND METHODS

The supporting technology (Scrambler Therapy ST5, undergoing trials at Pain Service, Umberto I Hospital, Surgery Department, Frosinone, Italy) was developed as a prototype to allow the required clinical trials to be conducted in order to evaluate the method (Figure 2).
It consists of a multiprocessor apparatus able to simulate five artificial neurons which allow five pain areas in the same person to be treated simultaneously. Application is by means of single-use surface electrodes applied to the skin area corresponding to the pain areas involved. The treatment is fully automated, including the dynamic parametrization required for the correct functioning of the method. This criterion, rendered inevitable by the active principle involved, ensures a very high degree of repeatability of the experimental data as it is not necessary to select the operating parameter manually except for the simple regulation of stimulus intensity, which is manually set at the perception threshold. On the average, each treatment sessions lasts 45 minutes; the required frequency is changed to suit the subject concerned and, after the initial attack therapy, may even consist of a single treatment every 24 hrs.

Patients

Eleven patients, (3 males and 8 females; mean age: 63.5 years, range 47-77), all suffering from intense drug-resistant visceral pain and at an advanced stage of oncological disease with widespread metastases, were recruited for the trial.
Inclusion criteria were: presence of very intense visceral pain (baseline visual analogue scale pain value greater or equal to 70) during drug treatment with or without neuropathic complications. Exclusion criteria were: pacemaker user, neurolithic blockage of the celiac plexus and other neurolesive pain control treatments.
Three patients (27.2%) had pancreatic cancer and the remaining 8 patients, although affected by a different type of cancer (4 colon, 4 gastric), displayed intense visceral pain, likely to be associated with neuropathic type complications due to the advancement of the metastatic process. No imaging data are available to support this since it was chosen not to force patients to undergo any further psychological stress and raise their concerns about the advancement of the disease. The life expectancy of all patients was less than two months. In all patients, the failure of all therapeutic approaches other than palliative therapy had also been ascertained.

Experimental Design

The trial program was based on a cycle of ten therapy sessions. Each session was performed at the patient's request when the pain

reappeared. The timing varied depending on the duration of the state of analgesia in the patient. At the completion of the ten sessions, each patient was allowed to continue the applications until death.
We evaluated the pain intensity before and after each treatment session, the duration of analgesia after treatment and the variation in drug consumption.
Pain intensity was evaluated using the visual analogue scale (VAS) [11, 12]. This linear scale consists of the visual representation of the pain amplitude as perceived by the patient. The amplitude is represented by a 100-mm line long having no reference marks. One extremity indicates absence of pain (0 value) and the other the worst imaginable pain (100 value). The scale was indicated before and after each treatment session by the patient marking the pain level experienced on the scale. This type of test can easily be repeated over time, has the advantage of simplicity, is widely used, is language-independent and is easily understood by the majority of patients.
Each patient was requested to keep a diary in which they noted the duration, expressed in hours, of the absence of pain (or, in the case of partial analgesic effect, from the beginning of the relapse phase) after each treatment, the intensity of the pain when it reappeared and the consumption of painkillers, if used.
The variation in the request for drug treatment is of considerable help in determining whether pain intensity is truly reduced appreciably as indicated by VAS scores. The treatment protocol entailed abandoning or reducing the basic pain control therapy in the case of effective pain reduction by scrambler therapy. Drugs (wherever appropriate) were eliminated in a stepwise fashion during the trial period depending on the molecule used, the baseline dosage and the response to scrambler therapy. A similar criterion was used to reduce the dosage and to vary the type of drug used in order to minimize any undesirable side effects in those cases in which it was not possible to achieve complete elimination. The variation in the request for drug treatment is of considerable help in determining whether pain intensity is truly reduced appreciably as indicated by VAS scores.
Compliance was evaluated through a questionnaire which took into account the degree of satisfaction for the treatment received (as for efficacy and tolerability), any possible adverse effects and the most relevant quality of life parameters (sleep, mood, interrelationships, etc.).

Main Outcome Measures

Remodulation (Raising) of the Pain Threshold

It was evaluated by comparing the pre-treatment VAS data between the first and the tenth treatment session.

Effectiveness within Each Individual Treatment Session

In our specific case, the effects due to the method were assessed by analyzing the pain intensity differences (PID: VAS decrease before and after each treatment). Data referring to the first treatment session is the only one that is not affected by remodulation of the pain threshold and, thus, by the compression of the relative differences in individual responses over the 10 treatment sessions.
The graphic analysis of successive VAS responses and of the percentage ranges of complete or significant pain remission after treatment completes the overall data expression. This was reported by stratifying the severity of pain recorded after treatment as follows: no further pain, VAS equal to 0; slight pain, VAS 1-20; intense pain, VAS greater than 20.

