Key Factors for Best Control of the Systemic Leakage During Hyperthermic Isolated Limb Perfusion (HILP) in ECC. A Critical Synthesis of Our Experience

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The L-PAM-ILP procedures under true hyperthermal regime (41.5-41.8°C) require both close control of the physical parameters of the treatment (temperatures profiles and time duration, artero-venous pressure, perfusate flow rate) and medical rationale (drug, dosage, fractioning, timing). All the above essential procedures must be supported by rigorous methodology, reliable operation of the medical devices and apparatus and real-time monitoring of the treatment parameters. Real-time monitoring is essential for proper trimming and modulation of the parameters during treatment. This paper delineates the technical improvements that we have implemented for drug leakage monitoring and control in the systemic circulation aimed at improving the therapeutic efficacy and at reducing the occurrence of unexpected complications.

Key Words: Leakage, Isolated perfusion, Chemo-hyperthermic treatments, Limbs tumour

The theoretical preliminary assumptions technically characterising the regional perfusion treatments delineate the realisation of conditions permitting strictly controlled endovascular administration of the cytotoxic anti-tumour agents, over a confined volume (the seat of the neoplasm). In the chemo-hyperthermic treatments of the limbs the above conditions are obtained through vascular isolation, insertion in extracorporeal circuit, blockage of the circulation collateral to the cannulated vessels and blockage of the surface vascularisation to reduce the perfusate leakage toward the systemic circulation. It is to be noted that the isolation effectiveness is relevant to reduce the systemic pharmacological toxicity of the treatment but it is also of help to reduce thermal loss from the limb to the trunk. In practice, uncontrolled heat loss from the limb mainly occurs through thermal conduction at the limb-root tissues only (1).

The vascular isolation (deep and superficial) when the approach is at the limb root, consists of a) cannulation of the main artery and vein (axillary or external iliac or femoral vessels), b) temporary ligature of the collateral branches and c) blockage of the superficial muscular-cutaneous circulation through constriction at the limb root with an Esmarch belt, according to the now standard technique devised and realized by Creech *et al.*. in 1958 (2). The temporary vascular isolation permits to: a) administer high cytostatic drug concentrations; b) contain the systemic toxic effects within acceptable limits; c) associate hyperthermia for synergic enhancement of the anti-tumour action of the chemotherapy; d) re-circulate the drugs during the whole perfusion time duration thus increasing exposure to the therapeutic effects; e) perform a wash-out process at the end of the perfusion prior to the limb revascularisation. These basic requirements represent the fundamental elements characterising the ILP treatments.

The considerations that follow represent a synthetic discussion of the improvements we have adopted following the outcome of our clinical and technological experience. As a matter of fact we realise that the overall methodological approach to be adopted in the perfusion procedure is to be fitted in each case to both the peculiarities of the neoplasm (hystological and evolutionary biological characteristics, specific location within the district) and to the treatment protocol (type/types of chemotherapeutic drugs, dosages, frac-

tioning and sequence, association with additional synergic anti-tumour agents, grade of toxicity) (3). With specific reference to the vascular isolation, it is to be stressed that maximum attention must be devoted to the above mentioned peculiarities to obtain safe and effective treatments with optimised biological effects of the cytotoxic agents through a complete and homogeneous perfusion throughout the district.

We are thus going to analyze and discuss the methodological improvements we have devised and implemented in connection with: a) optimization of the vascular isolation; b) development and implementation of the technique for continuous leakage monitoring during the hyperthermic isolated regional perfusion (HILP) treatments and c) real-time intra-operative monitoring and control of the main relevant physical parameters, namely circuit and body temperatures, arterial and venous pressure, perfusate flow rate. All three aspects above represent essential requirements for the containment of the leakage and must be subjected to close control, according to provisions derived from our long-lasting clinical and technical experience.

