Chemoembolization Adopting Polyethylene Glycol Drug-Eluting Embolics Loaded With Doxorubicin for the Treatment of Hepatocellular Carcinoma

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OBJECTIVE. The purpose of this study is to determine the efficacy and tolerability of transarterial chemoembolization (TACE) using polyethylene glycol (PEG) drug-elutable microspheres loaded with doxorubicin for treatment of hepatocellular carcinoma (HCC).

SUBJECTS AND METHODS. Forty-two patients with unresectable HCC, as determined by a tumor board, were assigned to undergo TACE and were treated with PEG drug-elutable embolics loaded with doxorubicin. Patients were prospectively enrolled and included 32 (76%) men and 10 (24%) women. Their median age was 65 years (range, 42–83 years). Patients were treated with 50 mg of doxorubicin loaded in 2 mL of PEG embolics (mean [± SD] diameter, 100 ± 25 μm) that were infused via a chemoembolization method. Data collected included previous cancer therapy, tumor size, number of lesions, history of TACE, tumor response (at 1, 3, and 6 months), type and intensity of adverse events, and quality of life (QOL) analysis.

RESULTS. One month after TACE, the overall tumor response rate was 79% (50% complete response, 29% partial response, 17% stable disease, and 5% progressive disease). At 3 months, the rates were 48% for complete response, 24% for partial response, 24% for stable disease, and 3% for progressive disease. At 6 months, the rates were 43% for complete response, 19% for partial response, 29% for stable disease, and 10% for progressive disease. TACE was well tolerated by all patients, with no evidence of procedure-related complications or systemic drug-related adverse events. Fever (33%), increase in transaminase level (17%), and pain (33%) were the most frequent adverse events, and their intensity was mostly mild (grades 1 and 2). The QOL scores were 80 at 1 month, 81 at 3 months, and 82 at 6 months after TACE.

CONCLUSION. These data suggest that PEG embolics are efficacious and safe for the treatment of HCC, as indicated by their good tolerability, QOL scores, and high tumor response.

Keywords: chemoembolization, doxorubicin, embolics, liver cancer, liver metastases, polyethylene glycol drug-elutable microspheres

DOI:10.2214/AJR.16.17477

Received October 14, 2016; accepted after revision January 29, 2017.

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AJR 2017; 209:430–434

0361–803X/17/2092–430

Transarterial chemoembolization (TACE) is recommended for unresectable stage B hepatocellular carcinoma (HCC) with no vascular invasion and extrahepatic diffusion [1–3], because it improves median survival [4, 5]. Drug-loadable or -eluting embolics deliver the chemotherapeutic drugs to the tumor through arterial feeders and release the drug in a controlled manner. This method lowers systemic exposure to chemotherapeutics while increasing their local concentration, resulting in a greater tissue necrosis than that achieved with conventional TACE [2, 3, 6].

The technology of TACE is constantly improving. A new generation of loadable embolics made of polyethylene glycol (PEG) has been developed [7]. PEG is a hydrophilic material, which guarantees good compressibility and elasticity and maximizes the time in suspension, thus improving catheter deliverability. PEG makes the microsphere more resilient to stress and attrition (< 1% are damaged during standard attrition testing). A recent report on feasibility showed good safety and tolerability of these embolics when used to treat primary or secondary liver tumors [8].

In this study, we enrolled a large number of patients who were not enrolled in any other previous study. We selected patients who were referred to undergo TACE because they had unresectable HCC and performed chemoembolization using the PEG embolics (LifePearl microspheres, Terumo Europe). Even though we have great experience in the use of DC Beads (Biocompatibles) for TACE, we decided to try these new beads to study their potential advantages and their further development.

