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ULUSLARARASI HAKEMLİ AKADEMİK SPOR SAĞLIK VE TIP BİLİMLERİ DERGİSİ
INTERNATIONAL REFEREED ACADEMIC JOURNAL OF SPORTS, HEALTH AND MEDICAL SCIENCES

MAVA-CYTARABINE POLİMER İLAÇ KONJUGATININ ANTİMİKROBİYAL VE ANTİKANSER ETKİLERİNİN İNCELENMESİ (1)

INVESTIGATION OF ANTIMICROBIAL AND ANTICANCER EFFECTS OF MAVA-CYTARABINE POLYMER-DRUG CONJUGATE

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Öz: Amaç: Kemoterapötik ilaçların etkinliğinin artırılması ve yan etkilerinin azaltılması ya da tamamen giderilmesine yönelik çalışmalara sıklıkla rastlanmaktadır. Bizim çalışmamızda, lösemi tedavisinde kullanılan Siterabin (CYT) ilacına, maleik anhidrit vinil asetat (MAVA) kopolimeri eklenmesi suretiyle dizayn edilen polimer-ilaç konjugatı (MAVA-CYT) kullanılarak, bu ilacın yan etkilerinin azaltılması ve antikanser ve antimikrobiyal etkilerinin araştırılması amaçlandı. **Yöntem**: Konjugasyon reaksiyonu 70 o C'de dimetilformamid (DMF) içinde trietilamin (TEA) katalizörlüğünde gerçekleştirildi. Kopolimerin yapısal karakterizasyonu yapıldı. Antikanser aktivitesi meme kanseri hücre hattında (MCF-7) ve sağlıklı Mouse fibroblast (L929) hücre hatlarında çalışıldı. Antimikrobiyal aktivitesi ise disk difüzyon tekniği kullanılarak değerlendirildi. Bulgular: FTIR and 1 H-NMR spektrumları aynı zamanda konjugasyon reksiyonunu da doğrulamıştır. Konjugatın, çalışılan 6 mikroorganizma üzerinde inhibisyon zonu oluşmamıştır. MAVA-CYT çiftinin inhibisyon yüzdesi (% 60,64) iken Siterabin'in ise en yüksek konsantrasyonda kanser hücrelerini öldürme oranı (% 70,17) olarak bulunmuştur. Sitotoksik aktivite testleri sonucunda, kopolimer-ilaç çiftinin (% 100), sadece ilacın ise (%89,86) canlılık oranına sahip olduğu görülmüştür. kopolimer-ilaç çiftinin L929 hücre hattı üzerinde 6 farklı konsantrasyonda sitotoksisitesi araştırıldığında, hücre canlılık oranı % 100'e yakın bulunmuştur. **Sonuç**: MAVA-CYST umut verici bir yeni antikanser ajan kaynağı olarak gözüküyor. Bu kanser hücrelerinde sitotoksik aktivite mekanizmalarını tanımlamak için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Siterabin, Kopolimer-İlaç Konjugatı, Antikanser

Abstract: Aim: Studies to increase the efficacy of chemotherapeutic drugs and to reduce or completely eliminate the side effects are frequently encountered. In this study, we aimed to reduce the side effects of anticancer and antimicrobial effects of the new conjugate by using newly obtained polymer-drug conjugate (MAVA-CYT) to Cytarabine (CYT) drug used in the treatment of leukemia. **Method**: The conjugation reaction was carried out at 70° C in dimethylformamide under triethylamine catalysis. Structural characterization of copolymer was performed. Anticancer and antimicrobial activity were determined by XTT test in breast cancer (MCF-7) Mouse fibroblast (L929) cell lines, and disc diffusion technique, respectively. **Results**: Conjugate was confirmed by FTIR and 1H-NMR spectra. No zone of inhibition was formed on the synthesized Conjugate 6 microorganism. While the inhibition percentage of MAVA-CYT pair was 60.64%, Cytarabine was found to have the highest concentration of cancer cells (70.17%). As a result of the cytotoxic activity tests, it was found that the copolymer-drug pair (100%) had only viability of the drug (89.86%). The toxic effect of the copolymer-drug pair on the L929 cell line at 6 different concentrations was not observed and cell viability was found to be 100%.**Conclusion**: MAVA-CYT appear to be a promosing source of new anticancer agent. Further studies are needed to identify the cytotoxic activity mechanisms on these cancer cells.