View of Possible Application of the Method at the Patient's Home

An assessment was made of how often treatment would be required to maintain optimal pain control together with the analysis of the persistence of analgesia expressed in hours.

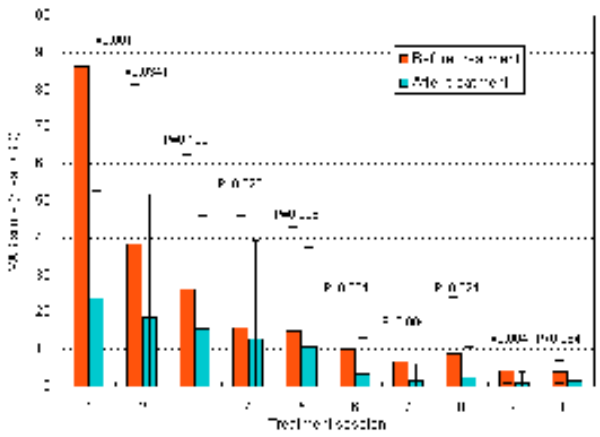

Figure 3. VAS trends before and after each treatment session.

ETHICS

Informed consent was obtained from all the patients recruited. The treatment protocol complied with the 1975 Helsinki guidelines as subsequently amended. The protocol was approved by the Bioethics Committee of the Umberto I Hospital of Frosinone, Italy.

STATISTICS

VAS and PID data are reported as mean values and standard deviations (SD). The statistical significance of VAS was measured by means of the paired t-test by running the SPSS/PC+ statistical package using a personal computer. Two-tailed P value less than 0.05 were considered statistically significant.

RESULTS

During the applications, all the patients reported a very rapid (in the order of a few seconds) disappearance of the perception of pain. All patients responded fully to the protocol and none reported undesirable side effects. Compliance was excellent.

VAS trends before and after each treatment session in the cycle are reported in Figure 3. The figure shows how the baseline VAS preceding the treatment has a mean value for the whole group of over 86 points out of a maximum of 100 (maximum imaginable pain), and that this decreases rapidly after the first treatment session (P<0.001). If we observe the trends for subsequent treatments, we find that, despite the reduction or elimination of the supporting painkilling drugs taken at the beginning of the trial, the baseline VAS drawn up prior to application is lower and lower, which indicates not only a persistent absence of pain, but a re-adaptation of the pain system, which is in agreement with the theoretical assumptions. Several slight fluctuations corresponding to the eighth and the tenth treatment sessions are likely due to complications in the oncological conditions of one of the patients, which contributed to a slight increase of the overall average.

The difference between pain intensity prior to scrambler therapy treatment (i.e. at full painkiller dosage) and baseline pain intensity in the absence of treatment at the tenth cycle (i.e. at the absence, or marked reduction, of painkilling drugs; see below) was also highly significant (-82.3±10.9; P<0.001).

Another factor to be taken into account in the evaluation of painkilling treatment is the determination of the pain intensity difference (PID) in VAS scores before and after each treatment session as shown in Figure 4.

During the reference period, nine out of

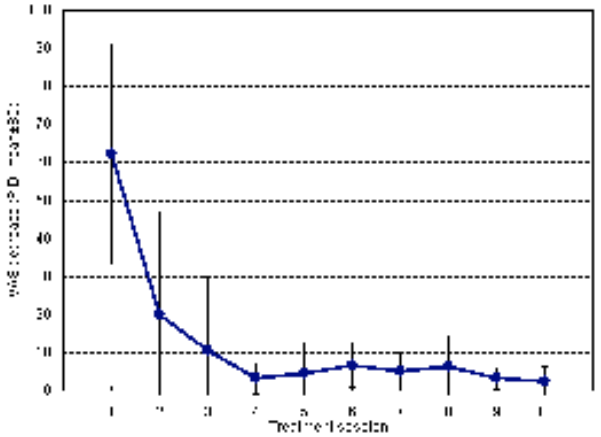

Figure 4. Pain intensity difference values (PID: mean±SD VAS score difference before and after each treatment). The gradual flattening of the curve is indicative of a reduction in the differences as the number of treatment sessions increases. The phenomenon is due to a rising pain threshold, which is reflected in a lower pre-treatment baseline VAS, while the post-treatment VAS can never be negative. Several peaks may realistically be ascribed to other possible causes as the disease progresses.