Vascular Isolation of the Limbs

The vascular isolation techniques available are to some extent dependent on hystotype and localisation of the tumour. We focus our attention on limb melanoma and soft-tissue sarcoma. Considering melanomas first, the technical opportunities offered by the regional perfusion appear especially desirable when considering the existence of sub-clinical metastatic regional diffusion (melanoma stage III according to the Anderson Hospital Classification). The concept of regional treatment thus intrinsically requires spatial uniformity. The active principles (drugs, heat, synergism) are required to act with equal intensity throughout the various districts of the limb. The therapeutic agents should be uniformly distributed throughout the limb in order that the sub-clinical targets be hit, along with the observable lesions (4,5). Basically, our starting assumption was that uniform extension of the treatment over the entire target region is to be given dominant priority and in that respect our specific decision was to perform the vascular isolation at the level of the axilla vessels in the upper limb and at the level of the external iliac vessels in the lower limb (in the case of a lower-limb second perfusion the femoral vessels are accessed). As an additional important advantage of this proximal access with large vessels involved, large-lumen cannulas can be adopted favouring high perfusate flow and consequentially a faster heating of the limb tissue. Vascular isolation procedures are detailed in previous publications (6,7) referring to a series of 267 perfusions (24 for the upper and 243 for the lower limb). We thorough analyze the provisions to obtain highly effective isolation, in particular as far as deep venous return is concerned.

In the upper limb case the axilla vessels are exposed, cannulation is performed with proximal vasotomy so that the cannula tips are positioned in the distal third of the axillary vein and artery. For the superficial vascular blockage an Esmarch belt is held in place by means of two modified Steinmann nails inserted in the subcutaneous layer of the anterior thoracic wall ("thoracic tourniquet" - Fig. 1). Through this configuration efficient tissue perfusion is guaranteed up to the limb root. Temporary exposure and ligature of the collateral sub-scapular vessels and of the cephalic vein proximally to its confluence with the axilla vein become necessary.

More complex critical aspects are present in the lower-limb case. It is known that the vascularisation of the pelvic district and in particular the internal pudenda vessels including their collateral branches show rather frequent anomalies or variances (8,9). In fact, in a previous study (10) dealing with an anatomical-surgical analysis of the iliac-obturatory and iliac-femoral vascularisation over a sample of 33 consecutive patients who had undergone perfusion treatment with either iliac or femoral approach, vascular variances or duplications were observed in six cases (18%) more frequently in reference with the venous vascularisation. These clinical evidences confined to the vascular district to be isolated led us to modifying the technique of the deep vascular blockage at the iliac level for extended and more complete isolation of the venous backflow (7). Surface isolation is obtained by constriction of the belt fastened to a pair of (modified) Steinmann nails inserted into the subcutaneous layer of the lower abdominal wall ("abdominal tourniquet" - Fig. 1). When positioning the cannulas inside the external iliac vessels care is taken so that the tips of the cannulas reach down to the common femoral vessels to ensure adequate arterial and venous flow. For the same reason when the femoral approach is adopted we perform the section of the inguinal ligament. After isolation of the common femoral vessels and of the distal segment of the external iliac vessels, vasotomies between tourniquets are performed immediately below the emergence of collateral vessels. The cannula tips are positioned in the middle portion of the common femoral vessels.

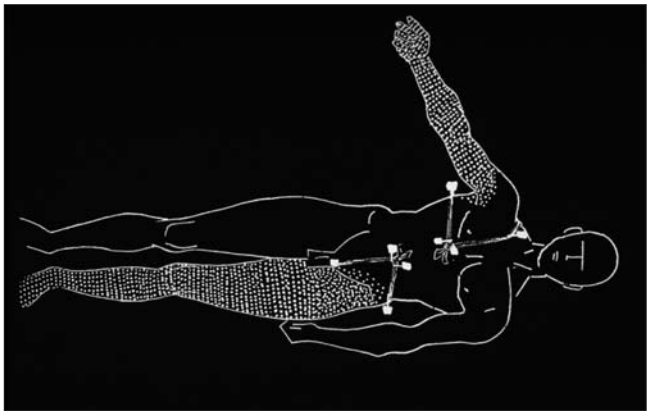

Fig. 1 - Toracic tourniquet (upper limb) and adbominal tourniquet (lower limb) allow the extension of the perfused area in whole limb.

The isolation technique based on the iliac approach developed during our initial clinical experience was the object of a study enrolling 81 patients suffering from lower limb melanoma treated with HILP-L-Pam. In 36 over 81 cases with melanoma stage I the therapeutic program was as follows: L-PAM (10 mg /l) with temperature 40-41°C; in 45/81 pts with melanoma stage II-III: L-PAM (10 mg/l and a additional bolus of 5 mg/l in 13/16 pts) plus D-actinomycin (1 mg) with temperature 41.5-41.8°C. This study aimed at verifying the feasibility of the procedures, evaluating the drug leakage and the systemic toxicity after iliac isolation using the standard technique (ligature of the obturatory vessels) associating to this in a first group (group A, 50 patients) the Internal Iliac Vein (IIV) clampage at its confluence and in a second group (group B, 31 patients) the proximal clampage of the Common Iliac Vein (CIV). The surface isolation was based on our technique according to which the belt is positioned such that the cannulas can be set in place without disturbing the surgical field both with the iliac approach and the femoral approach.