Here, we report our initial results on efficacy and short-term tolerability of TACE using PEG embolics loaded with doxorubicin in a

TABLE 1: Baseline Characteristics of 42 Patients With Hepatocellular Carcinoma

Characteristic	Value
Sex	
Male	32 (76)
Female	10 (24)
Age (y), median (range)	65 (42–83)
Child-Pugh class	
A	31 (74)
B	11 (26)
Tumor size (mm), median (range)	22 (6–140)
No. of nodules	
1–2	33 (79)
3–5	8 (19)
> 5	1 (2)
α-Fetoprotein level	
Median (range), μg/L	8.65 (2.8–51,110)
Patients with levels ≤ 100 μg/L	24 (57)
Patients with levels > 100 μg/L	5 (12)
Carbohydrate antigen 19-9 level	
Median (range), U/mL	5.8 (2–49)
Patients with levels ≤ 39.9 U/mL	26 (62)
Patients with levels > 39.9 U/mL	2 (5)
Previous surgery or thermoablation	
Thermoablation	9 (21)
Hepatectomy	2 (5)
Previous chemotherapy	
Sorafenib	5 (12)
Oxaliplatin plus capecitabine	1 (2)
Cisplatin plus capecitabine	1 (2)
Capecitabine	1 (2)
Tumor stage according to AJCC 7th edition [27]	
T1	9 (21)
T2	13 (31)
T3	14 (33)
T4	6 (14)
Tumor stage according to AJCC 6th edition [28]	
I	8 (19)
IIA	13 (31)
IIB	12 (29)
IIIA	5 (12)
IIIB	3 (7)
IV	1 (2)

Note—Except where noted otherwise, data are number (%) of patients. AJCC = American Joint Committee on Cancer.

series of 42 patients. The purpose of this study is to assess tolerability, quality of life (QOL), and tumor response of PEG embolics in oncology practice, for the treatment of HCC.

Subjects and Methods

Ethics

The study was reviewed and received institutional review board approval. The patients signed informed written consent before study enrollment and were included in the institutional all-comers registry.

Patient Selection Criteria

This was a prospective nonprofit cohort study including 42 consecutive eligible patients with unresectable HCC who were referred for TACE treatment at two Italian centers. The population characteristics are shown in Table 1. The cohort included 32 (76%) men and 10 (24%) women whose median age was 65 years (range, 42–83 years).

The inclusion criteria were age older than 18 years, histologic diagnosis of HCC, nonresectable disease as assessed after surgeon examination, Eastern Cooperative Oncology Group performance status 0–2, measurable tumor dimension, alanine aminotransferase and γ-glutamyl transferase levels less than three times the upper limit of normal, total bilirubin level less than 2.5 mg/mL, normal hematologic values, and life expectancy 3 months or longer. The main exclusion criteria were angiographic and selective visceral catheterization not indicated, significant extrahepatic disease, malabsorption due to celiac disease, lactose intolerance and inflammatory intestinal disease, active infection, peripheral neuropathy grade 2 or higher, pregnancy or breast-feeding, or other severe clinical impairment.

Transarterial Chemoembolization With Polyethylene Glycol Embolics Protocol

The TACE procedure was performed according to institutional protocol. Tumor arterial perfusion was assessed before TACE using diagnostic angiography, including selective celiac and superior mesenteric arteriograms. We used the Progreat catheter (Terumo Europe NV) for distal catheterization to avoid any extrahepatic leakage.

Dexamethasone (12 mg) and ondansetron (10 mg) were administered to patients before TACE to prevent emesis, and one vial of morphine (10 mg) was administered to reduce pain before the infusion procedure. Lidocaine (2% in 4 mL of saline solution; 80 mg) was given immediately before the infusion of the embolics [9].

We used PEG embolics that have been available in Europe since 2015 (LifePearl, Terumo Europe NV). They are not yet approved by the U. S. Food and Drug Administration for distribution in the United States.

