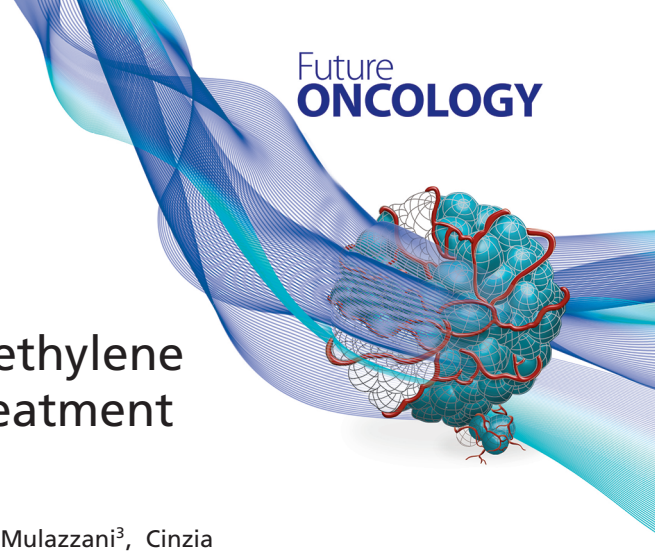
Drug Evaluation

Future ONCOLOGY



A review discussing the use of Polyethylene Glycol (PEG) microspheres in the treatment of hepatocellular carcinoma

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Transarterial chemoembolization (TACE) is indicated in unresectable hepatocellular carcinoma and allows the delivery of embolics inside tumor vascularization to reduce blood supply and release gradually the drug. This lowers the systemic exposure to chemotherapeutics, while increasing their local concentration and tissue necrosis that is higher than conventional TACE. The technology of TACE has seen the introduction of several types of embolics that are made of different materials. Available embolics for TACE include: drug-eluting beads (DC beads), acrylic copolymer, *tris*-acrylic microspheres and polyethylene glycol (PEG) microspheres. Few studies are available on PEG embolics and their use for TACE. This review focuses on the efficacy and safety of TACE performed with PEG microspheres for the treatment of hepatocellular carcinoma and discusses future therapeutic advantages.

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Keywords: polyethylene glycol (PEG) microspheres • safety • transarterial chemoembolization hepatocellular carcinoma • treatment response

The incidence of hepatocellular carcinoma (HCC) is continuously increasing and is influenced by several risk factors, such as presence of hepatitis B and C virus infection, degree of alcohol consumption and steatohepatitis [1,2]. Most patients present advanced stage of disease at HCC diagnosis and cannot be treated with surgery, transplantation or radiofrequency ablation [2].

Unresectable HCC are candidates for transarterial chemoembolization (TACE). The advantages of this technique are cytotoxic effect of the drug delivered at high concentration inside the tumor, reduction of systemic exposure and ischemic effect of the embolics used inside the tumor-feeding vessels [3]. Conventional TACE (cTACE) uses lipiodol for the embolization, increasing survival in selected patients [4].

Chemoembolization has seen the introduction of new types of embolics and several types of toxic drug to allow sustained release of chemotherapeutic agents at high concentration while minimizing the system toxicity [5]. Even if gelatin sponge is the most common type of embolic worldwide, DC-Beads (Biocompatibles UK Ltd., BTG group company, Farnham, UK) are now increasingly used and are made of sulfonate polyvinyl alcohol hydrogel [6]. Subsequently, other types of embolics have been introduced: acrylic copolymer (Hepaspheres®) and polyethylene glycol (PEG) microspheres (LifePearl®) [7].

PEG is a hydrophilic material and maximizes the time in suspension [7], thus improving catheter deliverability. PEG makes the microsphere more resilient to stress and attrition (<1% of damage during standard attrition testing) [7]. A recent report on feasibility shows good safety and tolerability of these embolics when used to treat primary or secondary liver tumors [8,9].

Future Medicine

This review discusses the clinical advantages and therapeutic effects of the use of LifePearl for the treatment of HCC.