The technique adopted in the insertion of the Steinmann nails permits to constrict the belt well above the limb root thus extending the treatment to a larger superficial tissue volume. In summary, the technical and clinical advantages of the superficial vascular blockage obtained with this procedure are: a) perfusion extended to the root of the limb (including the axillary/femoral nodal districts); b) absence of any interference with the surgical field (particularly when cannulating the common femoral vessels); c) simple, fast surgical action with minimal trauma. An important additional feature of the placement of the Esmarch belt here adopted avoids the direct compression of the neural plexus which was pointed out as a possible culprit for pressure-related nervous lesions in the standard procedure (11-13).

Immediate visual evidence of the effectiveness of surface blockage and of the extent and uniformity of the tissue perfusion over the critical limb root area is obtained with administration of sodium flourescein to the extracorporeal circuit. This is done after constriction of the Esmarch tourniquet and prior to the drug administration by observing the direct fluorescence observation under Wood light. The effectiveness of our isolation strategy is confirmed by the percentage leakage data (see Group A vs. Group B in the next section).

We now consider the sarcoma case. Increased performance of the isolation pattern is required to cope with the intrinsic high toxicity of the Tumour Necrosis Factor (TNF-α) drug. In the management of locally advanced extremity soft tissue sarcoma (STS) the HILP is a treatment option and the use of TNF-α in isolated hyperthermic perfusion combined with L-Pam or Dexorubicin is now a dominant option for local tumour control prior to limb sparing surgery. This neoadjuvant approach is performed to obtain a high tumour response rate that will allow for an accurate resection of the reduced tumour as secondary procedure that will result in minimal neuro-vascular trauma and limb salvage. The inclusion of TNF-α in the limb STS integrated therapy forced modifications in our surface vascular isolation technique at the limb-root level to assure the surface blockage to be compatible with the requirement of a low leakage (with respect to what is required with less toxic drugs). Optimal compromise can be reached taking into consideration that in the STS case the illness progression occurs through predominantly haematic metastases, differently from the melanoma where regional diffusion is mainly carried through the lymphatic circulation. We now position the Esmarch belt around the limb root (i.e. more distally than in the melanoma case) as a compromise to contain cutaneous and sub-cutaneous leakage but fastening is entrusted to a (single) modified Steinmann nail inserted subcutaneously for a length of 15 to 20 cm parallel to inguinal ligament ("modified femoral tourniquet" - Fig. 2).

Leakage Monitoring

Consider here again our preliminary study over 81 cases of lower limb melanoma who had been administered HILP (L-PAM plus true hyperthermia) with iliac vascular approach and temporary clamping of the IIV

or of the CIV. The leakage (L) to the systemic circulation is quantified in terms of average percentage of I^{125} - labelled human serum albumin value (quantity L in Eq.1 expressed as a percentage). The L values are given at 5, 10 and 30 min after the administration of RISHA-125. The value at 10 min was here included because that time corresponds approximately to the time constant of the rapid-decay phase of the concentration of Melphalan in the circuit caused by diffusion to the limb tissues (14,15). The data with iliac isolation guarantee values at 5 min constantly below the threshold value of 5% (3.6% for IIV and 0.8% for CIV). At 10 and 30 min the L values are within the range 7.1% to 27.5% for IIV and 1.4% to 9% for CIV. The above results suggest the CIV clamping as a more effective technique for better control of leakage (7).

Data on systemic toxicity evaluated in relation to the side effects and to the complications attributable to the antiblastic treatment and true hyperthemia were analysed with respect to the post-operatory course (30 days) and during follow-up. The results point out a much more favourable situation for the CIV cases, especially when considering that the large majority of the patients in that group were given enhanced treatment (additional L-PAM bolus) (7).

