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Long-term survival of patients with critical limb ischemia treated with iloprost: response rate and predictive criteria. A retrospective analysis of 102 patients

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Abstract. – OBJECTIVE: Critical limb ischemia (CLI) patients have poor long-term prognosis. We showed that iloprost improves outcomes (major amputation and survival) up a 5-year follow-up, but it is not known if in this length of time the survival curves, of clinical responders and non-responders, differ.

PATIENTS AND METHODS: A retrospective study enrolling 102 consecutive patients between 2004-2008, with clinical and instrumental (ultrasound, angiography, transcutaneous tensiometry of oxygen $TcpO_2$ and carbon dioxide $TcpCO_2$ in the affected and contralateral limbs) diagnosis of critical ischemia. All patients received the best medical therapy. Iloprost was administered (0.5-2 ng/kg/min 6 hours/day for 2-4 weeks) in all patients initially considered unsuitable for revascularization, repeating it regularly in time every six-twelve months in the case of positive response. The minimum expected follow-up was 4 years.

RESULTS: 71.5% of patients were treated with iloprost and the responder rate was 71.2%. Most of the patients were regularly retreated with repeated cycles. Initial median supine $TcpCO_2$ in symptomatic limb was higher in untreated patients than those treated (58 *vs.* 49 mmHg; $p < 0.05$) and in non-responders compared to responders (60 *vs.* 49 mmHg; $p < 0.05$). $TcpCO_2$ directly and significantly correlated with the highest risk of mortality and seems to represent a new accurate prognostic criterion of unfavourable short and long-term response to prostanoid. In iloprost group, major amputations were significantly reduced. Revascularization was significantly higher in non-responders (57.1% *vs.* 11.5%; $p < 0.05$). There was a significantly higher prevalence of subsequent myocardial infarction in the non-iloprost group (27.6% *vs.* 9.6%; $p < 0.05$).

The survival rate of non-responders was higher than untreated up until the second year (76.2% *vs.* 62%; $p < 0.05$). At 4 years we found higher survival in patients treated with iloprost (64.3% *vs.* 41% in untreated; $p < 0.05$) and in responders (75% *vs.* 38.1% in non-responders; $p < 0.05$).

CONCLUSIONS: Our results confirm the favourable role of iloprost on the long-term outcome in patients with CLI. In particular, the maximum benefit is obtained in responder patients treated with multiple cycles of infusion.

Key Words:
Critical limb ischemia, Iloprost, Prostanoid, Responder rate, Transcutaneous tensiometry.

Introduction

Critical limb ischemia (CLI) is a major healthcare issue, involving approximately 500-1000 people per million of the population and characterized by a poor long-term prognosis. At one year from diagnosis, when untreated, major limb amputation is required in 30% of patients, and overall mortality is 25%[1,2]. The treatment goals are, therefore, not only to relieve ischemic pain and heal ulcers, but also prevent limb loss, improve patient function and quality of life, and, primarily, prolong survival. The most consolidated approaches consist of surgical or endovascular revascularization as a first choice, but many CLI patients are often not eligible for such procedures: compared to the past patients tend to be elder, present greater comorbidities and severe

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general impairment. For the above reasons, in these CLI patients vascular rehabilitation may present further technical problems.

Patients who have a viable limb in whom revascularization procedures are not possible, or carry a poor chance of success or have previously failed, may be treated with prostanoids, particularly when the alternative is amputation. Among prostanoids, iloprost, a synthetic prostacyclin analogue, has the best evidence for positively influencing overall survival of patients and limb loss[1-6]. A recent Cochrane review[7] stated that prostanoids seem to have efficacy regarding rest-pain relief and ulcer healing, and iloprost also shows favorable results in the reduction of major amputations. The latest guidelines underline that prostanoid treatment should be considered not only as a first-choice therapy in the alternative to peripheral vascular rehabitation[8,9], but also as complementary/adjuvant therapy in candidates for surgical or endovascular revascularization[10,11].

