枢瑞

枸橼酸托瑞米芬片
Toremifene Citrate Tablets

TEAM 天衡制药

编 者 案

随着人类生产活动的开展和生活水平的提高，人们生活方式、生活习惯和赖以生存的生态环境的改变，导致了疾病的构成发生了明显的变化。近年来恶性肿瘤的发病率呈明显上升的趋势，其中妇女乳腺癌的发病率上升明显，已成为妇女恶性肿瘤的常见病，严重地威胁着广大妇女的身体健康！尤其在我国沿海地区、经济较发达地区和大、中城市，乳腺癌已经跃居女性恶性肿瘤之首。

当前，提高乳腺癌生存率、降低死亡率和提高患者的生活质量，已成为各国肿瘤防治工作者竞相研究的重点和热点。乳腺癌是一激素依赖性肿瘤，减低体内雌激素水平，即有利于乳腺癌的治疗。100 多年前，Beatson(1896 年)首次提出卵巢切除术可以使乳腺癌缩小，之后，相继有手术切除肾上腺、垂体的报道。自从激素受体被发现以后，内分泌治疗迅速发展，使得乳腺癌的内分泌治疗能有目的的选择。目前认为，只要有 10%的肿瘤细胞雌、孕激素受体阳性，内分泌治疗就可能有效。

他莫昔芬（Tamoxifen，TAM）是最常用的非甾体类抗雌激素药物，1986 年就通过美国 FDA 认证而成为绝经后淋巴结阳性乳腺癌的辅助内分泌治疗药物，1990 年又通过美国 FDA 认证成为绝经前或绝经后淋巴结阴性乳腺癌的辅助内分泌治疗药物。2000 年美国国立卫生研究所（NIH）乳腺癌辅助治疗会议推荐 TAM 作为所有激素受体阳性乳腺癌患者术后辅助内分泌治疗的标准药物。

1998 年总部位于英国牛津大学的早期乳腺癌试验协作组（EBCTCG）报告，雌激素受体阳性的乳腺癌患者术后口服 TAM 5 年，可使其 5 年复发率和死亡率分别相对减少 47%和 26%；辅助化疗后序贯应用 5 年 TAM 与单用其中的一种治疗方案相比，可进一步降低死亡率和复发率。在 ER（+）患者中，服 5 年组相对服 2 年组而言，在减少复发和提高远期生存率方面，分别获得大约 5%和 3%的额外疗效。并且这种受益的差异在 10 年、15 年后继续加大。TAM 还体现在使对侧乳腺发生癌变的危险度减少大约 50%。

目前 TAM 作为乳腺癌内分泌治疗的金标准药物在临床上已得到了广泛应用。TAM 比化疗耐受性好，有减少骨质疏松，降低血脂、纤维蛋白原，降低心血管疾病发生率等作用。因其具有雌激素样作用，因此可促进子宫内膜增生，绝经后患者使用有增加子宫内膜癌的发生率。在 10 年内约导致了 0.2%的子宫内膜癌及肺栓塞的发生。TAM 在治疗和预防乳腺癌的同时，是以增加其他肿瘤，特别是子宫内膜癌等为代价的，因此，TAM 作为所有激素受体阳性乳腺癌患者术后辅助内分泌治疗标准药物的地位正在被逐渐动摇。

托瑞米芬（Toremifene，TOR）是 1979 年欧洲研究者在 300 多种化合物中筛选出一种三苯乙烯衍生物，化学结构与三苯氧胺相似，由于其氯原子结构的存在，减低 DNA 加合物，减少了基因改变致癌性的可能。在 20 世纪 90 年代初期，该药进入临床试验，陆续在欧洲和北美等发达国家完成了III期临床实验，随后又进行了更大规模的临床观察，与 TAM 相比，TOR 对受体有更高的亲和力，进入细胞后与雌激素受体形成复合物，在核内停留时间较长。托瑞米芬对雌激素受体的选择性更强，引起子宫内膜癌的风险低于他莫昔芬，对于绝经后患者，比他莫昔芬产生更有利的血脂变化。托瑞米芬还可以逆转多药耐药 MPR 表达，有化疗增敏作用。

总体而言，TOR 是新一代的雌激素受体竞争性拮抗剂，三苯氧胺的衍生物，但有不同于 TAM 的许多特性：

1. 较强的抗肿瘤特性。动物实验发现托瑞米芬有很强的抗雌激素作用，但只有轻微的类激素作用。对绝经后雌激素受体阳性乳腺癌，TOR 比 TAM 能更有效降低

死亡率，明显提高乳腺癌患者生存率。对 TAM 无效者 TOR 也可有效，可作为乳腺癌的二线治疗。

2. 化疗增敏及逆转耐药。实验证明 TAM 和 TOR 均有逆转耐药及化疗增敏作用，但不同于 TAM 的是 TOR 在高剂量下可抑制 ER 阴性的小鼠子宫肉瘤生长，支持了托瑞米芬在高剂量时具有非 ER 依赖性抗肿瘤作用的观点，体外试验发现 TOR 对 ADM，VCR 等有化疗增敏作用，并能在人体耐受剂量水平下逆转多药耐药[5]。

3. 毒副作用小，耐受性好。动物实验表明 TOR 长期服药 6-12 个月未见明显的非内分泌器官的毒副作用。TOR 用药剂量为 TAM 致死剂量的 2-4 倍时，大鼠仍能安全生存。高剂量下无急性毒性，长期服用的安全性优于三苯氧胺。三苯氧胺有强致癌性，Hard 等对雌鼠研究显示，采用 TAM 每天 11.34mg/kg 和 22.6mg/kg 治疗 12 个月，肝细胞癌的发病率分别为 67%和 100%。采用 TOR 每天 12mg/kg 和 24mg/kg，甚至 48mg/kg，均未发生肝细胞癌。此外，TAM 可引起增生性结节，子宫内膜癌，研究证实，TOR 不致癌，亦不引起鼠肝细胞增殖。TOR 副反应较小且轻微，多为激素样反应，包括：面部潮红，多汗，恶心，呕吐，白带增多，头晕，水肿等，90%属轻微一过性，耐受性好。

4. 其他。TOR 能明显提高高密度脂蛋白，产生更有利于绝经后妇女的血脂改变，降低心肌梗塞发生，此外，TOR 有明显止痛作用，具有诱导转化生长（TGF-B）的产生和调节致癌基因表达从而抑制癌细胞的作用是 TAM 所缺乏的。

在中国，进口 TOR（商品名法乐通）进行乳腺癌治疗始于 1996 年，临床验证组报告作为一线治疗 TOR 的有效率为 33.3%，作为二线治疗有效率为 11.9%[6]，与国外报导相一致。遗憾的是，到目前为止，TOR 在中国的使用并不广泛，临床乳腺癌的抗雌激素治疗首选药物仍然是具有潜在致癌性的 TAM。主要原因是，到目前为止，中国市场使用的 TOR 仍然是进口产品，其远高于 TAM 的价格壁垒，使绝大多数的乳腺癌患者失去了使用 TOR 的机会。2003 年，国产 TOR（商品名枢瑞，宁波市天衡制药厂生产）上市，其价格适中，符合国情，使 TOR 在中国替代 TAM 广泛使用成为可能。