Key Words: Cytarabine, Copolymer-Drug Conjugate, Anticancer

Doi: 10.17363/SSTB.2019.33.4

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International Refereed Academic Journal of Sports, Health and Medical Sciences
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Ekim – Kasım – Aralık Sayı: 33 Güz Dönemi Yıl: 2019
ID:464 K:555 ISSN Print: 2146-8508 Online 2147-1711
(ISO 18001-OH-0090-13001706 / ISO 14001-EM-0090-13001706 / ISO 9001-QM-0090-13001706 / ISO 10002-CM-0090-13001706) (TRADEMARK)
(2015/04315- 2015-GE-18972)

INTRODUCTION

There are many factors limiting the effectiveness of the drugs used in chemotherapy. These include drug resistance, toxicity, tumor drug interaction, drug pharmacokinetics and pharmacology, and patient-related factors (Akyol, et al.,2004:162-163, Avcu, et al., 2008:62, Cingi, et al.,1996:213). The clinical use of many chemotherapy drugs is limited by their low therapeutic index due to toxic side effects (Li, et al., 2008: 886, Duncan, et al., 2003, 349). For this reason, various recommendations are being developed in order to ensure that the drugs are localized in the body where they need to go and to reduce their side effects (Young, et al., 2010:58). The serious side effects of the drugs used in the treatment of breast cancer and the insufficient effect of the drug on the tumor led researchers to develop new drug systems using polymers.

Due to the superior physicochemical properties of polymeric drugs, the fact that they have therapeutic properties not found in conventional small molecule drugs leads them to a new field of research. In other words, these macromolecules, also known as bioactive polymers, have been developed by interacting with drug active substances and useful molecules have been obtained for drug delivery systems (ISP) (Karakus, 2011:101).

In this type of synthesis; It is aimed that a drug active substance with an anti-tumor active substance can be bound to a synthetic polymer sample by chemical conjugation and the drug can be administered to the tumor cell in a controlled manner and the desired side effects can be minimized by increasing the effect in the desired direction (Pack, et al., 2005:582).

The Cytarabine molecule is also known as the cytosine β-D-arabinofuranoside hydrochloride crystal. This drug is a very effective antimetabolite in the treatment of leukemia. Cytarabine with antitumor effect is effective in acute non-lymphoblastic / lymphoblastic leukemia, chronic myelocytic leukemia, blast crisis, prophylaxis with treatment of meningeal leukemia, and diffuse histiocytic lymphomas (Galmarini, et al., 2001:879).

The essential feature of an antimicrobial agent is selective toxicity. The concept of selective toxicity was first introduced by Paul Ehrlich. The antimicrobial agent used in chemotherapy should be effective or even slightly toxic, even at low concentrations. For such an effect to occur; the antimicrobial agent should select microorganism cells as the target rather than mammalian cells (Derbentli, 2003:141-142).

In this study, we aimed to reduce the side effects of anticancer and antimicrobial effects of the new conjugate by using newly obtained polymer-drug conjugate (MAVA-CYT) to

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Cytarabine (CYT) drug used in the treatment of leukemia.

Materials and Methods

Synthesis and Purification of Copolymer

The maleic anhydride-vinyl acetate copolymer was synthesized and purified in a previous study. Briefly, the monomers of maleic anhydride (MA) and vinyl acetate (VA) were polymerized in a 1: 1 molar ratio of methyl ethyl ketone (MEK) in the presence of a benzoyl peroxide (BPO) initiator at 80 ° C for 24 hours. The unreacted monomer was removed from the residue by purification by standing at -20 ° C for 1 hour and drying in a vacuum incubator at 50° C for 24 hours (Karakus, et al., 2013:1593).

Synthesis and Purification of Conjugate

In a previous study, maleic anhydride vinyl acetate-Cyterabine (MAVA / CYT) conjugate of pure MAVA copolymer with CYT antitumor agent in 1: 1 molar ratio of dimethylformamide (DMF) in triethylamine (TEA-catalyzed 50° C (2 hours) and 70 The conjugate was last incubated with excess of cold ethyl alcohol for 1 hour at -20° C and purified by drying in a vacuum incubator at 50° C for 24 hours (Karakus, et al., 2015:77).