Despite many positive results and statements regarding rest-pain relief, ulcer healing and amputations reduction, until now there was no conclusive evidence based data on the long-term effectiveness and safety of different prostanoids in patients with CLI[7,12]. Furthermore, the follow-up of patients treated with iloprost was quite brief (6-24 months)[5,6,13,14]. Recently we described[15] a population of 181 consecutive CLI patients, 46% of whom treated with intravenous iloprost: compared to untreated patients they showed better outcomes in terms of significant reduction of major amputation (6% *vs*. 21%) and subsequent vascular surgery (4% *vs*. 32%) and significant improvement of survival rates (69% *vs*. 47%) at a 5 year follow-up. Our work was the first to assess the effect of iloprost on survival rate over such a long time, but we have not further distinguished the survival curves of CLI patients treated with iloprost between those clinical responders and non-responders to treatment.

It has been established that at least in a period of 6 months responder CLI patients have significantly fewer major amputations and mortality rates compared to non-responders[16], but no data is available over a longer period. The aim of this study is to evaluate, in another large population of CLI patients treated with several cycles of intravenous iloprost, in addition to the best medical treatment, if the favorable results obtained in our previous work are confirmed in this more recent research and if there are any different outcomes between responders and non-responders, in terms of their long-term survival or subsequent procedures, such as major and minor amputations and surgical or endovascular treatments.

Patients and Methods

Case-control, retrospective study performed in January 2013, conducted following the Declaration of Helsinki and current ethical standards. The study included 102 CLI patients consecutively admitted to different medical and surgical wards of the University Hospital of Pisa, Italy, between 2004-2008. The only inclusion criterion was the clinical and instrumental diagnosis of critical ischemia of the lower limbs. Ultrasound examinations and/or angiography of the lower extremities were performed in all patients to confirm the diagnosis. The instrumental evaluation included transcutaneous tensiometry of oxygen ($TcpO_2$) and carbon dioxide ($TcpCO_2$) in the affected and contralateral limbs, in supine and dependent positions, performed at the first visit and later at each assessment. Every patient was evaluated by a multidisciplinary team (Internist, Angiologist, Interventional Radiologist, Vascular Surgeon) to choose an adequate approach. All patients were treated with the best systemic medical therapy, in particular with anti-aggregants, statins and ACE-inhibitors or ARB (angiotensin receptor blockers). Iloprost was administered in all patients initially considered unsuitable for revascularization for high operative risk and /or significant comorbidities. The administration regimen was 0.5-2 ng/kg/min for 6 hours/day for 2-4 weeks, repeating it regularly in time every six-twelve months in the case of positive clinical and instrumental response. The response to iloprost was assessed one month after the last administration. Response criteria were considered: for stage III patients the complete disappearance of ischemic pain and regression to the stage of claudication; for stage IV patients the total disappearance of lower limbs ischemic pain, the complete healing of ulcers or a reduction equal to or greater than 50% of initial diameter and the demarcation of necrosis. After that we considered a medical assessment of global response, and we integrate our clinical judgment with the significant improvement of transcutaneous tensiometry measurements. In the years following diagnosis, all patients underwent repeated clinical and instrumental examinations. The data used in this study were obtained from medical records of patients. All patients and/or their families (and possibly general

practitioners) were contacted with an invitation for patients to undergo a new outpatient control when the visit had been previously programmed as usual in our clinics. In case of death, certificates were collected. Collected data included demographic and clinical characteristics, concomitant and previous diseases, major and minor amputations, complications of CLI, mortality rates, causes of death, and administered medical treatments.

Statistical Analysis

The differences between categorical and continuous variables after logarithmic transformation for non-normally distributed data were calculated using the χ^2-square test and one-way ANOVA. The statistical associations were calculated using multivariate logistic regression using the status in life and other outcomes as a binary variable (coded as 0 and 1). Odds ratio (95% CI) was used for relative risk estimate. Descriptive statistics were represented as the mean ± standard deviation (SD) or median for data in non-normal distribution. Statistical significance was considered at p-values < 0.05.

Results

Characteristics of Patients' Population

Table I shows baseline demographic and clinical characteristics and outcomes in the treated and untreated with iloprost groups.

Table I. Clinical characteristics and outcomes of CLI population.