现将我厂临床研究资料汇编成册，并精选国内外相关文献附后，供广大医师在临床应用时参考。本汇编资料中不足之处，真诚希望各位临床医师批评指正。

天衡制药市场部

2004. 4

目　　录

抗肿瘤新药——托瑞米芬

中国医学科学院
肿瘤医院（100021） 何小慧 冯奉仪综述
中国协和医科大学

摘要 托瑞米芬 新一代抗雌激素抗肿瘤新药，抗肿瘤作用机制与三苯氧胺（TAM）相似，基础和临床研究显示，其对乳腺癌的疗效相当于或高于TAM。一线治疗绝经后晚期乳腺癌的有效率为50%。毒副反应轻微，主要为消化道反应及雌激素样反应。尚未发现长期服用TAM所致的肝细胞癌和子宫内膜癌等副作用。

关键词 托瑞米芬 乳腺癌

托瑞米芬（fareston,toremifen,TOR）是由Farmos自1979年开始研制的新一代抗雌激素抗肿瘤新药，它是从350种化合物中严格筛选出来的，是非甾体类三苯乙烯的衍生物、分子式为$C_{20}H_{28}NOCL$，C_6H_8O。十余年来的基础和临床研究表明，其对乳腺癌的疗效相当于或高于三苯氧胺（TAM），且毒副作用轻，尚未发现长期服用TAM所致的肝细胞癌变、子宫内膜癌、增生性结节及视网膜改变等副作用，安全性优于TAM。现已推荐用于乳腺癌的一线治疗，并用于TAM治疗或其他药物无效的乳腺癌的治疗。

一、TOR抗肿瘤作用机制研究

TOR是雌激素的竞争性拮抗剂，TOR及其代谢产物4-OH-TOR可以竞争性地与乳腺癌癌细胞浆内的雌激素受体（ER）相结合，形成药物ER复合物进入细胞核内，在细胞核内与雌激素依赖基因结合，从而调节由雌激素引致的特异mRNA和蛋白质的合成，阻止细胞的分化、增殖。

TOR使乳腺癌消退的更确切机制尚不清楚，正常剂量下5%～10%的ER阴性患者有效，说明还有其他机制。体内及体外实验表明，TOR治疗后使具有肿瘤抑制作用因子（TGF-β）和TRPM-2基因水平增高，进而抑制肿瘤细胞的有丝分裂，并诱导癌细胞的程序性死亡。Warri等量[1]报道采用TOR治疗3天后60%的细胞出现凋亡，细胞有丝分裂接近0。

二、TOR的实验研究

在小鼠、大鼠体内进行的研究发现TOR具有很强的抗雌激素作用，但只有轻微的类激素作用。在啮类动物子宫重量实验中，若产生相同的子宫增长效应，TOR所需要剂量是TAM的40倍，但两者在产生最大雌激素效应方面无明显差异。TOR具有与TAM相同的抗雌激素作用，在小鼠、大鼠体内进行的逆转雌激素诱导子宫生长实验中，10mgTOR与1mgTAM可产生相同的抗雌激素效应。TOR抗雌激素和雌激素比例是TAM的4倍，显示出TOR较强的抗肿瘤特性。

TOR免疫学效应的确切机制尚不清楚，但其使雌性小鼠自身免疫性疾病的病程明显缩短。在体外TOR与TAM一样使外周淋巴细胞DNA合成抑制，并使抗体分泌细胞增加，提示TOR在人体内可能有免疫调节作用[2]。

体外实验显示，TOR对ER阳性MCR-7人体乳腺癌细胞有强抑制作用，当TOR浓度渐增高时（1μmol～10μmol/L）其对MCF-7的抑制作用逐步增强，在5μmol时S期及G_2/M期细胞的百分率明显减少，细胞碎屑数明显增加，药物去除后乳腺癌细胞的增长恢复正常[3]。另有实验发现，MCF-7在TOR浓度为1μmol/L时细胞停止复制当浓度为5μmol/L时所有肿瘤细胞在3天内被杀死，提示高剂量有消减MCF-7肿瘤细胞有作用[4]。体外及裸鼠活体研究表明，TOR使人类乳腺癌细胞系ZR-75-1细胞增殖受抑制，随TOR剂量增大，抑制作用更强[4]。不同于TAM的是高剂量TOR（100mg/kg或200mg/kg）可抑制雌激素受体阴性的小鼠子宫肉瘤的生长。这也支持了TOR在高剂量时具有非雌激素受体依赖性抗肿瘤作用的观点，体外试验还发TOR对蒽环类药物阿霉素（ADM）及长春新碱（VCR）等有化疗增敏作用。

在小鼠、大鼠、恒河猴身上进行了TOR的临床毒理学研究，小鼠的急性LD_{50}为2000mg/kg。动物实验表明，TOR无论是长期还是短期服用均未非常耐受[5]。长期服药6～12个月未见明显的非内分泌器官的毒副作用。在恒河猴身上的研究发现，药物剂量每日1mg/kg、10mg/kg、70mg/kg连用52周，未见明显的组织学、血液学及血液生化检查方面的异常[6]，在Ames实验中未见TOR致基因突变作用，亦未见致畸作用。TOR用药剂量为TAM致死剂量的2～4倍时，大鼠仍能安全生存。高剂量下无急性毒性及长期服用的安全充优于TAM。TAM有强致癌性。Hard等（1993）[7]对雌鼠研究显示，采用TAM每天11.34mg/kg和22.6mg/kg治疗12个月，肝细胞癌发病率分别为67%和100%。采用TOR每天12mg/kg和24mg/kg，甚至48mg/kg，均未见发生肝细胞癌。此外TAM可引起增生性结节、子宫内膜癌，大鼠两年致癌性的研究证实，TOR不致癌，亦不引起鼠肝细胞增殖。

TOR药物动力学研究显示，口服后几乎完全被人体所吸收[8]，其首过效应较小，口服吸收常在10～680mg间，

而吸收率是非剂量依赖性的，用药后 2～4 小时内达到血浆峰浓度。

TOR 经口及静脉注入大鼠，其分布于肺部浓度最高，而眼、骨及红细胞浓度最低。分布半衰期为 4 小时，同 TAM 一样与血浆蛋白结合，结合率为 99.7%[9]。这也影响其在体内的分布及药物排泄率。TOR 主要在肝内进行代谢转化，只有一小部分（10%）代谢物从肾排出，大部分通过胆汁和大便排出体外，因此可出现肝、肠循环。在体内一般经历 3 种类型的代谢转换。