PEG is a hydrophilic material, which guarantees good compressibility and elasticity and maximizes the time in suspension, thus improving catheter deliverability. PEG makes the microsphere more resilient to stress and attrition. Another innovation of these embolics is the addition of sulfonate bonding, which results in a drug-loading ability close to that of other available products, but favors the release of a higher quantity of the loaded drug versus other products. The tighter calibration (100, 200, and 400 μm diameter) of these embolics,

TABLE 2: Tumor Response at 1, 3, and 6 Months Among Patients With Hepatocellular Carcinoma

Time of Follow-Up (mo), Type of Response	No. (%) of Patients
1 (*n* = 42)	
Complete response	21 (50)
Partial response	12 (29)
Stable disease	7 (17)
Progressive disease	2 (5)
3 (*n* = 29)	
Complete response	14 (48)
Partial response	7 (24)
Stable disease	7 (24)
Progressive disease	1 (3)
6 (*n* = 21)	
Complete response	9 (43)
Partial response	4 (19)
Stable disease	6 (29)
Progressive disease	2 (10)

Note—Percentages do not total 100% because of rounding.

moreover, results in a more controlled TACE with optimized compressibility, allowing a precise and efficacious occlusion of capillaries, with potentially lower risks of nontarget chemoembolization. These microspheres are indicated for embolization of blood vessels supplying primary hypervascular tumors or metastases in the liver.

All but two patients received 50 mg of doxorubicin. The remaining two patients were given 100 mg of doxorubicin because they had tumors larger than 15 cm and multiple tumor arterial feeders.

The local pharmacist reconstituted a 50-mg vial of doxorubicin powder with 2 mL of sterile water for injection (25 mg/mL) and mixed it thoroughly to dissolve all the powder. In the meantime, the syringe containing the PEG embolics was prepared by standing it on the plunger for 10 minutes, allowing the embolics to settle. We used embolics with a mean (± SD) diameter of 100 ± 25 μm. We then used a 5-μm filter needle to expel packaging media, taking care not to compress the microspheres.

The drug solution was transferred by aspiration into the syringes using a needle. The syringe was then moderately agitated for about 1 minute, to homogenize the contents. The drug loading required 30 minutes, with gentle agitation of the microspheres every few minutes.

After drug loading, the syringe was left to stand again on the plunger for 10 minutes, and a 5-μm filter needle was used to eliminate drug supernatant. The embolics were then transferred to a 50-mL syringe for the infusion and were added with 5 mL of nonionic contrast solution and 5 mL of distilled water. The resulting solution was subsequently infused for 10–12 minutes (a usual infusion speed of 1 mL/min) under fluoroscopic monitoring of microspheres distribution, until the whole volume of microspheres was delivered. Tumor feeders were subsequently catheterized one after the other when needed.

We referred to TACE using PEG embolics and doxorubicin as "LIFDOX," adding the first three letters of the commercial name of the embolics (LifePearls) to the first three letters of the drug name, similar to previous work [2] in which TACE with DC Beads and doxorubicin was referred to as "DEBDOX."

Supportive therapy after TACE also included 1000 mg of ceftazidime twice a day for 72 hours to prevent infection, 10 mg of ondansetron after 6 hours to prevent emesis, IV hydration with 1500 mL of glucose saline solution for 72 hours to reduce postembolization syndrome, 10 mg of morphine after 6 hours to reduce postprocedure pain, and 50 mg of ranitidine for gastric protection.

The repetition of further TACE was discussed by a multidisciplinary group (interventional radiologist and oncologist), taking into account tumor burden, response, and tumor-feeding arteries assessment. Follow-up of patients was performed 1 month after TACE and was continued every 3 months until patients entered palliative care or the final stage of the disease and death.

Safety Assessment

The National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0, was applied for the description and intensity assessment of adverse events (AEs) [10].

Efficacy Assessment

CT scans of the abdomen and pelvis were performed within 1, 3, and 6 months after TACE and were assessed according to Response Evaluation Criteria in Solid Tumors indications [11–13]. Because TACE induced tumor necrosis, we used the European Association for the Study of the Liver's method for tumor response evaluation, because it is based on tumor progression with respect to changes in necrosis [12]. The baseline measures of the greatest tumor diameter were compared with those observed after each TACE procedure.

Quality of Life

The Palliative Performance Scale was used for QOL evaluation [14], under the hypothesis that better physical and social characteristics and better health perception would already be attained 1 month after TACE.

Statistical Analysis

Medians and ranges were used to report continuous data, such as patient age, tumor size, and tumor marker levels, whereas proportions were expressed as percentages. Statistical tests to assess significance included chi-square and *t* tests. A statistically significant difference between samples was indicated when $p < 0.05$.