	Overall population No. = 102	Non-Iloprost No. = 29	Iloprost No. = 73	Significant differences
Age (mean ± SD; years)	75 ± 8	74.2 ± 6.8	75.9 ± 8.9	
Males	43% (n = 44)	41.3% (n = 12)	43.8% (n = 32)	
Diabetes mellitus	53% (n = 54)	72% (n = 21)	45% (n = 33)	$p < 0.05$
Hypercolesterolemia	62% (n = 63)	48.2% (n = 14)	67% (n = 49)	
Hypertension	81% (n = 83)	79% (n = 23)	82% (n = 60)	
Smokers (active)	7% (n = 7)	14% (n = 4)	4% (n = 3)	$p < 0.05$
Smokers (previous)	51% (n = 52)	62% (n = 18)	47% (n = 34)	
Previous surgery/PTA	29% (n = 30)	34% (n = 10)	27% (n = 20)	
Previous controlateral amputation	4% (n = 4)	7% (n = 2)	3% (n = 2)	
Stage Leriche-Fontaine III	21% (n = 21)	28% (n = 8)	18% (n = 13)	
Stage Leriche-Fontaine IV	79% (n = 81)	72% (n = 21)	82% (n = 60)	
Coronary artery disease	53% (n = 54)	48% (n = 18)	55% (n = 40)	
Previous myocardial infarction	28% (n = 29)	31% (n = 9)	27% (n = 20)	
Atrial fibrillation	25% (n = 25)	17% (n = 5)	27% (n = 20)	
COPD	25% (n = 26)	21% (n = 6)	30% (n = 22)	
Previous stroke	12% (n = 12)	7% (n = 2)	14% (n = 10)	
$TcpO_2$ median in symptomatic limb				
Supine mmHg (range)	3 (0-30)	2 (0-30)	3 (0-30)	
Dependent mmHg (range)	35 (0-60)	25 (1-60)	35 (0-59)	
$TcpCO_2$ median in symptomatic limb				
Supine mmHg (range)	50 (37-180)	58 (40-180)	49 (36-140)	$p < 0.05$
Dependent mmHg (range)	40 (35-80)	40 (35-80)	39 (35-70)	
Iloprost treatment				
1 cycle	Not applicable	Not applicable	47.9% (n = 35)	
2-3 cycles			24.7% (n = 18)	
> 3 cycles			27.4% (n = 20)	
Survival				
1 year	86.2% (n = 88)	76% (n = 22)	90.4% (n = 66)	
2 years	77.4% (n = 79)	62% (n = 18)	83.5% (n = 61)	
3 years	68.6% (n = 70)	52% (n = 15)	75.3% (n = 55)	
4 years	57.8% (n = 59)	41% (n = 12)	64.3% (n = 47)	$p < 0.05$
Subsequent procedures				
Major amputations	4.9% (n = 5)	13.8% (n = 4)	1.4% (n = 1)	$p < 0.05$
Minor amputation	11.7% (n = 12)	13.8% (n = 4)	10.9% (n = 8)	
Vascular surgery	24.5% (n = 25)	24.1% (n = 7)	24.6% (n = 18)	

PTA: percutaneous transluminal angioplasty; SD: standard deviation; $TcpO_2$: transcutaneous tissue oxygen tension; $TcpCO_2$: transcutaneous tissue carbon dioxide tension; COPD: chronic obstructive pulmonary disease.

The minimum duration of follow-up for the overall population was 4 years, with a median of 5.2 years.

More than two-thirds (71.5%) of CLI patients were treated with iloprost, while the remaining underwent percutaneous angioplasty (16.6%), peripheral bypass (4.9%), chronic spinal cord stimulation (3%) or gene therapy or vasoactive infusion (4%). The majority (79%) was in stage IV Leriche-Fontaine and 29% had already had previous surgery or PTA.

Regarding drug therapy, at the first visit, 67.6% were taking antiplatelet therapy (in the non-iloprost group the percentage was even higher: 72.4%), and 63.7% were taking anticoagulants (heparin, warfarin), so almost all patients were in anti-thrombotic therapy. 49% were using ACE-inhibitors and 23.5% ARB. Little more than half (57.8%) was taking statins, without significant differences between the treated and untreated groups.