TOR 清除半衰期为 5 天，因此与 TAM 一样，若每人用药约需 4 周才达到稳态浓度，一般来讲，药物剂量越大达到稳态浓度的时间越短。

三、TOR 的临床研究

Ⅰ期临床研究

大量的Ⅰ期临床试用表明，TOR 的最大耐受剂量（MTD）为每天 460mg，副作用类似 TAM，主要为胃肠道反应，如恶心、呕吐、腹部疼痛不适、厌食、便秘、腹泄、食欲增加；雌激素效应反应，如面部潮红、阴道排液及阴道出血；中枢神经系统反应，如头晕、失眠等；但 90%属温和及轻微，偶发生个别特异性反应包括过敏反应、高钙血症、血栓栓塞、口痛、乳房痛、视力减退、干眼、血小板减少、白细胞减少。 Hamm 等（1992）[10]报道对 107 例患者分别采用 TOR10mg、20mg、40mg、60mg、200mg、400mg 连续用药 8 周，结果恶心 31%，呕吐 12%，面部潮红 29%；3 例发生高钙血症，5 例因症状严重而停药。同时发现 TOR 的最低剂量（20mg/d）可阻止雌激素对阴道表皮细胞作用。结合临床及临床前研究结果，订下了 TOR 一线治疗乳腺癌的剂量为 60mg/d，二、三线用药剂量为每天 200mg 和 240mg。

Ⅱ期临床研究

大量的Ⅱ期一线临床试用资料表明 TOR 治疗绝经后 ER 阳性或不详的晚期乳腺癌患者有良好疗效，Valavaara[11]综合分析了 TOR 一线治疗晚期绝经后乳腺癌的资料显示，采用 TOR 每天 20mg、40mg 和 60mg 治疗，有效率分别为 21%、52%和 60%。综合近 300 例绝经后晚期乳腺癌患者接受 TOR 治疗的结果，总有效率约为 50%（45%～54%）。而耐受性良好者副作用轻微，若包括病情稳定的患者，高达 74%～92%的患者从治疗中获益。

许多学者对常规化放疗、内分泌治疗无效或复发的乳腺癌患者采用高剂量 TOR 二线治疗，Vogel（1993）[12]报道高剂量 200mg/天治疗晚期 TAM 治疗失败的乳腺癌患者，仅获得 5%的有效率，显示 TOR 与 TAM 有交叉耐药。Pyrhones 等（1994）[14]也证实了其结果。临床资料还显示 TOR 对受体阴性的难治性乳腺癌无效。

Ⅲ期临床研究

Hayes 等（1995）[15]报道对 648 例 ER 阳性或不详的晚期乳腺癌患者分别采用每日 TAM120mg，TOR60mg、TOR200mg3 组进行对比研究治疗，结果显示客观有效率（CR+PR）为 TAM 组 19%，TOR 组 21%，TOR_{200} 组 23%。3 组比较均无显著性差异，副作用除 TOR_{200} 组发生恶心明显增高外，其余无明显不同，生活质量测定 3 组亦无明显不同。Stenbygaan（1993）[16]亦报道了相似的结果。临床研究还显示 TOR 治疗子宫内膜癌有一定疗效，有效率为 20%。

综上所述，TOR 为新一代抗雌激素抗肿瘤新药，化学结构式与 TAM 相似，实验研究表明对多种实验性肿瘤有抗肿瘤作用，其抗肿瘤作用机制亦与 TAM 相似，但其具有的诱导转化生长因子（TGF-β）的产生和调节致癌基因表达从而抑制癌细胞的作用是 TAM 所缺乏的。临床研究结果显示 TOR 最大耐受剂量为每天 460mg，推荐一线治疗乳腺癌剂量为每天 60mg，二、三线用药剂量分别为每天 200mg 和 240mg。二、二线治疗晚期乳腺癌的有效率为 50%和 0～30%。毒副所应主要为消化道反应及雌激素样反应，90%属轻微及一过性，尚未发现长期服用 TAM 所致的肝细胞癌变及子宫内膜癌等副作用，安全性大于 TAM，值得临床上进一步应用。

参考文献

1 Warri AM, Huovinen R1, Laine AM, et al. J Natl Cancer Inst, 1993;85(17):1412

2 Paavonen T, Aronen H, Pythonen S, et al. APMIS. 1991;99(2):163

3 Grenman R, Laine KM, Klemi Pj. et al. J Cancer Res Clin Oncol,1991;117(3):223

抗雌激素抗肿瘤新药托瑞米芬

吴洪斌 (复旦大学附属肿瘤医院药剂科 上海 200032)

【中图分类号】R979.1 【文献标识码】B 【文章编号】1007-4406(2001)04-0253-02

托瑞米芬(torem ifene, 商品名法乐通 Fareston)是由芬兰 Fam os 研究组 1979 年开发研制的新一代抗雌激素抗肿瘤药物, 是非甾体类三苯乙烯的衍生物, 其相对分子质量为 598, 分子式 $C_{26}H_{28}NOCl.C_6H_8O_7$, 已由芬兰奥立安药厂生产。十余年来的基础与临床研究表明[1,2], 托瑞米芬的抗肿瘤作用机理与三苯氧胺相似, 对乳腺癌的疗效相当于或高于三苯氧胺, 较高剂量应用对乳腺癌的疗效更好, 但不良反应较轻, 尚未发现长期服用三苯氧胺所致的肝细胞癌变、子宫内膜癌、增生性结节及视网膜改变等不良反应, 安全性优于三苯氧胺。现已被推荐用于早晚期乳腺癌的一线治疗, 并用于三苯氧胺或其他药物治疗无效的乳腺癌的治疗。

1 托瑞米芬的抗肿瘤作用机理

托瑞米芬是雌激素的竞争性拮抗剂, 可以竞争性地与乳腺癌癌细胞浆内的雌激素受体(ER)相结合, 形成药物 ER 复合物进入细胞核内, 在细胞核内与雌激素依赖基因相结合, 从而调节由雌激素引致的特异 mRNA 和蛋白质的合成, 阻止细胞的分化、增殖[3]。

2 托瑞米芬的实验研究

研究发现托瑞米芬具有很强的抗雌激素作用, 但只有轻微的类激素作用。体外实验显示[4], 托瑞米芬对 ER 阳性 MCF-7 人体乳腺癌细胞有强抑制作用, 当托瑞米芬的浓度渐增高时(1~ 10 μmol/L), 其对 MCF-7 的抑制作用逐步增强, 在 5 μmol/L 时 S 期及 G_2/M 期细胞的百分率明显减少, 药物去除后乳腺癌细胞的增长恢复正常。另有实验发现[5], MCF-7 人体乳腺癌细胞在托瑞米芬浓度为 1 μmol/L 时细胞停止复制, 当浓度为 5 μmol/L 时所有肿瘤细胞在 3 d 内被杀死, 提示高剂量托瑞米芬有消减 MCF-7 肿瘤细胞的作用。体外及裸鼠活体研究表明, 托瑞米芬可使人体乳腺癌细胞系 ZR-75-1 细胞增殖受抑制, 剂量越大, 抑制作用越强。不同于三苯氧胺的是高剂量的托瑞米芬(100 mg/kg 或 200 mg/kg)可抑制雌激素受体阴性的小鼠子宫肉瘤的生长, 这也支持了托瑞米芬在高剂量时具有非雌激素受体依赖性抗肿瘤作用的观点。体外试验[6]还发现托瑞米芬对蒽环类药物阿霉素及长春新碱等有化疗增敏作用。同时动物实验表明, 托瑞米芬无论是长期还是短期服用均非常耐受, 未发现明显的组织学、血液学及血液生化检查方面的异常, 未见有致基因突变作用、致畸作用, 高剂量下无急性毒性, 长期服用的安全性优于三苯氧胺。