Characteristics of LifePearl microspheres

LifePearl can be used in primary and secondary liver cancer therapy [8–10] and since their launch in 2015, have been used by interventional radiologists to perform Drug-Eluting Microspheres TACE (DEM-TACE) procedures.

LifePearl are biocompatible, not reabsorbable, hydrophilic and precisely calibrated PEG microspheres that can be loaded with different chemotherapeutic agents (doxorubicin, irinotecan, idarubicin and epirubicin) and release them in a controlled manner [7,11,13].

Idarubicin seems to be the most effective on three HCC cell lines *in vitro* [11,12]. Doxorubicin remains the most used drug for HCC treatment and therefore this review focuses only on doxorubicin.

PEG maximizes the time in suspension of the LifePearl microspheres, which is 6.0 min ± 0.1, compared with 3.1 min ± 0.2 for DC-Beads, improving their deliverability [6,7]. They also have a steady, continuous and lasting elution of doxorubicin over an extended period of time (139 min to elute 75% of the total released doxorubicin) [7,13].

The presence of sulfonate bonding (SPAc) is another important characteristic of LifePearl that has been first introduced by DC beads to ionically bind to doxorubicin. This allows a loading performance comparable to that of other available products [6,7,13,14].

The main advantage of LifePearl is the higher quantity of drug released 30 ± 5%, than DC-Beads and HepaSphere that can elute 21 ± 2% and 8 ± 3%, respectively [7,13].

Microphores diameter

LifePearl microspheres have a tight calibration [6,7] and are available in different size 100 ± 25, 200 ± 50 and 400 ± 50 µm diameter. The choice of the right diameter is done by the interventional radiologist according to the type of patient's vascularization, in order to induce arterioles occlusion and reduce risks of nontarget embolization and adverse events (AEs) [6–8].

Dosage & loading of doxorubicin onto LifePearl microspheres

LifePearl are available in syringes, each one containing 2 ml of microspheres that can load 37.5 mg of doxorubicin per milliliter. The maximum dosage of doxorubicin is 150 mg per patient corresponding to the maximum systemic dose [15]. In the reviewed papers, the doxorubicin dosage was 100 mg, only in two cases 50 mg was used, because of the small size of tumor to be treated [8,9].

As concerning the loading, a 50-mg vial of doxorubicin powder is reconstituted by adding 2 ml of sterile water for injection (25 mg/ml) and mixed thoroughly. The LifePearl syringe with the selected diameter microspheres (Terumo Europe NV, Leuven, Belgium) is prepared according to manufacturer instructions. The syringe is placed on the plunger for 10 min in order to allow microspheres settling. Packaging solution is eliminated with a 5-micron filter needle without compressing the microspheres.

Doxorubicin is transferred by aspiration in the LifePearl syringe that is then carefully mixed by inversion for about 1 min in order to homogenize the content. The whole loading process requires 30 min, carefully mixing the microspheres every few minutes.

The syringe is placed on the plunger for 10 min and the drug supernatant is removed with a 5-micron filter needle. At this point, the microspheres can be transferred to a 50-ml infusion syringe after adding 5 ml of distilled water and 5 ml of nonionic contrast solution. Infusion is performed at a 1 ml/min speed in about 10–12 min, under fluoroscopic monitoring of contrast medium distribution mimicking the pearl distribution. Tumor feeders are catheterized singularly if needed.

Indications for TACE with LifePearl microspheres

LifePearl microspheres indication is the treatment of unresectable single or multiple liver tumors of Barcelona Clinic Liver Cancer B class or recurrent HCC that are refractory to systemic therapy. PEG embolics have a rigorous calibration and drug-loading time comparable to those of other embolics [6,7,13].

Clinical indications include presence of advanced disease that is not indicated to surgery and/or refractory to systemic therapy, Eastern Cooperative Oncology Group 0–2, Child-Pugh A and B, Barcelona Clinic Liver Cancer A

Table 1. Tumor response with Recist 1.1.