Results

The Sample

We collected data from 42 consecutive patients who were treated with PEG embolics at two Italian centers. Five (12%) patients had increased (> 100 μg/L) α-fetoprotein levels, and two (5%) patients had increased (> 39.9 U/mL) carbohydrate antigen 19-9 levels. Thirty-one of 42 (74%) patients received one treatment, eight patients (19%) received two treatments, and three patients (7%) received three treatments with PEG embolics.

The median tumor size was 22 mm (range, 6–140 mm). Most patients ($n = 33$; 79%) had one or two nodules, eight (19%) patients had three to five nodules, and one (2%) patient had more than five nodules.

Tumor Response

One month after TACE, the overall tumor response rate was 79% (50% complete response, 29% partial response, 17% stable disease, and 5% progressive disease). At 3 months, 48% of patients had a complete response, 24% had a partial response, 24% had stable disease, and 3% had progressive disease. At 6 months, complete response, partial response, stable disease and progressive disease rates were 43%, 19%, 29%, and 10%, respectively (Table 2 and Fig. 1).

Quality of Life

QOL analysis at 1, 3, and 6 months after treatment showed that physical and social functioning were improved for most of the patients. Patients also expressed a better health perception. Palliative Performance Scale values increased slightly from 1 to 6 months after TACE (80 at 1 month, 81 at 3 months, and 82 at 6 months) (Table 3).

Tolerability

We observed no complications during the TACE procedure, which was well tolerated by all of the patients who were treated. There was no abdominal pain—in particular, there

TABLE 3: Quality of Life Analysis for 42 Patients With Hepatocellular Carcinoma

Time of Follow-Up (mo)	Palliative Performance Scale Score, Median (Range)
1	80 (50–100)
3	80 (60–100)
6	90 (60–100)

TABLE 4: Adverse Events Among 42 Patients With Hepatocellular Carcinoma

Adverse Event	No. (%) of Patients
Fever	14 (33)
Pain	14 (33)
Transaminase increase	7 (17)
None	8 (19)

Note—Percentages do not total 100% because of rounding.

were no complaints during the injection—as observed with other types of eluting microspheres. Eight (19%) patients did not report any AE correlated to the treatment.

Fever (33%), transaminase increase of more than 2.5 times the upper limit of normal (17%), and pain (33%) were the most reported AEs and most were grade 1 or 2 (Table 4). No grade 3 or 4 AEs were reported. These AEs resolved without complications.

Discussion

Most patients with primary liver cancer receive a diagnosis late in the disease course, when curative treatments, such as liver resection, liver transplant, or ablation, cannot be applied [15]. Therefore, for patients with unresectable primary liver cancer, liver-directed therapies are the preferred choice. Several different techniques have been used for the treatment of primary or metastatic tumors [14, 16, 17]. Intraarterial therapies are well known to increase drug concentrations inside the tumor with less systemic exposure [4, 16, 17]; however, particular attention must be paid to possible serious AEs, which may lead to biliary sclerosis, and misplacement of the catheter, which may lead to systemic leakage [4, 16]. Technologic improvements of the TACE method include the introduction of microspheres that can be loaded with the drug and then act as both an embolic and a drug-delivery device, when injected into the hepatic arteries and tumor feeders, which have shown promising results in HCC.

Indeed, the use of a drug-loadable embolic allows significant reduction of systemic AEs, as reported in several studies, including two randomized clinical trials [18, 19]. This is linked to the lower systemic passage, also shown in pharmacokinetic studies that compared TACE with drug-loadable microspheres and conventional TACE with emulsion of ethiodized oil (Lipiodol, Guerbet) and drug followed by nonloaded embolic material [18, 20].

New-generation loadable microspheres include PEG embolics, which provide a narrower range in size as a result of the more rigorous calibration. PEG embolics also provide a drug-loading time close to those of other available products, but also a higher quantity of the loaded drug released than with other products. Indeed, in vitro, it has been reported that PEG embolics, DC Beads, HepaSphere (Merit Medical), and Tandem (Boston Scientific) microspheres eluted 30% ± 5%, 21% ± 2%, 8% ± 3%, and 6% ± 0% of the loaded doxorubicin, respectively [7].