Iloprost Treatment

The majority of patients were treated with iloprost (71.5%): the load of serious comorbidities (such as coronary artery disease, previous myocardial infarction, atrial fibrillation, COPD, previous stroke) was similar between the two groups.

There was a significantly higher prevalence of subsequent myocardial infarction in the non-iloprost group (27.6% *vs.* 9.6%; $p < 0.05$).

In iloprost group the responder's rate was 71.2%: subsequently, the majority was regularly retreated with further administrations: 2-3 cycles in 26.9% of cases and 4 cycles or more in other 38.4%, while the great majority (81%) of non-responders to a first apparently clinically ineffective cycle of iloprost discontinued treatment.

Table II shows the baseline demographic and clinical characteristics and the outcomes observed in patients treated with iloprost, subdivided into responders and non-responders to treatment.

Table II. Clinical characteristics and outcomes in responders and non-responders to iloprost.

	Iloprost responders No. = 52	Iloprost non-responders No. = 21	Significant differences
Age (mean ± SD; years)	76.2 ± 9.3	75.2 ± 8.1	
Males	36.5% (n = 19)	61.9% (n = 13)	$p < 0.05$
Diabetes mellitus	50% (n = 26)	33.3% (n = 7)	
Hypercolesterolemia	67.3% (n = 35)	66.6% (n = 14)	
Hypertension	86.5% (n = 45)	71.4% (n = 15)	
Smokers (active)	1.9% (n = 1)	9.5% (n = 2)	$p < 0.05$
Smokers (previous)	36.5% (n = 19)	71.4% (n = 15)	$p < 0.05$
Previous surgery/PTA	32.7% (n = 17)	14.2% (n = 3)	
Previous controlateral amputation	1.9% (n = 1)	4.7% (n = 1)	
Stage Leriche-Fontaine III	19.2% (n = 10)	14.2% (n = 3)	
Stage Leriche-Fontaine IV	80.7% (n = 42)	85.7% (n = 18)	
$TcpO_2$ median in symptomatic limb			
Supine mmHg (range)	3 (0-30)	2 (0-10)	
Dependent mmHg (range)	40 (0-59)	30 (5-52)	
$TcpCO_2$ median in symptomatic limb			
Supine mmHg (range)	49 (36-140)	60 (47-110)	$p < 0.05$
Dependent mmHg (range)	40 (35-55)	40 (37-70)	
Iloprost treatment			
1 cycle	34.6% (n = 18)	81% (n = 17)	
2-3 cycles	26.9% (n = 14)	19% (n = 4)	
> 3 cycles	38.4% (n = 20)	0% (n = 0)	
Survival			
1 year	94.2% (n = 49)	81% (n = 17)	
2 years	86.5% (n = 45)	76.2% (n = 16)	
3 years	82.7% (n = 43)	57.1% (n = 12)	
4 years	75% (n = 39)	38.1% (n = 8)	$p < 0.05$
Subsequent procedures			
Major amputations	0% (n = 0)	4.7% (n = 1)	
Minor amputation	9.6% (n = 5)	14.3% (n = 3)	
Vascular surgery	11.5% (n = 6)	57.1% (n = 12)	$p < 0.05$

PTA: percutaneous transluminal angioplasty; SD: standard deviation; $TcpO_2$: transcutaneous tissue oxygen tension; $TcpCO_2$: transcutaneous tissue carbon dioxide tension.

Survival

Figure 1 shows the survival curves of overall population and of patients treated and not treated with iloprost, while Figure 2 shows the further partition of treated in responders and non-responders.

The survival rate of overall population at 1, 2, 3 and 4 years was, respectively, 86.2%, 77.4%, 68.6%, 57.8%.

At the fourth year of follow-up, the group of patients treated with iloprost showed a significantly better survival rate than those untreated (64.3% *vs.* 41%; $p < 0.05$), and in responders survival was further significantly increased compared to non-responders (75% *vs.* 38.1%; $p < 0.05$).