Systemic leakage measured with RIHSA-125 in the ILP with L-PAM is a reliable and simple method. Our technique (RIHSA-125) was originally based on this a-posteriori quantitative determination; later, real-time leakage evaluation became essential (in connection with TNF-α). Recently, within the integrated therapies of the locally advanced soft tissue extremity sarcomas (STS) we have adopted a protocol of perfusional chemo-hyperthermia in association with tasonermina - TNF-α (Beromun®) to improve the therapeutic effect of ILP treatments. Note that the TNF-α protocol can also be adopted in the bulky limb melanomas or in a second perfusion (5). Our preferred procedure was selected and defined in cooperation with the Nuclear Medicine Unit, AOU Careggi for continuous leakage monitoring during IHLP using a mobile gamma probe and 99mTC - Albumin micro-colloid (albumoscint), according to the Beromun ILP Procedure Guide (1999 Boehringer Ingelheim Pharma KG) (16). In detail, accepting 10% of leakage as higher level for safe delivery of drug (TNF-α), 1/10 of the tracer dose (3.5 MBq) of 99mTc-HAS was i.v. injected in systemic circulation the day before surgery and counts detected over cardiac blood pool by means of mobile gamma probe. During this reference test, the count rate is recorded over the heart region every 5 min (average of 5 consecutive counts) and is continued for 45 min. A curve of effective 99mTc-HAS radioactivity decay (physical and biological) is calculated and fitted. The cardiac area of maximum count rate is marked on patient skin. During surgery the tracer dose (35 MBq) is injected into the circuit of perfusion system and countinuous monitoring is performed with counts registered over cardiac area, in the same geometry of the reference test and a curve of radioactivity is fitted. The value of leakage percentage needs for TNF-α administration is assessed in the first 10 min after the tracer drug is injected. If the leakage percentage is lower than 10% or its progressive growth is lower than 10% in the first 10 min TNF-α is then administered. The count rate is continued for 45 min to register possible sudden change of leakage during this time.

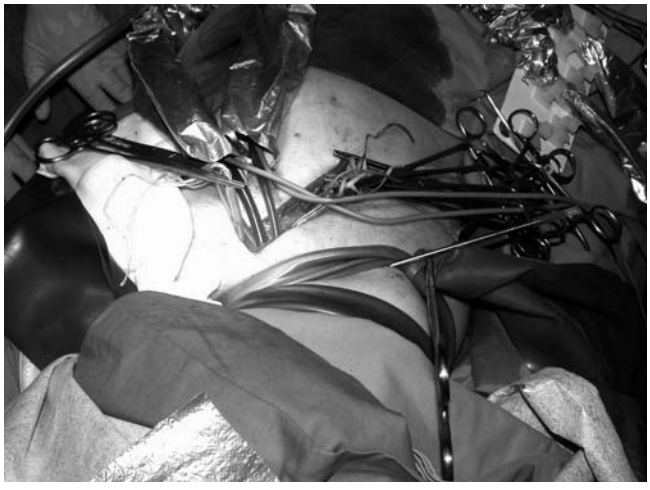

Fig. 2 - Femoral tourniquet (modified) for STS lower limb perfusion (see text for details).

The clinical feasibility of the above leakage continuous monitoring procedure was tested in a series of 16 patients with lower limb tumour, subdivided into two groups, Group A for melanoma and Group B for sarcoma. Group A: the leakage was monitored in 8 iliac-HILPs. The deep and superficial isolation was performed according to our vascular isolation for melanoma protocol. The therapeutic schedule was: HT 41.5°C plus L-PAM (10 mg/l) and additional L-PAM bolus (5 mg/l) after 30 min from the start of the active phase. Group B: 8 patients with locally advanced STS were selected for TNF-α perfusion that included 7 iliac-ILPs and one femoral reperfusion. The "modified femoral tourniquet" technique was implemented for surface vascular isolation. One of the patients was not admitted to TNF-α protocol due to excessive systemic leakage and was treated according to the protocol of group A. The remaining 7 patients had HT 40°C plus

TNF-α Beromun® (2 mg standard dose); after 30 min from the start of the active phase, the average limb temperature was increased to 41.5°C, an L-PAM bolus (10 mg/l) was administered and the perfusion treatment was continued for 60 min for a total duration of 90 min.

The systemic leakage observed in group A (continuous per-operatory monitoring) corresponded to mean values below 5% at 5 min, 16.8% at 10 min and 33.2% at 30 min and these data are seen to be essentially coincident with those obtained with the a-posteriori evaluated RISHA-125 method, when keeping into account that continuous monitoring is performed with counts over the cardiac area where a high concentration of the Technetium tracer is present and an overestimate is likely to occur. For this reason it is likely that this technique overestimates drug leakage. The 7 iliac-ILPs of group B recorded 5% average leakage at 5 min (range 1.0-15.1), 6.7% at 10 min (range 0.9-16.8) and 12.1% at 30 min (range 3.2-28.6). In the femoral re-perfusion case of group B the systemic leakage showed a fast initial rate of rise with average values of 25.4%, 40.2% and 78.2% at 5, 10 and 30 min respectively. In spite of this high leakage value it was in this special case decided to continue the treatment according to the TNF-α protocol, with the standard 2 mg dosage: no appreciable toxicity manifestations were observed. In all group B cases no side-effects produced by TNF-α were observed and the precautionary post-operation intensive care unit permanence was below 24 hrs.