A recent comparison of TACE with different types of doxorubicin-eluting microspheres for the treatment of HCC showed tumor responses of 54% for conventional TACE, 65% for DC Beads, and 64% for QuadraSpheres (Merit Medical) [21]. Our reported results for HCC are in the upper range of what was reported in that previous publication, with 79% of tumor response, including 50% of complete response and 29% of partial response.

No severe general drug-related AEs were observed as a consequence of TACE using PEG embolics. Generally, postembolic syndrome, pain, nausea, and vomiting were frequently seen, but they resolved without complications. Treatment tolerance in our study is in line with that in previous reports [3, 9, 22–26].

Regarding QOL, data analysis showed an improvement in physical and social functioning and a better health perception among patients at 1, 3, and 6 months after the TACE. This result was in agreement with previous data on QOL using DC Beads [10, 23], suggesting that the LifePearl microspheres are similar in terms of QOL to previously marketed products.

In our previous study, we showed the results of 10 patients with HCC treated with PEG embolics, resulting in seven (70%) with complete response and three (30%) with partial response. We did not observe any stable disease or progressive disease because of the small size of the sample. Those data, moreover, were retrospective.

In the present report, however, we collected the data prospectively and the sample size was larger, including 42 patients. The tumor response of these patients also was high in this case, with 50% of patients having a complete response and 29% having a partial response 1 month after TACE. Nevertheless, some patients did not respond to the therapy, with 17% experiencing stable disease and 5% experiencing progressive disease.

The purpose of our first study [8] was to report whether PEG embolics could be used safely and to test their handling. In the present report, we showed more realistic results on tumor response than those presented in our previous study. The benefits on tumor response were also maintained in later time points, even if the percentages of stable disease and progressive disease increased (Table 2).

The main limitations of this study are the limited number of patients and the short period of observation; further studies are required to assess long-term efficacy and safety in a larger number of patients. Our results, however, are interesting because this is one of the first reports on the application of TACE with PEG embolics loaded with doxorubicin in patients with unresectable primary liver cancer

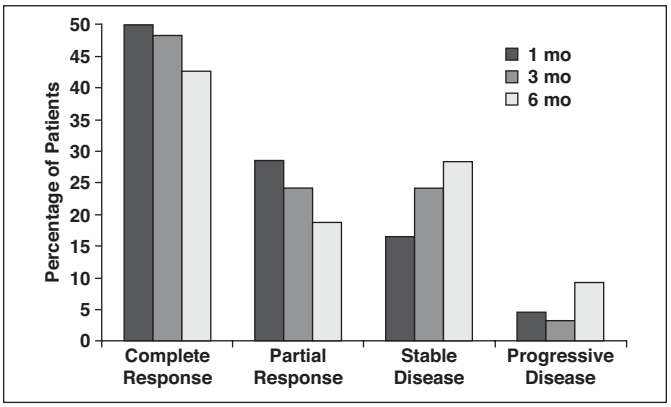

Fig. 1—Tumor response among 42 patients with hepatocellular carcinoma.

in an oncology practice. We observed good feasibility and tolerability of the procedure, and we observed AEs similar to those that occur with other microspheres using the same premedication therapy [10, 23–26].

A significant advantage of PEG embolics used for TACE is their longer time in suspension, reported to be 504 ± 12 seconds for Tandem microspheres, 357 ± 7 seconds for PEG embolics, 185 ± 11 seconds for DC Beads, and 172 ± 20 seconds for HepaSphere [7]. This feature avoids the interventional radiologist having to keep moving the syringe, or remixing the microspheres through a three-way stopcock, and therefore probably delivers a more homogeneous flow of microspheres.

Conclusion

PEG embolics preloaded with doxorubicin can be a new step forward in the TACE field, for the treatment of primary liver cancer, showing tumor responses and low levels of toxicity. Future work is needed for the confirmation of these data.

Acknowledgments

We thank Claire Jones and Elin Pyke of Mudskipper Ltd. for providing editorial language support.

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