	Aliberti *et al.* (2016) [8]		Aliberti *el al.* (2017) [9]		Gomes *et al.* (2018) [17]		Argirò *et al.* (2017) [18]		De Baere *et al.* (2018) [19]		Malagari *et al.* (2018) [20]		Fiorentini *et al.* (Unpublished Data)	
1 mo	**N = 10 n**	**%**	**N = 42 n**	**%**	**N = 283 n**	**%**	**N = 49 n**	**%**	**N = 71 n**	**%**	**N = 20 n**	**%**	**N = 10 n**	**%**
CR	8	80	21	50	179	63	32	65.3					2	20
PR	2	20	12	29	63	22	9	18.3					5	50
SD	0	0	7	17	16	6	7	14.2					1	10
PD	0	0	2	5	25	9	1	2.2					2	20
3 mo			n = 29		n = 147									
CR			14	48	104	70.8			26	37.1	8	40		
PR			7	24	2	1.4			26	37.1	5	25		
SD			7	24	6	6.1			16	22.9				
PD			1	3	32	21.7			2	2.9				
6 mo			n = 21		n = 115									
CR			9	43	69	60					12	58.3		
PR			4	19	5	4.3					2	8.4		
SD			6	29	7	6.1								
PD			2	10	34	29.6								
9 mo					n = 81									
CR					50	61.7								
PR					2	2.5								
SD					15	18.5								
PD					14	17.3								
12 mo					n = 57									
CR					39	68.4								
PR					0	0								
SD					4	7								
PD					14	26.6								

CR: Complete response; mo: Month; PD: Progression disease; PR: Partial response; SD: Stable disease.

and B, normal hematological values, alanine aminotransferase and gamma-glutamyl transferase less than three-times upper limit of normal levels; total bilirubin < 2.5 mg/ml [8,9,16].

Tumor response to TACE with LifePearl microspheres

Data available in the literature include three studies that used Recist 1.1 for tumor response evaluation [8,9]. They used 100 ± 25 µm diameter LifePearl microspheres that were loaded with 50 mg of doxorubicin. The first paper [8] includes ten patients with HCC and tumor response is eight (80%) complete response (CR) and two (20%) partial response (PR) at 1-month follow-up. The second paper [9] has a larger number of patients: 42. Tumor response is reported at 1, 3 and 6 months after TACE (Table 1).

CR is observed in 21 (50%) patients and PR in 12 (29%) patients at 1-month follow-up. Stable disease (SD) is shown in seven (17%) patients and progression disease (PD) in two (5%) patients. Objective response rate (ORR) is 79, 72 and 62% at 1, 3 and 6 months' time point, respectively. These data suggest the positive efficacy of TACE with LifePearl microspheres for HCC treatment (Figure 1).

Gomes *et al.* present retrospective data on 302 HCC patients treated during a 20-month period. One-month follow-up CT shows 179 (63.2%) CR, 63 (22.3%) PR, 16 (5.7%) SD and 25 (8.8%) PD, with an ORR of 85.5% as evaluated with mRECIST. The ORR at 3 and 6 months of follow-up is 72.2 and 64.3%, respectively [17] that are similar to those reported by Aliberti *et al.* [9]. These high ORR are maintained also at later time points: 64.2 and 68.4% at 9 and 12 months, respectively [17]. Transplanted patients have a 57.7% rate of complete pathologic response [17].

Tumor response of ten patients (Unpublished Data) showed CR in two (20%) patients and PR in five (50%) patients at 1-month follow-up, with an ORR of 70%. SD is present in one (10%) patients and PD in two (20%) patients (Table 1).

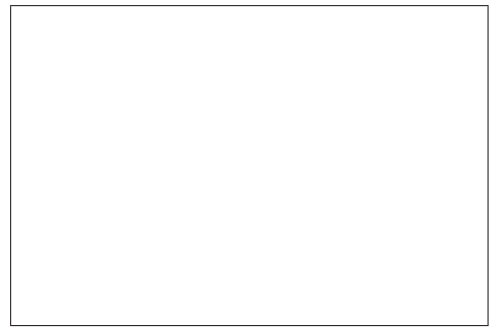

Figure 1. Computed tomography: hepatocellular carcinoma before and after treatment.
(A) Before treatment: hypervascular nodule of HCC in the left lobe;
(B) One month later: partial response with reduction of contrast enhancement;
(C) Three month after treatment: partial response with tumor shrinkage;
(D) Six month after treatment: complete response with not evidence of viable tissue in the left lobe; outcome of ablation in the right lobe.
White arrow indicates the tumor treated.
HCC: Hepatocellular carcinoma.