Development and Innovation of the Technical Support System

A technological research program during a three-year period (2001-2003) was conducted to improve the existing treatment support system at our Regional Reference Centre. The need and opportunity arose after a twenty-year experience of clinical applications over a total of 337 treatments of chemo-hypertermia perfusion through continuous evolution and updating of the medical, physical and engineering aspects of the various procedures. A Technical Reference Group (TRG), comprising physicians and engineers having specific experience in the field, coming from the research and the industry world was set up. The program was aimed at obtaining high levels of reliability and manoeuvrability.

Until recently the perfusion support apparatus available to the various international treatment centres was assembled from already existing medical apparatus designed for various specific purposes (extra-corporeal heart-lung circulation, heat exchange, temperature monitoring, heat delivery etc.). All these pieces of apparatus, while certified for their specific use, were not certified as an ensemble *i.e.* as an integrated support system for chemo-hyperthermal perfusion treatments as required by the applicable European Economic Community (EEC) directives (Fig. 3). Additionally, their operation as a system was complex and cumbersome. A significant desirable improvement for clinical studies was the availability of efficient data acquisition capabilities, for data transfer, processing and analysis both during operation and for subsequent evaluation through the generation of mass-memory archives.

The system requirements and the technical and operative specifications are derived from clinical and operation principles identified during our experience. An important addition to the already existing features of our previous assembled system was the incorporation of data acquisition and presentation for: a) readiness and visibility of the treatment variables; b) real-time data transfer to permanent memory as a function of time; c) user friendliness of the man-machine interaction. A general mandatory requirement was conformity to the applicable EEC Medical Device Directive for safety and control of the apparatus.

On the basis of the above requirements the TRG identified an industrial apparatus (Performer LRT® of RanD) which integrated all our base requirements after interactive modifications prompted by the TRG, specifically dealing with the perfusion treatment of the isolated limb in high hyperthermal regime (Fig. 4). The corrective actions and technical improvements were as follows. The perfusate flow was substantially increased (essentially doubled from the starting values of 300-400 ml/minute). The number of data-transmission channels was increased to take into account the significant increase of the number of temperature-monitoring probes required by our procedure from 6 to 8. New needle probes having low diameter and adequate length for deep muscle temperature measurements were found and incorporated. Faster rate of rise of the tissue temperature was obtained with a more efficient thermal delivery through the heat exchanger in cooperation with the already mentioned increase of perfusate flow rate. The target temperature control was defined and set to be based on the value right at the input to the patient (the arterial cannula) rather than at the output of the heater to compensate for any temperature drop along the tubing from the machine to the patient. At the same time, all exposed circuit parts

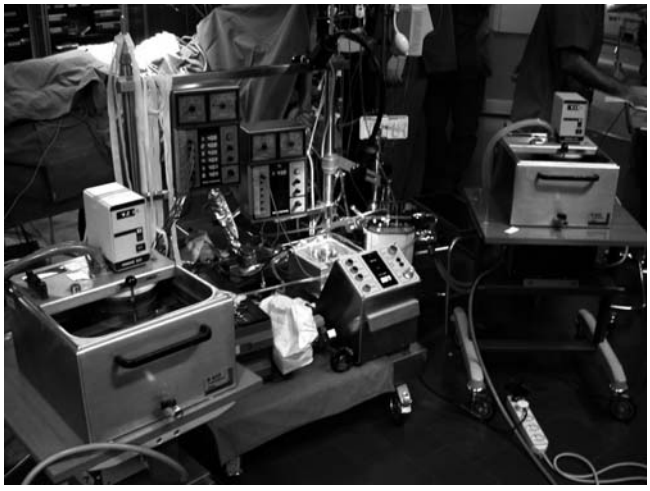

Fig. 3 - Our old support system. Assembled system of several devices.