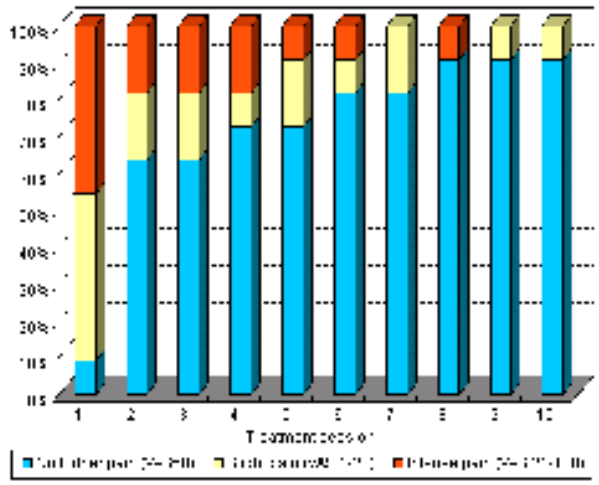

Figure 5. Percentage of patients stratified according to the severity of pain recorded after treatment: no further pain (VAS=0), slight or very slight pain (VAS 1-20), more intense pain (VAS>20).

eleven patients (81.8%) are seen to have stopped requesting painkillers between the second and the fifth treatment session. The remaining two patients (18.2%) considerably reduced their dosage and undertook mild therapy.

Figure 5 shows the percentage of patients stratified according to the severity of pain recorded after treatment. As treatment progresses, the effectiveness of analgesia which takes place between the 2nd and the 5th treatment session increases even after the elimination (or reduction) of drugs.

In view of the possible application of the method at the patient's home, an assessment was made of how often treatment would be required to maintain optimal pain control (Figure 6). Right from the first treatment session, 7 patients (63.6%) were able to get by on a single treatment session every 24 h or more, a percentage that rose to 90.9% by the end of the cycle. The remaining patient (9.1%) is situated in a window in which an average of 2 treatment sessions are required every 24 h.

DISCUSSION

In recent years, our physiopathological and biochemical knowledge concerning pain has increased considerably, without however being accompanied by a corresponding increase in the effectiveness of pain management therapies in the case of severe pain such as that of pancreatic cancer, or of visceral pain in general. Perhaps the most important experience emerging from the research leading up to the conception of scrambler therapy is the possibility of obtaining truly significant results through a change in approach and perspective in analyzing a problem and that medical science can benefit extensively from the advancement in knowledge which can lead to clinical applications when analytical multidisciplinary approaches are followed. It should be considered that several ideas emerging from the study of scrambler therapy can be usefully applied in other fields. It must be emphasized that the decision not to interrupt the perception of pain by blocking the pathways but rather to control its properties by manipulating a metavariable system, currently seems to be a solution that is as innovative as it is successful and which perhaps represents the beginning of a new era in previously untreatable pain therapy.

As far as the gastric cancer case is concerned, where a marked improvement of pain was achieved with a drastic but not a complete reduction of pharmacological therapy (from ketorolac 90 mg/day plus tramadol 400 mg/day, to only ketorolac 30 mg/day), we suspect that this was due to an incomplete involvement of pain pathways which must

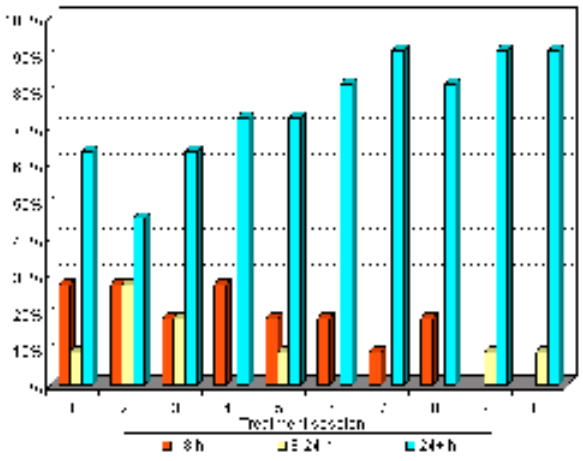

Figure 6. Distribution of the patients according to the mean duration of absence of pain after each single application.

have been only partially affected by surface receptors. This is in agreement with the observation that, in the last two sessions, the duration of analgesia was prolonged throughout 24 h.

CONCLUSION

The preliminary results obtained using scrambler therapy are extremely encouraging, both in terms of enhanced pain control after each treatment session and in view of the possible maintenance of effectiveness over time. In the latter case, in agreement with theoretical predictions, a gradual reduction is found in baseline VAS as well as unchanged effectiveness until death results. This can be verified both by analyzing the VAS trend and by processing the differences in PID data. However, one of the aims of the treatment was precisely the reduction of these differences to a minimum by raising the pain threshold. From our data it can actually be seen how the VAS values observed before each treatment session decrease, unlike the trend normally observed in terminal patients [13, 14, 15]. Finally, all patients responded fully to the protocol and none reported undesirable side effects. Compliance was excellent.