The survival rate of non-responders patients was higher than that of untreated up until the second year of follow-up (76.2% *vs.* 62%; $p < 0.05$).

Procedures

All procedures, when necessary, were performed in the first 13 months from the initial observation of patients.

In the iloprost group, the rate of major amputations was only 1.4% (the only patient that underwent amputation had been considered non-responder), significantly less than in the non-iloprost group (13.8%) ($p < 0.05$).

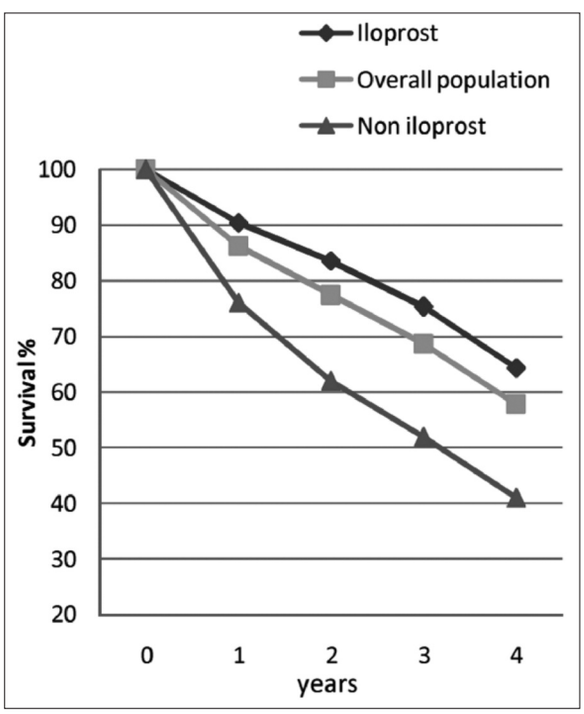

Figure 1. Survival curves in patients treated vs. untreated with iloprost.

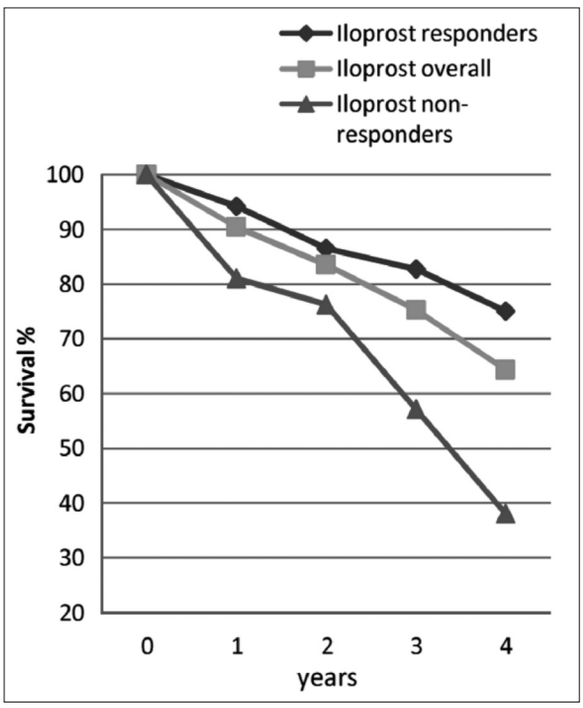

Figure 2. Survival curves in patients treated with iloprost: responders vs. non-responders.

No significant differences were observed for the subsequent surgical revascularization between the iloprost and non-iloprost groups, but the difference was significantly higher in the non-responder group compared to responders (57.1% *vs.* 11.5%; $p < 0.05$).

Transcutaneous Microcirculatory Measurements

Regarding the transcutaneous microcirculatory parameters initially obtained at symptomatic foot in patients treated or not with iloprost, we showed an overall marked microcirculatory $TCpO_2$ impairment expressed by very low oximeter values (median supine $TCpO_2$: 3 mmHg *vs.* 2 mmHg, respectively) without significant differences found between the two subgroups (Table I).

Vice versa, the values of median supine $TcpCO_2$ in the symptomatic limb in the subgroup of patients untreated with iloprost was significantly higher than those treated (58 *vs.* 49 mmHg; $p < 0.05$).