Fig. 4 - The integrated support system Performer LRT for Locoregional perfusion therapies.

between machine and patient, both toward the patient and back, were protected against heat loss to the room to avoid the need to over-heat the perfusate in the heat exchanger in the attempt to compensate.

Improved treatment control in pharmacologically aggressive treatments

Recent protocols imply the adoption of more aggressive drugs rather than more traditional means, which implies having increased toxicity with respect to the more traditional ones (e. g. Melphalan). The increase in reliability, accuracy and operability obtained with the integrated system brought out some aspects of relevant interest. The time profile of the limb temperature and of the circuit flow can be finely adjusted during treatment with the help of the ready and highly visible data display (temperature, flow rate, pressure). One dominant advantage is connected with leakage control. In fact, soon after the target temperature is reached (namely 40°C with TNF-α and 41 to 41.8°C with Melphalan) we can take advantage of the very slow cooling rate of our thermal isolation provisions (limb plus external thermal protection) to substantially reduce the perfusate flow rate with the ensuing reduction of circuit pressure, hence reduction of leakage, without appreciable temperature decay.

As it is broadly acknowledged, other factors, in addition to vascular isolation are determinant for the amount of leakage, consequently influencing heavily the amount and occurrence of acute post-perfusion local and systemic toxicity (17). High values of flow rate and diameter of venous cannula are known to influence the leakage to the systemic circulation (18). The perfusate flow rate is a relevant factor in determining the venous pressure in the district; a difference of 10 to 15 mmHg (1.3 to 2.0 kPa) between system and circuit is considered an adequate compromise for acceptable values of physiological flow and low leakage. In the hyperthermal perfusion at high temperatures (41.8°C), as used in our methodology, a flow rate of 800 ml/min it needed in the average for iliac perfusion to reach the required temperature (40°C) within an acceptable time interval (20-30 min). The flow rate required may cause elevated venous pressured, which increases the systemic leakage. To prevent such critical events, particularly when using the TNF-α -L-PAM protocol, the flow rate can be directly adjusted to systemic leakage information by real-time continuous monitoring with isotopes during isolated perfusion. Typically, when the limb temperature reaches 40°C, the flow rate is reduced to 300 to 400 ml/min prior to the TNF-α administration and during the subsequent 30 min, taking at the same time care that the various temperatures remain substantially constant in time. This action, in association with the radioimmunosiotopic monitoring of the leakage, allows to contain the percent values of the systemic leakage within predeterminated limits. In the second phase of the treatment (from 30 to 90 min) the perfusate flow rate is again raised step by step to the value of 800 ml/min (typical) so that the temperatures will raise to the thermal range of 41.5 to 41.8°C and in the meantime the melphalan is administered (Figg. 5a-5b-5c).