3 药物动力学

研究[5]表明托瑞米芬口服后几乎完全被人体所吸收, 其首过效应较小。在给药剂量 10~ 680 mg 之间时, 其吸收率是非剂量依赖性的。通常在用药后 2 ~ 4 h 内达到血浆峰浓度。若 60 mg/d, *po*, 约 4 wk 达到稳态血浓度, 若 200~ 400 mg/d, *po*, 2 wk 内就可达到稳态血浓度。托瑞米芬的分布半衰期为 4 h, 分布于肺部的浓度最高, 与三苯氧胺一样与血浆蛋白结合, 结合率为 99.7%。主要在肝脏内代谢转化, 大部分通过胆汁和大便排出体外, 只有小部分从肾脏排出, 出现肝肠循环。

4 临床研究

国外临床验证数据[1]表明, 托瑞米芬治疗 ER 阳性或不详的晚期乳腺癌患者有良好的疗效, 作为一线治疗晚期乳腺癌疗效肯定相等于三苯氧胺, II 期临床 400 例显示有效率为 20% ~ 50%。对常规化疗、放疗、内分泌治疗无效或复发的乳腺癌患者采用高剂量托瑞米芬二线治疗, Asaishi 等[6]报道 120 mg/d 给药治疗晚期三苯氧胺治疗失败的乳腺癌患者, 有效率为 14%, Vogel 等[7]报道给药 200 mg/d, 有效率为 5%, Phrhonen 等[8]报道给药 240 mg/d, 有效率 4%。国内托瑞米芬临床验证组报告[9]作为

一线治疗托瑞米芬的有效率为 33.3%，作为二线治疗有效率为 11.9%，与国外报导相一致。

临床研究表明，托瑞米芬每天给药≥120 mg 可有效地逆转阿霉素耐药；480 mg/d，连用 7 d 能逆转肺癌多药耐药；600 mg/d，连用 7 d 加顺铂治疗非小细胞肺癌被证实能产生协同增效作用且非常耐受；对肺转移及软组织转移的乳腺癌患者疗效更明显。同时临床研究还发现[10]，托瑞米芬对早期乳腺癌患者有降低血脂的效果，并且与三苯氧胺不同，能明显提高高密度脂蛋白胆固醇，所以比三苯氧胺对于早期乳腺癌患者预防冠心病更为有效。作为绝经后早期乳腺癌患者术后辅助治疗，托瑞米芬可预防骨质丧失，减少骨折的出现，有预防骨质疏松的潜能。

5 不良反应

主要为胃肠道反应，如恶心、呕吐、腹部疼痛不适、厌食、便秘、腹泻、食欲增加；抗雌激素效应反应，如面部潮红、阴道排液及阴道出血；中枢神经系统反应，如头昏、失眠等[11]。但 90% 以上的症状属温和及轻微。偶发生过敏反应、高钙血症、血栓栓塞、口痛、乳房痛、视力减退、干眼、血小板减少、白细胞减少等。

托瑞米芬被世界卫生组织列为非致癌、无基因毒性的药物。耐受性好，能减少骨质丧失，改善血脂。是美国 FDA 二十年来继三苯氧胺后首个被批准的治疗乳腺癌的最新一代抗雌激素药物，也是目前唯一可以替代三苯氧胺在绝经前、后妇女治疗早、晚期乳腺癌的药物，在临床上值得进一步推广使用。

【参考文献】

[1] Hamm J. Phase Ⅰ and Ⅱ studies of toremifene. Oncology, 1997, 11: 19

[2] Gams R. Phase Ⅲ trials of toremifene *vs* tamoxifene. Oncology, 1997, 11: 23

[3] Warri AM, Huovinen RL, Laine AM, *et al*. Apoptosis in toremifene-induced growth inhibition of human breast cancer cells *in vivo* and *in vitro*. J Natl Cancer Insti, 1993, 85: 1412

[4] Coradini D, Biffi A, Cappelletti V, *et al*. Effects of toremifene and its main metabolites on growth of breast cancer cell lines. Anticancer Res, 1991, 11: 2191

[5] Anttila M, Valavaara R, Kivinen S, *et al*. Pharmacokinetics of toremifene. J Steroid Biochem, 1990, 36: 249

[6] Asaishi K, Tominaga T, Abe O, *et al*. Efficacy and safety of high dose NK 622 (toremifene citrate) in tamoxifene failed patients with breast cancer. Gan to Kagaku Ryoho, 1993, 20: 91

[7] Vogel CL, Shemano I, Schoenfelder J, *et al*. Multicenter phase Ⅱ efficacy trial of toremifene in tamoxifene refractory patients with advanced breast cancer. J Clin Oncol, 1993, 11: 345

[8] Phrhonen S, Valavaara R, Vuorinen J, *et al*. High dose toremifene in advanced breast cancer resistant to or relapsed during tamoxifene treatment. Breast Cancer Res Treat, 1994, 29(3): 223

[9] 冯奉仪，许立功，何友谦，等. 法乐通治疗乳腺癌临床总结. 癌症杂志，1999，18(3)：21

[10] Saarto T, Blomqvist C, Ehnholm C, *et al*. Antiatherogenic effects of adjuvant antiestrogens: a randomized trial comparing the effects of tamoxifen and toremifene on plasma lipid levels in postmenopausal women with node-positive breast cancer. J Clin Oncol, 1996, 14(2): 429

[11] Tominaga T, Abe O, Izuo M, *et al*. A phase Ⅰ study of toremifene. Breast Cancer Res Treat, 1990, 16(Suppl): 27

(2000-08-10 收稿)

法乐通治疗晚期乳腺癌临床总结

何小慧[1] 冯奉仪[1] 许立功[2] 唐惟瑜[2] 何桂芬[2] 江泽飞[3]
宋三泰[3] 刘冬耕[4] 何友兼[4] 杨 莹[5] 周美珍[6]

【摘 要】 目的:考察法乐通治疗晚期绝经后乳腺癌的疗效及其不良反应。方法:法乐通一线治疗每日一次60 mg口服,二线治疗每日一次120 mg口服。结果:共60例,有效率18.3%。一线治疗18例,有效率33.3%。二线治疗42例,有效率11.9%。淋巴结和骨转移疗效较好,肝转移、肺转移及胸壁转移也有一定疗效。一线治疗较二线治疗、未用内分泌治疗较曾用内分泌治疗、绝经时间长(≥10年)较绝经时间短(<10年)以及疗后无瘤间期长(≥5年)较疗后无瘤间期短(<5年)疗效好,不良反应轻微,主要为恶心、纳差。结论:法乐通是治疗晚期绝经后乳腺癌有效和安全的抗雌激素抗肿瘤新药。

关键词:乳腺肿瘤/药物疗法;法乐通/不良反应
中图号:R737.9;R730.53 文献标识码:A 文章编号:1000-467X(1999)03-0309-02

Clinical trial of toremifene in postmenopausal patients with advanced breast cancer

HE Xiao-hui, FENG Feng-yi, XU Li-gong, et al.
Cancer Institute (Hospital) Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