Also, the comparison of microcirculatory parameters at the symptomatic limb between responders and non-responders patients showed no significant differences regarding supine and dependent oximetry, while we found significantly

more severe supine $TcpCO_2$ values in non-responders *vs.* responders (60 *vs.* 49 mmHg, respectively; $p < 0.05$) (Table II).

Finally, we found a significant correlation between the values of median supine $TcpCO_2$ at the forefoot of symptomatic limb and overall mortality of CLI patients, both in patients treated and untreated with iloprost, and in the responders and non responders groups (Figure 3).

Elevated values of supine $TCpCO_2$ at symptomatic limb are therefore directly and significantly correlated with higher risk of mortality.

Discussion

The majority of patients in our series, differently from the indications of the present published guidelines[1,3,17], were subjected in the first instance to conservative medical therapy with iloprost rather than revascularization. This approach was the result of a careful interdisciplinary decision and was influenced not only by the eventual surgical and/or endovascular feasibility, but also by the consideration of the age of our cases (mean 75 years; 33/102 ultra-octogenarians) and precarious general conditions due to severe comorbidities. Indeed, Biancari et al[18] showed that the most important criteria to predict 30-day post-operative outcomes (mortality and amputations) after infra-inguinal revascularization were represented by the presence of gangrene, diabetes mellitus, coronary artery disease and urgent operation, that are aspects strictly related to the complexity and comorbidities of CLI patients. In our series we found a significant presence of above-mentioned conditions: 79% of our patients presented with ulcers or gangrene, 53% were diabetics and 53% had coronary artery disease. Furthermore, some authors[19] recommend an algorithm in which the medical and wound therapy alone may be a viable option for CLI patients with stable and uncomplicated tissue loss and poor surgical candidates (for age > 75 years or significant coronary artery disease or several chronic kidney diseases). For all these reasons we have preferred a conservative medical treatment with iloprost in most of our CLI patients.

The prevalence of severe comorbidities resulted particularly relevant in patients treated with iloprost, so the favorable effect on survival curve observed in this group cannot have been positively influenced by a lower disease burden of patients themselves. After that, the optimal medical therapy, such as antiplatelet, was equally represented both in groups treated and untreated with iloprost.

The most favorable survival curves emerged in patients treated with iloprost, that represent the majority of our case series, and, among these, in responders, once again representing the maximum part of the treated ones. A similar pattern was described for major amputations.

One explanation for the significantly worse prognosis in term of long-term survival found in non-responders might be attributed to the lower use of repeated cycles with iloprost, which may have an effect on systemic protection from global cardiovascular risk and overall survival[15]. Our data clearly show that survival of non-responder pa-