There are further studies that used mRECIST to assess tumor response [18–20]. Argirò *et al.* include 49 HCC patients and report an ORR of 83.6%, with a CR of 65.3% and PR of 18.3 (Table 1) [18].

Several other studies with LifePearl used for the treatment of HCC, either Terumo sponsored or Investigators initiated are in the final stage of patients follow-up or still enrolling patients. Those studies include:

- Pharmacokinetics study of LifePearl loaded with doxorubicin (N = 25; 9 patients dose escalation study and 16 patients at the 150 mg dose). Final study results were presented at CIRSE, September 2018;
- PARIS study (N = 102 patients), with the main objective to assess liver toxicity of DEM-TACE using LifePearl. Enrollment in the study is finished and preliminary results were presented at CIRSE, September 2018.
- Barcelona study (study of first 50 patients treated in one hospital and followed for at least 1 year). First results were presented at CIRSE 2017 and manuscript is under preparation. The authors report an ORR of 83.3% assessed at a mean of 146 days using RECIST 1.1 criteria [21].
- Study of LifePearl loaded with doxorubicin, delivered via an occlusion balloon (Occlusafe, Terumo Corporation, Tokyo, Japan) to optimize tumor filling (N = 20). The results were presented at JFHOD congress in March 2018. Reported overall response rate was 90% with 72% of major pathological necrosis [22].
- Study of LifePearl loaded with idarubicin, delivered via Occlusafe (enrollment ongoing).
- Italian registry (100 patients registry of all patients treated with LifePearl). This study is currently enrolling patients.

Data reported at CIRSE congress are from PARIS Registry [19] and LIFEPEARL-DOXO study [20]. The PARIS Registry shows an overall response rate of 74.2% (37.1% CR and 37.1% PR) and a disease control rate of 97.1% after a median follow-up of 108 days in 71 patients affected by HCC in different stages of disease [19].

The LIFEPEARL-DOXO study, even if is a pharmacokinetic study, reports also data on tumor response of 20 HCC patient, showing an overall response rate of 65% (40% CR) and disease control rate of 85% at 3 months after TACE [20]. Tumor response is improved at the 6-month follow-up with an ORR of 66.7% (58.3% CR) and DC of 83.3% [20].

Imaging evaluation of TACE with LifePearl microspheres

CT scan is commonly used to assess tumor response after TACE. The analysis of CT images 1 months after treatment is useful for planning of following therapy and can be useful for prognosis determination.

The analysis of vascular imaging showed the disappearance of contrast medium uptake in all HCC cases, with a maximum diameter reduction of 100% in CR and greater than 20% in PR [8] (Figure 1), and Recist 1.1 is used for tumor response evaluation.

Quality of life

Palliative Performance Scale is used for quality of life (QoL) assessment by Aliberti *et al.* [8,9]. This scale assesses ambulation, activity and self-care level, oral intake ability and cognition level. The scale rages from 0% (death) to 100% (fully active) and every decrease in 10% is a fairly significant decrease in physical function [23].

QoL evaluation shows that physical and social functioning is fully active (80% score) in most of HCC patients, who also have a positive health perception at 1 month after TACE with LifePearl microspheres [8,9]. QoL analysis at later points (3 and 6 months) suggests the physical and social functioning of HCC patients is maintained as fully active, with Palliative Performance Scale scores of 81 and 82% at 3 and 6 months, respectively [9].