Structural Characterization of Copolymer and Conjugate

MAVA copolymer and MAVA-CYT conjugate were prepared as KBr pellets (2 mg sample, 100 mg KBr) for FTIR spectrophotometer (MATTSON 1000 Unicam, USA) and recorded at 400-4000 cm -1 at 4 cm -1 intervals. Nuclear magnetic resonance, 1H-the NMR analysis NMR 400 MHz (Bruker Avance III, Karlsruhe, Germany), 6 mg samples of 0.8 ml dimethyl sulfoxide (DMSO) were made by preparing (Technology Research Center, University of Erciyes, Antalya, Turkey) (Karakus, et al., 2015:78).

Water Solubility of Conjugate

MAVA copolymer dissolves slowly in water due to its high molar mass. It is the anhydride ring that slows down the dissolution (Figure X). On the other hand, after conjugation, the anhydride ring in maleic anhydride is opened to form an amide bond, which results in the continuous carboxyl group after the binding of the CYT drug (Figure 1). Here, in the MVA-CYT conjugate consisting of n units, the blue colored part is the CYT drug and the remaining black part is the main chain of the MAVA copolymer. Thus, increasing carboxyl groups showed the solubility enhancing properties in water as can be predicted theoretically.

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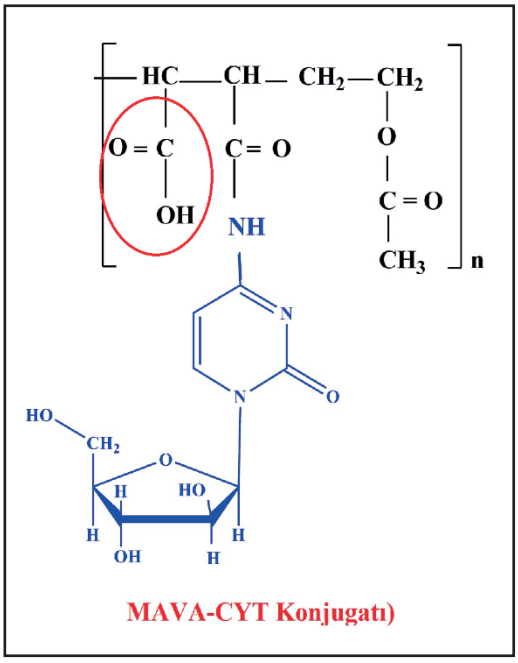

Figure 1. Prescribed chemical structure of the MAVA-CYT conjugate (Karakus, et al., 2015:79).

Antimicrobial Activity

Staphylococcus aureus of MAVA and MAVA-CYT (ATCC 25923), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), Meticillin-Resistant *Staphylococcus aureus* (ATCC 43300), *Enterococcus faecalis* (ATCC 29212) and *Candida albicans* (ATCC 29212); antimicrobial effects on microorganisms were investigated by using Disk Diffusion test. Bacterial strains were inoculated into Brain Heart Infusion Broth at 37 ± 0.1° C and fungal strains were inoculated into Sabouraud Dextrose Broth and incubated at 25 ± 0.1° C for 24 hours. Bacterial and yeast solutions from these cultures were adjusted to the standard of 0.5 in the McFarland apparatus (0.5 McFarland standard = 1-2 x 10^8 CFU / ml) (CLSI, 2011:45-48).

MAVA and MAVA-CYT were diluted in sterile tubes containing 1 ml of DMSO starting from high doses (4/1, 2/1, 1/1, 1/2, 1/4, 1/8). Dilutions were impregnated with 25 µl of sterile 6 mm blank discs (OXOID blanc disc). Mueller - Hinton Agar and Sabouraud Dextrose Agar surface, 0.5 McFarland standard bacteria and yeast solutions prepared by spreading the whole plaque surface with the help of sterile swab. After waiting for a while to dry their surfaces, the diluted samples were prepared and the impregnated discs were gently pressed and placed 20 mm between them. Only sterile discs impregnated with DMSO were used for negative control (Tunc, 2013:49, CLSI, 2011:47).

Anticancer Activity

Anticancer activities of MAVA-CYT conjugate and CYT at 6 different concentrations were determined using XTT test on MCF-7 and L929 fibroblast cell lines. Cells were grown in DMEM (Dulbecco's Modified Eagle's Medium) medium and 10% FBS + 1% Penicillin-Streptomycin medium in an oven at 37 ° C and 5% CO_2. For the XTT cell

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metabolic activity assay, 96 well plates were prepared in 100 µl ($1x10^4$ cells / well) per well. 6 different concentrations of MAVA-CYT and CYT, 500 µg / ml, 250 µg / ml, 125 µg / ml, 62.5 µg / ml, 31.25 µg / ml, 15.62 µg / ml were added to the wells and Incubated for 24 hours. XTT (Cell proliferation kit, Roche) solution was prepared and 10 µl was added to each well and incubated at 37 ° C for 4 hours. Optical density at 450 nm was measured by ELISA. Results were calculated with the formula using positive and negative control values as % inhibition for MCF-7 and % viability for L929 (Tunc, 2013:55-58, Arik, et al., 2017:9).