【Abstract】Objective: To observe the efficacy and toxicities of toremifene in postmenopausal patients with advanced breast cancer. **Methods**: From September 1996 to March 1998, 60 postmenopausal patients with advanced breast cancer were enrolled in this study. Toremifene (TOR) has been assessed both as initial (first-line) and second-line treatment following failure of other measures such as hormonal treatment and/or cytotoxic chemotherapy. The patients with first-line were assigned to receive daily 60 mg TOR. The patients with second-line were assigned to receive daily 120 mg TOR. **Results**: The overall response rates (complete response and partial response) was 18.3% in all patients. The overall response rate was 33.3% in 18 patients as first-line treatment. The overall response rate was 11.9% in 42 cases patients as second-line treatment. The response rates of lympohatic and bone metastases were higher. The response rates inpatients with first-line treatment, no prior hormone treatment and longer menopausal time (≥10 years) were higher than that in patients with second-line treatment, prior hormone treatment and shorter menopausal time (<10 years) (not statistically different). The response rates in patients with longer disease-free interval (≥5 years) were higher than that in patients with shorter dissease-free interval (<5 yeays) (statisically dlifferent). The most common adverse effects were nause and anorexia. **Conclusion**: TOR was an effective and safe antiestrogens and antiumor agent in postmenopausal patients with advanced breast cancer.

Key words: Breast neoplasms/drug therapy; Toremifene/adverse effect.

法乐通(Fareston, Toremifene TOR)是由芬兰奥立安药厂生产的新一代抗雌激素抗肿瘤新药,是非甾体类三苯乙烯的衍生物,国外基础和大量临床研究显示其对绝经后晚期乳腺癌有较好的疗效。美国FDA已经批准在许多国家上市。现将1996年9月至1998年3月用该药治疗的60例病人的临床总结报告如下。

收稿日期:1998-10-28;修回日期:1998-12-20
作者单位:1. 中国医学科学院中国协和医科大学肿瘤研究所肿瘤医院(北京,100021)
2. 上海医科大学肿瘤医院
3. 北京307医院;4. 中山医科大学肿瘤医院
5. 北京复兴医院;6. 北京医院

1 材料和方法

1.1 药物

本试验采用的药物法乐通均为芬兰奥立安药厂

生产,规格为 60 mg/片,30 片/瓶。

1.2 病例选择

经病理或细胞学证实的局部复发或远处转移的晚期乳腺癌患者,有客观肿瘤观察或测量指标;绝经期后(包括年轻,双卵巢切除术后者),雌激素受体(ER)阳性或不详;一般状况 KPS 评分 ≥50,预计生存期 ≥3 月;血象、肝肾功能正常;作为疗效观察的肿瘤局部 1 月内未作过放疗;无脑转移,非炎性乳腺癌。

1.3 一般资料

入选本组的女性乳癌患者 60 例,均可评价疗效及不良反应;年龄 39~83 岁(中位 58 岁);绝经时间 1~34 年(中位 10 年),< 10 年 36 例,≥10 年 24 例;ER 阳性 19 例,不详 40 例,阴性 1 例;复发或远处转移后初治患者 18 例,化疗和其他内分泌药物无效的难治患者 42 例(单化疗 25 例,化疗加内分泌治疗 16 例,单内分泌治疗 1 例);手术及其他治疗方式治疗后至本次复发或远处转移的无瘤间期 < 5 年者 38 例,≥5 年者 22 例;有淋巴结转移者 25 例,肺转移 25 例,胸壁转移 18 例,骨转移 15 例,肝转移 10 例,乳腺 9 例,胸膜转移 7 例,肾上腺转移 1 例。出现 1 个部位转移者 23 例,多个部位转移者 37 例。

1.4 治疗方法

(1)分组原则和方法:根据患者先前的治疗状况分为二组,一线治疗(未做过化疗和/或内分泌治疗或术后辅助化疗和/或内分泌治疗已停止 ≥1 年),二线治疗(停止化疗 ≥1 月,停止内分泌治疗 ≥2 月)。一线治疗 18 例,二线治疗 42 例。(2)给药方法:一线治疗病人每日一次口服法乐通 60 mg,二线治疗病人每日一次口服法乐通 120mg,服药 6~8 周,治疗 6 周后评价疗效,CR,PR,S 继续治疗至 8 周,P 则停药。用药未满 6 周不统计疗效。

1.5 疗效评定标准

根据 WHO(1981)统一标准,完全缓解(CR):可见的病变完全消失,超过一个月。部分缓解(PR):肿块缩小 50%以上,时间不少于 4 周。稳定(S):肿块缩小不及 50%或增大未超过 25%。进展(P):一个或多个病变增大 25%以上或出现新病变。总有效率 = CR + PR。

2 结 果

2.1 疗效

入组63例,失访3例,全组能评价疗效及不良反应者均为60例。结果,PR 11 例,S 26例,P 23例,有效率18.3%。一线治疗18例,PR6例,S7例,P5例,有效率33.3%。二线治疗42例,PR5例,S19例,P18例,有效率11.9%,过去曾用内分泌治疗17例,PR1 例,S9例,P7例,有效率5.9%,未用内分泌治疗43例,PR10例,S17例,P16例,有效率23.3%,不同转移部位与疗效关系见表1,其中淋巴结和骨转移疗效较好,有效率分别为32.0%和26.7%。绝经时间 < 10年者36例,PR4例,S16例,P16例,有效率11.1%。绝经时间 ≥10年者24例,PR7例,S10例,P7例,有效率29.2%。疗后无瘤间期 < 5年者38例,PR3例,S15例,P20例,有效率7.9%。疗后无瘤间期 ≥5年者22例,PR8例,S11例,P3例,有效率36.4%。影响疗效的因素分析显示,乳腺癌一线治疗较二线治疗、未用内分泌治疗较曾用内分泌治疗以及绝经时间长(≥10年)较绝经时间短(< 10年)疗效较好,但因病例数少,未见统计学上有显著性差异($P > 0.05$)。但本组结果显示,疗后无瘤间期长(≥5年)较疗后无瘤间期短(< 5年)疗效明显好,统计学上有显著差异($P < 0.05$)。

表1 不同转移部分与疗效关系

转移部位	例数	疗效				有效率(%)
		CR(%)	PR(%)	S(%)	P(%)	
淋巴结	25		8(32.0)	13(52.0)	4(16.0)	26.7
肺	25		4(16.0)	13(52.0)	8(32.0)	16.0
胸壁	18		2(11.1)	7(38.9)	9(50.0)	11.1
骨	15		4(26.7)	7(46.7)	4(26.7)	26.7
肝	10		1(10.0)	3(30.0)	6(60.0)	10.0
乳腺	9		1(11.1)	6(66.7)	2(22.2)	11.1
胸膜	7		0	4(57.1)	3(42.9)	0
肾上腺	1		0	0	1(100.0)	0

2.2 不良反应

按 WHO 分级标准分级,全组未见 ≥Ⅱ度的不良反应,不良反应均为Ⅰ度,其中:恶心 9 例(15.0%),纳差 6 例(10.0%),阴道排液、面部潮红、肝功能损害各 4 例(各 6.7%),头晕、失眠、上腹不适各 3 例(各 5.0%),乏力 2 例(3.3%),便秘、呕吐各 1 例(各 1.7%)。