Tolerability

No complications during TACE procedure with LifePearl microspheres are reported by Aliberti *et al.* [8,9]. Gomes *et al.* report only one case of liver abscess [17]. The treatment is well tolerated by every patient that do not report abdominal pain. As concerning the postprocedural AEs, eight (19%) patients do not report any AE correlated to the treatment [9].

Most frequent AEs are: fever (33%), transaminase increase (17%) and pain (33%). Their intensity is mild–moderate and resolved without complication. Other treatment-related AEs include 15% mild gastritis and 5% dehydration [8]. No grade 3 or 4 AEs are reported [9].

The most frequent complications of latest study are postembolization syndrome in 18 patients (6%), liver abscess in 5 (1.7%), puncture-site hematoma in 3 (1%) and in 57 (11.6%) biochemical toxicities. Argirò *et al.* report an increase in hepatic laboratory tests in 12 (24.5%) patients, but only four (8%) patients developed symptoms requiring specific medical treatment [18]. One (2.2%) patient reports a hepatic abscess in the treated area [17].

The safety assessments of the PARIS Registry show AEs $\geq$ grade 3 intensity in 21 (30%) patients; 14 (20%) of these had AEs related to procedure: abdominal pain (four patients), hypertension (three patients) and fatigue (two patients), whereas eight (11%) had LefePearls-related AEs: hypertension (three patients) and abdominal pain (two patients) [19].

The LIFEPEARL-DOXO study shows three patients with AEs $\geq$ grade 3 intensity: two (8%) abdominal pain and one (4%) increase of aspartame aminotransferase that, however, were not related to LifePearls and there is no significant toxicity related to systemic exposure to doxorubicin [20]. This is correlated to the results of the pharmacokinetic study that shows a peak of plasma doxorubicin concentration at 5–14 min after end of injection of micropspheres, whereas almost no drug is detected in the plasma at 1-month postprocedure [20].

There is a tight correlation between the amount of doxorubicin accumulated in the heart and the incidence of cardiac events [24]. The cumulative dose limit for doxorubicin as systemic therapy usually does not exceed 500 mg/m^2, reducing considerably the incidence of severe cardiac events [24]. The dosage of doxorubicin for each TACE ranges from 50 mg to a maximum of 150 mg that is much lower than the amount of systemic chemotherapy [24]. The cardiac evaluation with EKG and echocardiography does not show any significant variation before and after the last TACE treatment in the studies of Aliberti *et al.* [8,9]. For this reason, the TACE can be considered safe as concerning the cardiac profile, unless in the presence of concomitant heart disease in patients. Hence, patient selection is very important.

Survival

Survival analysis is shown by Gomes *et al.*, reporting a progression-free survival rate of 65.1% (95% CI: 58.4–71.0%) at 12 months, with a mean time to event and standard error of 14.3 $\pm$ 0.5 months and median time to event not estimable because of the low number of events [17].

Overall survival at 12 months is 93.2% (95% CI: 87.8–95.9%), with a mean time to event of 18.6 $\pm$ 0.4 months and median time to event not estimable because of the low number of deaths [17]. Their median follow-up is 11.9 months [17].

Discussion

Most HCC patients are diagnosed when the disease is intermediate or advanced stage and curative treatments, such as liver resection, liver transplant or ablation, cannot be performed [2]. For this reason, the choice of treatment is very challenging [25]. TACE with drug-eluting embolics is indicated for these patients and has the advantage of delivering cytotoxic agents directly inside the tumor, hence minimizing the system toxicity [26].

LifePearl microspheres are new embolic agents that have recently been released for drug delivery in TACE procedures [8,9,17]. These PEG embolics have comparable indications for use in TACE as those of DC-Beads and cTACE.

Data available on tumor response of TACE using LifePearl microspheres loaded with doxorubicin in HCC show response rates (ORR) ranging from 79 to 88.5% 1 month after treatment [8,9,17,18]. These responses seem higher than those reported by other authors using different types of doxorubicin-eluting microspheres: 65% for DC Beads, and 64% for QuadraSpheres (Merit Medical) and cTACE that have tumor response of 54% in HCC [27]. More studies are required to compare the response to TACE with different embolics.