Statistical analysis

Statistical analysis of the results was performed with SPSS (Mann-Whitney U Test, 16.0 for Windows) program. A p value of <0.05 was considered statistically significant.

RESULTS

Structural Characterization of Copolymer and Conjugate

In our previous study, FTIR and ^{1}H-NMR analysis of the synthesized, purified and structural characterized MAVA-CYT conjugate showed that conjugation was performed successfully and the expected copolymer and conjugate main structures were obtained. (Karakus, et al., 2013:1593, Karakus, et al., 2015:79).

Antimicrobial Activity

Staphylococcus aureus of MAVA and MAVA-CYT (ATCC 25923), *Escherichia* coli (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), Meticillin-Resistant *Staphylococcus aureus* (ATCC 43300), *Enterococcus faecalis* (ATCC 29212) and *Candida albicans* (ATCC 29212); There was no antimicrobial effect on microorganisms. Inhibition zones were formed around the antibiotic discs used as positive controls. (Figures 2)

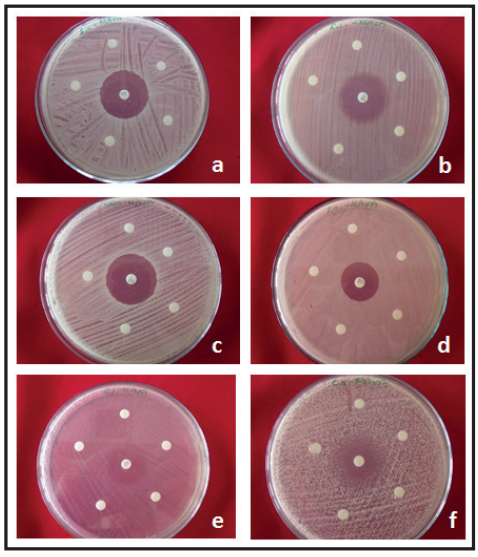

Figure 2: a, b, c, d, e, f

Anticancer Activity

Anticancer activities of MAVA-CYT conjugate and CYT at 6 different concentrations were determined using XTT test on MCF-7 and L929 cell lines. The MAVA-CYT pair

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had an inhibition percentage (60.64%) close to the control (88.53%). Cytarabine's highest concentration of cancer cells (70.17%) is close to the negative control (88.53%). The killing rate of MAVA-CYT was significantly lower than the percentage of copolymer-drug pair compared to the killing rate of Cytarabine. ($p < 0.05$) (Figure 3).

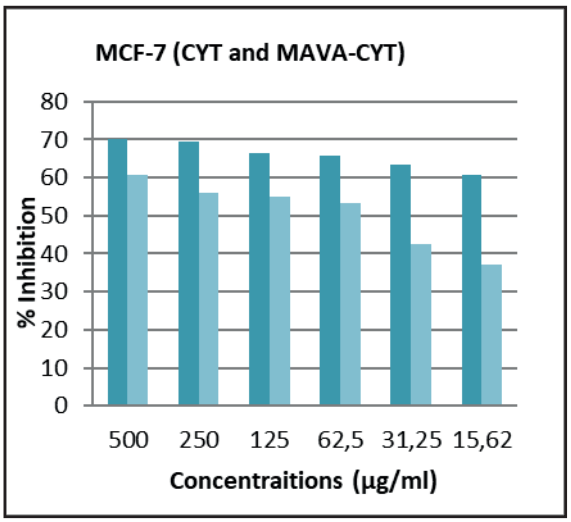

Figure 3: MCF-7 of different concentrations of CYT and MAVA-CYT percentage of killing cells.

For the positive and negative control and for each different drug and copolymer-drug concentration, 6 wells were averaged separately. % Viability was calculated using the relevant formula and the graph on the right was obtained (Figure 4).

When the lowest concentrations of Cytarabine and MAVA-CYT were compared, a significant difference was observed between the two data. ($p < 0.05$). Furthermore, the copolymer-drug pair (100%) had a higher viability rate than the drug (89.86%) alone. In fact, the toxicity of the copolymer-drug pair is almost non-existent.