3 讨 论

法乐通是由芬兰 Farmous 研究组自 1979 年开始研制的新一代抗雌激素抗肿瘤新药,是非甾体类三苯乙烯的衍生物,化学结构式与三苯氧胺(Tamoxifen TAM)相似,其抗肿瘤作用机制亦与 TAM 相似,但其具有的诱导转化生长 (下转 335 页)

(上接310页) 因子(β-TGF)的产生和调节致癌表达从而抑制癌细胞的作用是TAM所缺乏的[1]。国外十余来年的基础和临床研究表明其对绝经后晚期乳腺癌的疗效高于或相当于TAM。且毒副作用轻,尚未发现长期服用TAM所致的肝细胞癌变、子宫内膜癌、增生性结节及视网膜改变等副作用[2],安全性优于TAM,现已推荐用于乳癌的内分泌一线治疗及用于TAM或其它内分泌治疗无效的二线治疗。

国外法乐通治疗晚期绝经后乳腺癌的效果已积累了许多资料。芬兰学者Valavaara[3](1988)报道应用TOR 60 mg/天持续至少6周治疗46例绝经后ER阳性的晚期乳腺癌患者,结果8例CR,17例PR,有效率54%,1990[4]年该作者综合近300例绝经后晚期乳腺癌患者接受TOR一线治疗结果,有效率50%,若包括病情稳定者,高达74%~92%的患者从治疗中获益。我们一线治疗病例18例,PR6例,有效率33.3%,包括病情稳定者,72.2%的患者从治疗中获益,较文献报道结果略差。可能与本组病例较晚,均为Ⅳ期和转移部位较多(≥2个37例,占72.2%)有关。国外许多学者对常规化疗、放疗、内分泌治疗无效或复发的乳癌患者采用TOR作为二线治疗,综合国外文献300例Ⅱ期临床二线治疗结果显示0-33%的有效率,25%~79%病情稳定,本组二线治疗42例,PR5例,S19例,缓解率11.9%,45.2%获得病情稳定,与文献结果基本一致。文献报道TOR与TAM有交叉耐药,Vogel等[5]报道对于102例绝经前或绝经后的晚期TAM治疗失败的乳腺癌患者采用TOR 200mg/天,结果有效率5%,23%获得病情稳定,本研究组17例过去曾用内分泌治疗者,缓解率为5.9%,43.3%获得病情稳定,与之相仿。Pyrhonen等[6]用TOR治疗214例晚期绝经后乳腺癌病人,缓解率31.3%。我们用法乐通治疗晚期绝经后乳腺癌病人60例,PR11例,S26例,P23例,缓解率18.3%,较之略差,可能与本组病例多为ER不详有关(60%)。我们的结果还显示疗后无瘤间期长和绝经时间长的患者对法乐通的治疗效果好。文献报道法乐通耐受性良好,不良反应轻微,主要为胃肠道反应和抗雌激素效应反应,我们的结果显示不良反应与文献报道一致。

综上所述,法乐通是治疗晚期绝经后乳腺癌有效和安全的抗雌激素抗肿瘤新药,可推荐作为晚期绝经后乳腺癌的一线内分泌治疗和常规化疗、内分泌治疗无效或复发的乳腺癌患者的二线治疗,值得进一步临床推广应用。

参 考 文 献

[1] Huovinen R, Warri A, Collan Y. Mitotic activity, apopotosis and TRPM-2 mRNA expression in DMBA-induced rat mammary carcinoma treated with anti-estrogen toremifene [J]. Int J Cancer, 1993, 21, 55(4): 685.

[2] Hard GC, Iatropoulos MJ, Jordan K, et al. Major difference in the hepatocarcinogenicity and DNA adduct forming ability between toremifene and tamoxifen in female Crl: CD(BR) rats [J]. Cancer Res, 1993, 53(19): 4534.

[3] Valavaar R, Pyrhonen S, Heikkinen M, et al. Toremifene, a new antiestrogenic compound, for treatment of advanced breast cancer. Phase II study [J]. Eur J Cancer Clin Oncol, 1988, 24(4): 785.

[4] Valavaara R. Phase II trials with toremifene in advanced breast cancer: a review [J]. Breast Cancer Res Treat, 1990, 16 suppl: S31.

[5] Vogel CL, Shemano I, Schoenfelder J, et al Multicenter phase II efficacy trial of toremifene in tamoxifen-refractory patients with advanced breast cancer [J]. J Clin Oncol, 1993, 11(2): 345.

[6] Pyrhonen S, Valavaara R, Modig H, et al. Comparison of toremifene and tamoxifen in postmenopausal patients with advanced breast cancer: a randomized double-blind, the 'nordic' phase III study [J]. Bri J Cancer, 1997, 7(2): 270.

〔编辑及校对:杨允贵〕

Breast Cancer Research and Treatment **65:** 119–124, 2001.

Report

Phase III randomized trial of toremifene vs tamoxifen in hormonodependant advanced breast cancer

A. Milla-Santos, L. Milla, L. Rallo, and V. Solano
The Medical Oncology Service, Nuestra Senyora Del Pilar Hospital, Barcelona, Spain

Key words: advanced breast cancer, toremifene, tamoxifen, postmenopausal, positive hormonal receptors, randomized trial

Summary

Purpose. Ef cac y and safety of toremifene (TOR) 60 mgs/dayly/o.r. was compared with tamoxifen (TAM) 40 mgs/dayly/o.r. in a group of postmenopausal women with advanced breast cancer, without previous systemic therapy for advanced breast cancer.

Material and methods. The study was a prospective double-blind randomized trial. All treated patients presented with positive estrogen receptors. Main end points were response rates, toxicity pro le analysis, time to progression and survival. WHO and ECOG criteria were employed for response evaluation while toxicity was assesed according to WHO guidelines. Curves were constructed by means of Kaplan–Meier methodology and were compared by means of log-rank test.

Results. From January 1996 to January 1999 a total of 217 patients were included in the study (106 in the TOR branch and 111 in the TAM arm). Both groups of patients were homogeneous regarding the main prognostic factors. A response rate of 64% (68/106) was observed in the TOR group as compared with a 52% (58/111) in the TAM group. Median times to progression and overall survival were not signi cantly different. A lower incidence of undesirable effects was apreciated in the TOR arm.

Conclusions. Our data suggest that TOR is an ef cient and well-tolerated agent for the therapy of postmenopausal women with hormonal positive receptors advanced breast cancer, and must be considered an alternative to TAM as rst line therapy for ERC advanced breast cancer patients and as well as an adjuvant treatment.