The implementation of the above methodological

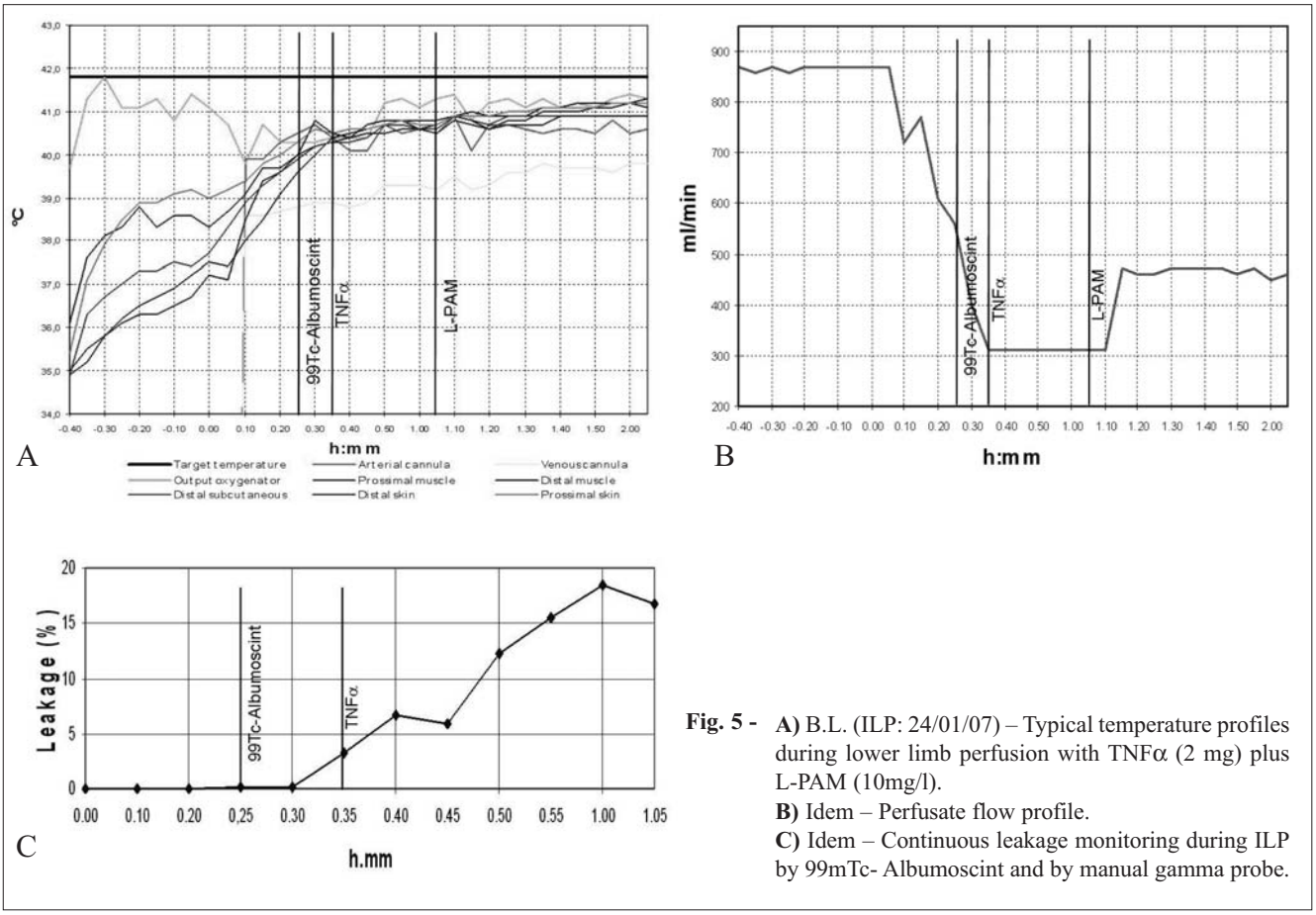

Fig. 5 - **A)** B.L. (ILP: 24/01/07) – Typical temperature profiles during lower limb perfusion with TNFα (2 mg) plus L-PAM (10mg/l).
B) Idem – Perfusate flow profile.
C) Idem – Continuous leakage monitoring during ILP by 99mTc- Albumoscint and by manual gamma probe.

strategy is based on our research activity regarding the following operative functions. In previous studies we have analysed the theoretical and experimental principles to be followed to obtain true hyperthermia with the required time and space uniformity (1,19,20). Essential requirements are: a) two simultaneous and mutually independent heat sources must be available: the heated perfusate and a warm-water blanket; b) heat losses from limb to the room must be kept adequately low, so that an essentially adiabatic (hence isothermal) situation exists. This means, among other technical requirements, that the theoretically optimal situation for temperature uniformity throughout the limb corresponds to keeping the internal source (the perfusate) and the external source (the blanket) at the same temperature. Fast temperature rise, on the other hand, corresponds to high perfusate flow rate and to high thermal exchange (direct contact) between blanket and skin. Thermal loss to the environment is minimised by wrapping the thermal blanket inside an emergency blanket (metallised plastic foil) and by similarly protecting the tubing that interconnects the apparatus and the patient with a loose jacket made of the same metallised plastic. The temperature drop from heater to patient can be kept as low as 0.3°C which is an interesting figure from the point of view of the system operation. The limb heating procedure adopted allowed us to produce uniform and stable temperature.

Another relevant point is the preliminary operation checks and verifications on the integrated support system Performer LRT modified according to our design requirements have shown correspondence with the expected performance during preliminary clinical tests in particular with reference to ready response and user- friendliness. Special relevance was demonstrated to be attributable to the data acquisition and processing subsystem. The various tissue temperatures are graphically displayed, which is essential for the continuous global evaluation of the situation (21). The real-time visual display of the treatment data proved highly effective in assisting the operator when con-

trolling the treatment in process and in trimming and varying the parameters to optimise the course according to the protocol and to the specific clinical variables of each patient. A methodologically important feature in the clinical application, especially in reference to the TNF -L-PAM treatment protocol, is the real-time monitoring of the parameters and particularly of the flow-rate/systemic leakage ratio to assist in effectively driving the treatment. At least the real time continuous leakage monitoring during the treatment allows to take immediate corrective actions, which bring the drug leakage down to accettable safety levels (16).