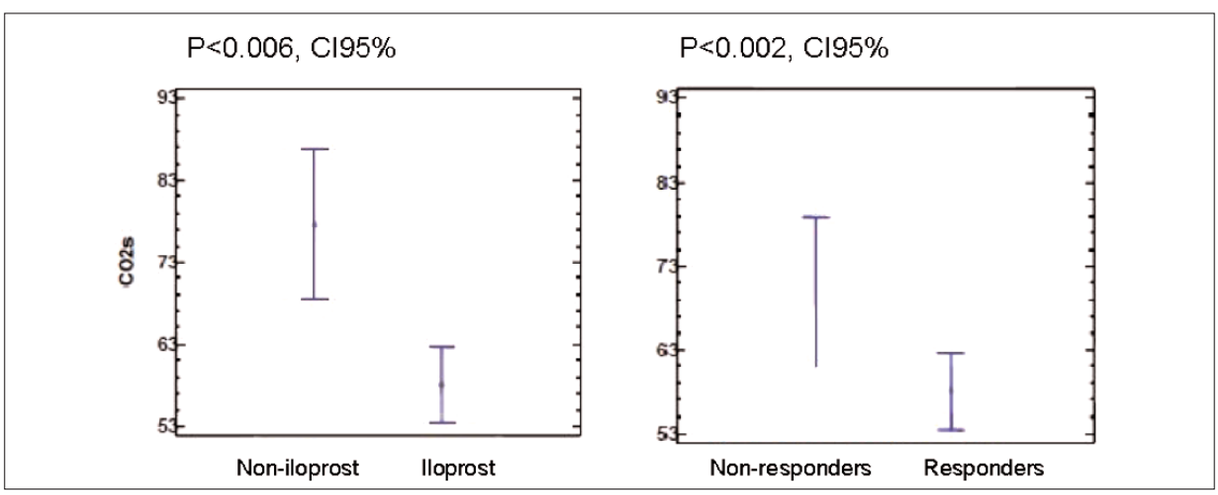

Figure 3. Supine $TcpCO_2$ at symptomatic limb and risk of death.

tients was better than that of untreated ones until the second year of follow-up, so the concept and criteria of non-response should perhaps be revised. Patients initially labeled clinically as non-responders should be treated with repeated cycles of iloprost since it is possible to observe a positive clinical response to a repeated cycle after a previous clinically ineffective one. The response to iloprost must be measured on long-term outcome, especially the survival, as we have recently demonstrated[15] and as recent experiences on effects of statins on overall survival of CLI patients have shown[20].

After that we have found a significantly higher prevalence of myocardial infarction in patients untreated with iloprost (27.6% *vs*. 9.6%; $p < 0.05$), suggesting a global protection from major vascular events provided by iloprost treatment and thus justifying in part the reason for the reduction of mortality that we have observed.

Therefore, we can state that repeated cycles of iloprost can be an appropriate response to the assertion of Varu et al[19] for which "these high-risk patients are victims to the limitations of surgical and medical management and the potential for increased morbidity".

In a previous study[21] we showed that the microcirculatory worsening measurements represented by lower oxygen values and higher carbon dioxide parameters are the prognostic indexes for risk of limb loss with highest sensibility. High values of supine $TcpCO_2$ in symptomatic limb are correlate with local metabolic acidosis, and this work shows that they are significantly associated with diminished response to iloprost. So, they could be proposed as new accurate prognostic criteria of unfavorable response to treatment. Up to now we only knew that no predictive criterion of long-term results could be established, except initial clinical severity and clinical change evaluated one month after treatment[22].

It should be noted that the supine $TcpCO_2$ in symptomatic limb was significantly higher both in patients untreated with iloprost and in non-responders, and in CLI patients represents not only the most sensible prognostic factor for limb loss (that notoriously correlates with survival) but also directly correlates with mortality. From all this, it is clear the need to diagnose and treat critical limb ischemia pharmacologically early before microcirculatory damage becomes irreversible.

Finally, we did not observe any differences in rates of subsequent surgical revascularization between the iloprost and non-iloprost groups, aspect that is in line with our thinking that the two strategies are complementary and not alternative to each other, while the difference was significant in the non-responder group compared to responder, due to the extreme attempt of surgical approach for the extremely high risk of limb loss in non-responder patients.

Our clinical management of CLI patients reflects our way of thinking and approaching this condition, further stressing the paradigm of not immediately revascularizable critical ischemia[10,11] and the necessity of a continuous clinical reassessment of patients in his complexity. It testifies as iloprost can no longer be considered as a therapy reserved only for patients unsuitable for revascularization and it should be the frontline of treatment. For many patients, in particular those seriously ill, we can initially wait for and reserve the surgery at a later time, for patients repeatedly non-responders to conservative medical therapy with iloprost; thereafter the assessment of $TcpO_2$ and $TcpCO_2$ at symptomatic limb can improve our decision-making process.

Conclusions

Iloprost in CLI patients is not an alternative to peripheral revascularization s and should no longer be considered appropriate only for unreconstructable patients, but since it is effective for relieving pain and healing tissue loss, improves post-revascularization outcomes and quality of life and, moreover, is the only treatment with demonstrated positive effect on long-term survival, should be proposed to all patients affected by severe ischemic disease of lower limbs.

Conflict of Interest

Alberto Farina is an employee of Italfarmaco S.p.A. The other Authors declare that there are no conflicts of interest.

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