The following conclusions may be drawn from these preliminary results:

- scrambler therapy produced a statistically significant pain control response;
- the absence of the pain control response was increasingly prolonged for many hours after the end of the session as the number of treatment sessions increased, indicating a favorable remodelling of the pain system;
- no undesirable side effects were reported;
- all the patients displayed excellent compliance with the treatment;
- the support of painkillers rapidly proved unnecessary in 9 patients out of 11 and was reduced to very low levels in the remaining two.

This extremely positive outcome suggests performing more extensive trials of scrambler therapy in order to obtain further knowledge. In view of the completeness and the extent of the results, it may reasonably be assumed to be a very productive approach and thus in the near future it will be possible to treat pancreatic cancer pain easily and without side effects. The intensity and difficult management of this pain has always been considered a focal point of the disease and significant efforts should be made to improve the patient's quality of life, which often amounts to prolonging the life itself.

Received October 2nd, 2002 – Accepted December 6th, 2002

Keywords Analgesics; Cybernetics; Drug Resistance; Hyperalgesia; Information Theory; Pain, Intractable; Pain Threshold; Palliative Care; Pancreatic Neoplasms

Abbreviations CV: conduction velocity; NCPB: neurolithic celiac plexus blockage; PID: pain intensity difference; VAS: visual analogue scale

Acknowledgements We wish to thank Prof. AF Sabato and Dr. S Spaziani for their knowledge of oncological pain and treatment protocols.

Correspondence
Giuseppe Marineo
Delta Research & Development
Università degli Studi di Roma Tor Vergata
Via di Mezzocammino, 85
00127 Rome
Italy
Phone: +39-06-5237.1173
Fax: +39-06-5237.1171
E-mail address: g.marineo@mclink.it

References

1. Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, et al. Abdominal pain in patients with resectable pancreatic cancer with reference to clinicopathologic findings. Pancreas 2001; 22:279-84. [AN 21187273]

2. Di Sebastiano P, Friess H, Di Mola FF, Innocenti P, Buchler MW. Mechanisms of pain in chronic pancreatitis. Ann Ital Chir 2000; 71:11-6. [AN 20288327]

3. Yamamuro M, Kusaka K, Kato M, Takahashi M. Celiac plexus block in cancer pain management. Tohoku J Exp Med 2000; 192:1-18. [AN 21012934]

4. De Conno F, Caraceni A, Aldrighetti L, Magnani G, Ferla G, Comi G, Ventafridda V. Paraplegia following coeliac plexus block. Pain 1993; 55:383-5. [AN 94167133]

5. Abdalla EK, Schell SR. Paraplegia following intraoperative celiac plexus injection. J Gastrointest Surg 1999; 3:668-71. [AN 20021999]

6. Iftikhar S, Loftus EV Jr. Gastroparesis after celiac plexus block. Am J Gastroenterol 1998; 93:2223-5. [AN 99036287]

7. Vranken JH, Zuurmond WW, de Lange JJ. Increasing the efficacy of a celiac plexus block in patients with severe pancreatic cancer pain. J Pain Symptom Manage 2001; 22:966-77. [AN 21585990]

8. Rykowski JJ, Hilgier M. Efficacy of neurolytic celiac plexus block in varying locations of pancreatic cancer: influence on pain relief. Anesthesiology 2000; 92:347-54. [AN 20153078]

9. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia S. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. Br J Surg 1998; 85:199-201. [AN 98162436]

10. Shannon CE, Weaver W. The mathematical theory of communication. Urbana, IL: The University of Illinois, 1949.

11. Dixon JS, Bird HA. Reproducibility along a 10 cm vertical visual analogue scale. Ann Rheum Dis 1981; 40:87-9. [AN 81132411]

12. Flandry F, Hunt JP, Terry GC, Hughston JC. Analysis of subjective knee complaints using visual analog scales. Am J Sports Med 1991; 19:112-8. [AN 91247547]

13. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 1: clinical considerations. J Pain Symptom Manage 2001; 21:144-50. [AN 21126086]

14. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 2: basic mechanisms that could shift dose response for analgesia. J Pain Symptom Manage 2001; 21:255-64 [AN 21136475]

15. McCormack K. Fail-Safe Mechanisms That Perpetuate Neuropathic Pain. Pain: Clin Updates 1999; VII:3.