Introduction

The use of tamoxifen (TAM) has been well established in the therapy of advanced breast cancer. In non-selected groups of patients, a response rate of about 30% have been reported [1]. On the other hand, in patients expressing positive estrogen receptors a 60–70% response rate can be obtained [2]. This wide range is probably due to the high variability of prognostic factors in different patient populations and a heterogenous criteria applied in the evaluation of responses. The mechanism by which TAM inhibits the growth of breast cancer cells is unclear. To this respect, Parker [3] investigations suggest that growth factors as TGF a and TGF b are induced by TAM. The undesirable effects of TAM have been widely discussed. Both at experimental and clinical levels, several investigations have pointed out that TAM increases the risk of hepatocarcinoma in rats [4] and the risk of endometrial and gastrointestinal cancers in humans [5, 6], although this particular data must be interpreted cautiously. Finally, Lahti et al. [7] indicated an increment in the number of endometrial polyps in patients receiving TAM.

Such arguments clearly suggest that an antiestrogen that lacks these undesirable characteristics should conserve the bene cial effects of TAM. TOR is a new molecule pharmacologically analogous to TAM, with estrogenic and anti-estrogenic properties, that was rst synthesized in 1981. TOR is structurally similar to TAM, differing only by a single chlorine atom, and has a similar pharmacologic pro le. The major difference

between the two drugs is detected in the preclinical setting – chronic TAM administration is hepatocarcinogenic in the rat liver, whereas TOR is not [8]. To act as an antiestrogen in humans and, as TAM acts, binds the ER in target cells. Their mechanism of action is complex. Genomic actions are through to be mediated by ER oncogen expression, autocrine and paracrine growth factors secretion, and regulation of apoptosis [9]. Clinical trials investigating the ef cacy of TOR as rst line therapy in postmenopausal women with advanced breast cancer (ER C /unknown) have demonstrated that this drug have similar antitumoural activity to that of TAM [10].

On the basis of the said data, in January 1996 we implemented a Phase III prospective randomised double-blind trial to compare TOR versus TAM in a group of postmenopausal advanced breast cancer patients who expressed positive ER main end points being response rate, toxicity analysis, statistical evaluation of the median time to progression and survival. The results are reported in the present paper.

Material and methods

Patients selection

Eligible patients were postmenopausal women with histopathological documented advanced breast cancer, with positive ER at either the primary tumor or metastatic sites. Patients must present bidimensionable measurable lesions or evaluable lytic bone metastases. Patients with prior adjuvant chemotherapy were admitted, meanwhile those patients who had received previously chemotherapy/hormonotherapy for advanced disease were refused. A performance scale (ECOG) of 0–2 was also required. Additional criteria included adequate bone marrow, renal, liver and cardiac functions. Signed, informed consent was obtained from all patients before inclussion in the study. Finally, patients who presented with brain metastases, in matory breast cancer, pulmonar lymphangitis or second malignancy were excluded from the trial.

Treatment plan

Patients were randomised between two different options:

Option A: TOR 60 mgs/dayly/o.r.
Option B: TAM 40 mgs/dayly/o.r.

The TAM dose was tried provided that such dose is considered as standard for metastatic disease in our Department. Prior to be included in the study, patients underwent medical history, physical exam, laboratory tests, toracoabdominopelvic CT scan, and nuclear bone scan.

After 3 months of the therapy was started, evaluation was made using the same method employed at baseline. WHO criteria [11] for measurable disease was followed, while ECOG criteria [12] for non measurable but evaluable bone spread was employed. The side effects incidence was evaluated following WHO guidelines [13]. Patients with positive response continues the same therapy to evaluate its role in the maintenance of the response, until a relapse or unacceptable toxicity were detected.

Statistical methodology

Patients were ramdomly allocated between the two options following the Meinert's methodology [14]. The Fisher's Exact test and the ^{2} test with Yates's correction [15] were used to compare qualitative variables. The Maentel–Haenszel test with Fleiss correction was used to compare qualitative variables in repeated measures [16]. To analyse quantitative variables in repeated measures, ANOVA for repeated measures was used [17]. To calculate and compare the cumulative hazard function, the Mantel–Cox test was performed [18]. Shapiro–Wilk's test was used to asses Gaussian adjustment [19]. Homogenicity of variances was tested using the Levene test [20]. The Mann–Whitney test [21] was used to compare differences in quantitative variables within groups. All tests were two-tailed. a level was x ed at 0.05.

Remission duration was calculated from the date of remission to relapse or to the data the patient was last known to be free of disease. Survival was evaluated from the beginning of the treatment to the death or to the data when the patient was last known to be alive. Curves were constructed following the Kaplan–Meier methodology [22]. They were compared by means of log-rank test [23].

The statistical analysis was performed using Jeppsen 486/66 computers with the following programmes : BMDP Dynamic v 7.0 (BMDP Statistical Software Inc, Los Angeles, California, USA, 1993), and BMDP New System (BMPD Statistical Software Inc, Los Angeles, California, USA, 1994) for graphic visualization.

Table 1. Patients characteristics

	Treatment arm	
	Toremifene .n D 106/	Tamoxifen .n D 111/
Age range	56–75	55–75
Mean age	61.3	60.8
Dominant metastatic sites		
Visceral	39 (36.8%)	31 (28%)
Bone	40 (37.7%)	52 (47%)
Soft tissue	27 (25.5%)	28 (25%)
Median number of metastatic sites	2	
range	1–6	1–6
ECOG PS		
0	74 (70%)	77 (69%)
1	19 (20%)	26 (23%)
2	7 (10%)	8 (8%)
Prior adjuvant Chemotherapy		
CMF	31 (29%)	37 (33.3%)
Doxorubicin	28 (26.4%)	31 (28%)

Table 2. Response rates

	Treatment arm	
	Toremifene (%)	Tamoxifen (%)
Complete responses	13 (12.2)	9 (8.1)
Partial responses	27 (25.4)	27 (24.3)
Stable disease	28 (26.4)	22 (19.6)
Progressive disease	38 (36)	53 (48)
Global response rate	68 (64)	58 (52)
CR C PR	40 (37.6)	36 (32.4)

Table 3. Median time to progression, median survival and 95% CI

	Treatment arm		
	Toremifene	Tamoxifen	p value
Median Time to progression (months)	11.9	9.2	0.217
95% CI	9.7–13.3	6.2–10.8	
Hazard ratio	1.016		
95% CI	0.80–1.32		0.823
Progressed	87 (82%)	100 (90%)	
Median Survival (months)	15.4	12.3	0.196
95% CI	12.6–19.4	9.8–14.5	
Hazard ratio	0.97		
95% CI	0.74–1.29		0.532
Dead	73 (68.8%)	81 (72.9%)	

Ethics

The pocedures followed were in accordance with the standards of the responsible Institutional Committee on Human Experimentation and with the Helsinki Declaration of the World Medical Association amended in 1975 and 1983.

Results

Epidemiological data and baseline characteristics

From January 1996 to January 1999, a global of 217 patients have been included in the trial (106 in TOR group and 111 in the TAM group). All patients were considered eligible for the study purposes. The treatment groups were comparable with regard to age, metastatic sites, and baseline parameters. No statistically signi cant differences were detected that might indicate a lack of homogeneity between groups (Table 1).

Response rates

The response rates for the two therapeutic groups are listed in Table 2. The clinical bene t (complete responses C partial responses C stable disease) was 64% (68/106) in the TOR group while in the TAM group this gure was 52% (58/111). If only CR C PR are considered, the respective rates were 37% (40/106) in the TOR group and 32% (36/111) in the TAM group. Response rates were not statistically different between the two therapeutic arms.