Published results in the literature show an CR rate between 38.5 and 70% and an ORR ranging between 72.7 and 100% [28–32]. ORR ranges are 65–74.2% and 62–66.7% at 3 and 6 months, respectively, after TACE with LifePearls as shown in the available studies [9,17,19,20]. These high ORR are maintained also at later time points: 64.2 and 68.4% at 9 and 12 months, respectively, as shown by Gomes *et al.* [17].

The PARIS Registry and the LIFEPEARL-DOXO study report the same DC of 85% at the 3-month follow-up [19,20] that does not change at 6 months as shown by DC of 83.3% [20].

No significant complication is observed during the procedure by Aliberti *et al.* [8,9], only Gomes *et al.* report a liver abscess after procedure completion [17]. No severe AEs are reported in the postprocedure follow-up [8,9,17]. The most frequent AEs are related to the postembolic syndrome, including pain, nausea and vomiting that are resolved without complications. AEs $\geq$ grade 3 intensity that are related to Lifepearls are reported by PARIS Registry and include hypertension (three patients) and abdominal pain (two patients) [19]. Tolerability is comparable with that shown in previous reports [33,34] showing 8% of AEs $\geq$ grade 3 intensity of TACE with DC Bead(™) loaded with doxorubicin. For this reason, LifePearls may be considered safe as other type of available embolics.

QoL evaluation suggests that physical and social functioning is fully active (80% score) in most of HCC patients at each time point observed (1, 3, 6 months) [8,9].

Progression-free survival rate of 65.9% and overall survival rate of 93.5% at 1 year are comparable to OS of 93.6% at 1 year reported by Malagari *et al.* using DC-Beads [28].

Conclusion

PEG embolics loaded with doxorubicin applied to patients with unresectable HCC result in good feasibility and tolerability of the procedure. Available data are from different centers and include a small number of patients because of the novelty of the product in study. For this reason, further standardized and randomized studies are needed to confirm with these data.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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Executive summary

Background

- Polyethylene glycol is a hydrophilic material, which maximizes the time in suspension, thus improving catheter deliverability.
- LifePearl® are biocompatible, not reabsorbable, hydrophilic and precisely calibrated polyethylene glycol microspheres that can be loaded with different chemotherapeutic agents (doxorubicin, irinotecan, idarubicin and epirubicin) and release them in a controlled manner.

Microspheres diameter

- LifePearl microspheres are available in different size 100 ± 25, 200 ± 50 and 400 ± 50 μm diameter, and sold inside syringe, each one containing 2 ml of microspheres that can load 37.5 mg/ml of doxorubicin. The maximum dosage of doxorubicin is 150 mg/patient corresponding to the maximum systemic dose.

Indications for transarterial chemoembolization with LifePearl microspheres

- Clinical indications include presence of advanced disease that is not indicated to surgery and/or refractory to systemic therapy, Eastern Cooperative Oncology Group 0–2, Child-Pugh A and B, Barcelona Clinic Liver Cancer A and B, normal hematological values, alanine aminotransferase and gamma-glutamyl transferase less than three-times upper limit of normal levels; total bilirubin < 2.5 mg/ml.

Tumor response to transarterial chemoembolization with LifePearl microspheres

- Data available on tumor response of transarterial chemoembolization using LifePearl microspheres loaded with doxorubicin in hepatocellular carcinoma show response rates ranging from 79 to 88.5%, 1-month after treatment.

Tolerability

- The treatment is well tolerated by every patient that did not report abdominal pain. As concerning the postprocedural adverse events, eight (19%) patients did not report any adverse events correlated to the treatment.

Quality of life

- Quality of life is improved as a consequence of transarterial chemoembolization procedure with LifePearl microspheres and patients report better physical and social functioning health perception.

Survival

- Survival analysis is shown by Gomes *et al.*, reporting a progression-free survival rate of 65.9% and overall survival rate of 93.5% at 1 year. Their median follow-up is 11.9 months (95% CI: 11.0–13.0 months).

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