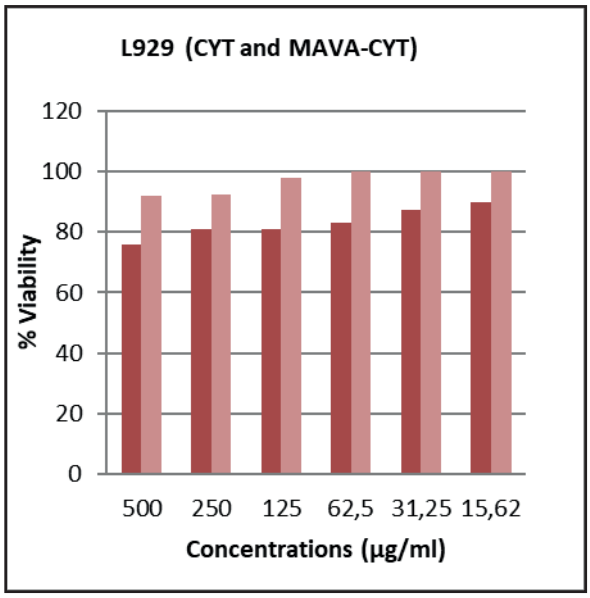

Figure 4: L929 cells of different concentrations of CYT and MAVA-CYT percentage of viability on.

DISCUSSION

In the study of Karakuş et al., MAVA copolymer was synthesized in methyl ethyl ketone (MEK) by free radical polymerization using benzoyl-peroxide (BPO) as a radical initiator at 80 ºC. Karakus et al. In his study in 2008, conjugation with Cytosine β-D-arabinofuranoside hydrochloride (CYT), an

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anti-leukemic chemotherapeutic agent, was successfully carried out in dimethylformamide at 70 °C under the catalysis of triethylamine (TEA) (Karakus, et al., 2013:1592). Structural characterization of copolymer and copolymer-drug (MAVA-CYT) conjugate was performed by Fourier Transform Infrared (FTIR) and Nuclear Magnetic Resonance (^{1}H-NMR). These spectra confirm the conjugation reaction. Antiproliferative activity of MAVA-CYT was also performed by BrdU-cellproliferation-ELISA analysis using C6 and HeLa cells (cisplatin and 5-fluorouracil positive control). It was observed that the conjugate had a slight antiproliferative effect against C6 cells, whereas it did not have antiproliferative effect against HeLa cells, especially at low concentrations (<100 µg / ml) (Karakus, et al., 2013:1593). Saito et al. Chemically modified L-asparaginase enzyme obtained from *E.coli* and showed antitancer properties with poly ethylene glycol and maleic anhydride. They tested this modified enzyme on mouse lymphoma cells and showed that it increased anti-activity by suppressing anti-asparaginase antibody production (Saito, et al., 2007:408). Yadav et al., Binding to siterabine PEGylated PLGA (poly (lactic-co-glycolic acid)) nanoparticles, mouse lymphoid leukemia cells reported that they increase the concentration of drug in the blood compared to pure drug (Yadav, et al., 2011:740). Visco et al. Demonstrated that bendamusitne and cytarabine exert a very potent and significant effect on inducing apoptosis on MCL cells. Similar results were obtained by measuring mitochondrial damage or decreased metabolic activity in all cell lines (Visco, et al., 2012:74). Stella et al. Have linked poly (H (2) NPEGCA-co-HDCA) copolymer to this anticancer drug to accelerate the metabolism of gemcitabine in plasma. They tested the cytotoxicity of this conjugate on human cervical carcinoma cell lines (KB3-1) and human breast cancer cell lines (MCF-7) and reported that they reduce toxic effects at a certain concentration (Stella, et al., 2007:75).

CONCLUSION

In this study, this conjugate showed a lower anticancer effect on the MCF-7 cell line than Cytarabine drug. However, when the cytotoxicity of the copolymer-drug pair (MAVA-CYT) was investigated at 6 different concentrations on the

L929 cell line, cell viability was found to be close to 100%. When compared with drug toxicity, conjugate; it has been shown that there is no significant toxic effect compared to the drug.

RECOMMENDATIONS

According to all results, it can be said that MAVA / CYT conjugate has very promising properties. MAVA / CYT conjugate animal

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assays may be a new cancer drug candidate looking at the anticancer effects.

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