Discussion

Our research team has a record of more than 20 years of research and clinical activity in the field of hyperthermic treatments in oncology. At our Institution 275 isolated limb perfusion were performed during this time. The surgical technique for the limb isolation, the treatment regimes and the support apparatus technologies were modified with time on the basis of our experimental evidence and of the obtained clinical results. Treatment procedures derived from the optimisation of the method have thus been made available, with reliability, repeatability and safety properties in conformity with our fundamental design requirements, particulary in connection with the improvements in the technique of vascular isolation and with the isolated perfusion chemotherapy in high hyperthermia regimes (borderline "true hyperthermia").

The vascular isolation is essentially based on the blockage of the deep venous return and on the optimum placement and the constriction of the Esharch belt at the limb root both for upper and lower limb. The advanced obtained with our thoracic and abdominal tourniquets respectively for the superficial vascular blockage have proved to be of extreme importance in minimizing neurological damage and in extending the perfusion on the entire limb.

For the lower limb melanomas treated according to our specifically evolved iliac perfusion technique (7) the heat supply method and the circuital temperature level never exceeding 42°C during whole treatment, have made it possible the administration of the active principles (drugs, heat, synergism) up to the top, most effective, hence critical, levels as far as concentration and exposure time duration are concerned.

A series of 114 consecutive treatments (1) in adherence to the above methodological frame for perfusions in L-PAM-ILP with borderline true hyperthermia has demonstrated feasibility, repeatability and above all acceptability with respect to acute local and systemic toxicity and of long-term functional morbidity of the limb. We did not observe any increase of locoregional toxicity related to the administration of melphalan (standard dosage of 10 mg/l of limb volume) in true hyperthermic conditions. Notably, no neuromuscular toxicity effects were observed in any of the patients, apart from moderate and transient systemic toxicity symptoms (20, 22). We are thus led to believe that the long-term neuropathy effects reported by several Authors cannot be simply attributed to the cytostatic drug nor to the high hyperthermia, but may well be directly related to damage caused by standard application of the Esmarch bandage to the limb root (femoral tourniquet). We can also assert that high hyperthermia (41.5-41.8°C) associated to chemotherapy (L-PAM) is a safety procedure.

The results obtained with our procedure have allowed improvements in the pharmacological protocol of the lower limb perfusion for increased therapeutic efficacy. We have later adopted a therapeutic schedule where an additional bolus of L-PAM (5 mg/l of limb volume) is administered 30 min after the standard (10 mg/l) dose to maintain a high L-PAM concentration for a longer time duration (23,24).

The rationale of the pharmacological protocol is based on studies of the melphalan pharmacokinetics in the normo/mild/hyperthermia perfusions. The data of the pharmacokinetics study demonstrated a 40 to 50% decrease of melphalan concentration within 10 min which was interpreted to be due to the fast uptake of melphalan in the tissues (15,25). In a previous study we were able to demonstrate (26) that the half-life of melphalan is about 20 to 30 min even at comparatively high temperatures (true hyperthermic condition $\geq$41°C). Thus the added half dose 30 min after the main starting dose was believed to be optimal to maintain high concentration, hence action, during the entire active phase of the treatment (60 min). Our preliminary data on a series of 93 consecutive HILP treatment with double L-PAM bolus demonstrate that the procedure is safe and feasible. The acute local and systemic toxicity are accettable (27).

The analysis of the data automatically acquired with the Performer LRT integrated support system great value had conformed to the direct, real-time monitoring of the behaviour of the various temperatures versus time in graphical format. This facilitates managing the treatment for optimal perfusate flow and accurate control of the venous return, improving uni-

formity and stability of the temperature profile during the active phase (21). Prompt response to the regulations with ensuing possibility to adapt the variables to specific case-by-case circumstance has confirmed the results evidenced during the preliminary clinical application.

The continuous peroperative monitoring of the leakage allows us to warrant the management of the treatment with the steady surveillance of the systemic leakage correlated to others physiologic parameters acquired and worked up by support systems during the treatment. In the pharmacologically more aggressive treatments (drugs, high dose) the possibility to keep the leakage at strictly fixed levels, is an essential requirement that we have realized with the employment of innovative support system and management of functional principles during the operative stage.

In conclusion, the current experience suggest this innovative procedures could represent an important advance for leakage control. It is hoped that the proposed improvements will be supported by further clinical investigation.

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