Median duration of response and survival analysis

At the moment of the data cut-off (January 2000), 19 (18%) patients in the TOR group and 11 (10%) in the TAM arm were continuing on follow-up without any evidence of tumoural progression. The results of the median duration of response and overall survival are presented in Table 3 and Figures 1 and 2.

Although no statistically signi cant differences were detected between groups, a marginal higher risk of tumoural progression was seen in TAM group as compared with this tendency for the TOR group and as

Table 4. Adverse drug reactions

	Treatment arm	
	Toremifene (%)	Tamoxifen (%)
Thromboembolic events	3 (2.8)	9 (8)
Occular disorders	1 (0.9)	7 (6.3)
Cardiac events	–	2 (1.8)
Hepatic abnormalities	4 (3.7)	13 (11.7)
Fluid retention	1 (0.9)	14(12.6)
Abdominal pain	–	3 (2.7)
Headache	1 (0.9)	5 (4.5)
Asthenia/anorexia	2 (1.8)	7 (6.3)
Somnolence	–	5 (4.5)
Sweating	6 (5.6)	11 (9.9)
Hot ashes	5 (4.7)	13 (11.7)
Vaginal bleeding	4 (3.7)	22 (19.8)
Nausea & vomiting	5 (4.7)	13 (11.7)
Endometrial carcinoma	–	2 (1.8)

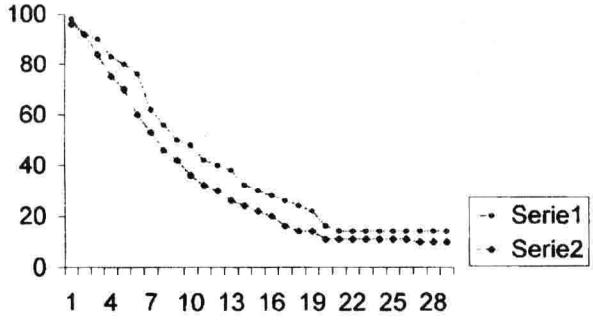

Figure 1. Median duration of response (months). Serie 1 D Toremifene. Serie 2 D Tamoxifen.

is indicated by the hazard ratios analysis (1.016; 95% CI limits or the hazard ratios D 0.80–1.32; *p* D 0.823). Median duration of response was 11.9 months for the TOR group and 9.2 months for the TAM group (*p* D 0.217).

Regarding survival, 72 patients (68%) had died in the TOR group by the cut-off data meanwhile 89 patients (80%) had died in the TAM group. The hazard ratios for death analysis were respectively 0.97 (95% CI D 0.74–1.29; *p* D 0.532) with no statistical differences detected between arms (*p* D 0.196).

Toxicity

In the TAM group, a slightly higher incidence of undesirable effects was observed (Table 3). The incidence of thromboembolic events, hepatic abnormalities, and occular disorders (catarats), occurred with higher

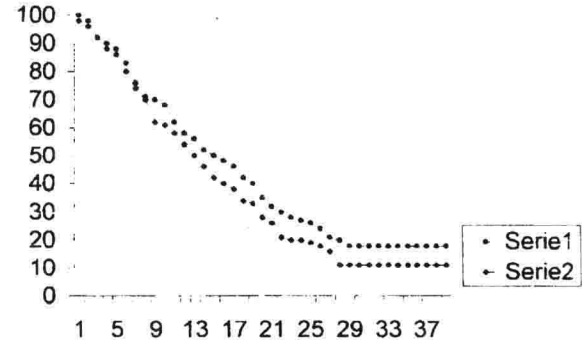

Figure 2. Overall survival (months). Serie 1 D Toremifene. Serie 2 D Tamoxifen.

assiduity in the TAM group, although no signi cant statistical differences were detected. Other effects as anorexia, oedema, sweating, vaginal bleeding, etc were mild or moderate and no differences regarding incidence rates were observed. Two endometrial carcinomas were found among TAM patients while no second malignancies were recorded in patients receiving TOR. As to, all deaths were related with tumoural progression and not with the treatment itself.

Discussion

TAM is currently the standard hormonal treatment for hormonal dependant breast cancer, both for metastatic disease and in the adjuvant setting. The overall response rates reported varies from 20% to 70% [2]. As it was previously expressed, several prognostic factors (overall ER C and soft tissue/bone metastases) have been identi ed to select patients who most likely will respond to TAM therapy. The side effects of TAM have been widely discussed. The main concern is the increment in endometrial and gastrointestinal cancers occurred in long-term TAM-treated patients [5, 6, 24–27].

To avoid such undesirable effects, another antiestrogen, TOR, which is triphenylethylene derivative related to TAM, has been tested in the treatment of advanced breast cancer. Basically, TOR differs in its nonclinical toxicology from rst generation congener TAM. TAM produces DNA adducts and tumours in rat liver, whereas assays for DNA adduct formation with TOR have been negative to weakly positive, and TOR does not produce liver tumours in rats. To this respect, Williams et al., studies [28] provided evidence that TOR is no genotoxic.

At the time when our study was started, the results of a randomized trial comparing the ef cacy and safety of two TOR doses (60 mgs; 200 mgs) versus TAM (40 mgs) in a group of 648 patients were published [29], and two important trials with similar methodology were in progress. Their results have been recently published [30, 31]. In these studies, patients with positive/unknown/negative ER were included. This concern represent the main difference with our own trial, in which only patients with ERC were admitted. The resting requirements were similar regarding menopausal status, performance status and absence of previous therapies for advanced disease.

The present trial shows that in the treatment of ERC advanced breast cancer patients, TOR seems to be slightly superior to TAM. The response rate of 64% in the TOR group and the median time to progression of 11.9 months are consistent gures with the data obtained from previous phase II trials in ERC patients [29–31]. Although response rate, median time to progression and median survival were superior for the TOR arm, no statistical differences were detected between arms.

In our trial, major adverse reactions resulting in death or discontinuation of the therapy were not appreciated. However, a higher incidence of thromboembolic events, hepatic abnormalities and occular alterations were observed in the TAM treated patients, meanwhile these disorders were rare in the TOR patients group. In two instances an endometrial carcinoma was diagnosed in patients receiving TAM. Although second malignancies is of little issue in patients with advanced disease, it is a very important concern in the adjuvant setting. To this respect, the widespread use of TAM as an adjuvant and even in chemoprevention, has raised the question of its safety regarding its potential carcinogenetic effects in experimental models and in human beings.

From our data we can conclude that TOR is slightly superior to TAM regarding response rate, median time to progression and median survival, and present a less incidence of undesirable effects. Considering the ef cacy and safety of TOR, this drug need to be quali ed as a reasonable alternative to TAM in ERC advanced breast cancer patients, as adjuvant therapy and in the chemopreventive setting.

References

1. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN: Use of tamoxifen for breast cancer: Twenty-eight years later. J Clin Oncol 13: 513–529, 1995
2. Isaacs CJD: Hormone replacement therapy in women with a history of breast carcinoma. Hematol Oncol Clin N Am 8(1): 179–195, 1994
3. Parker MG: Growth regulation by nuclear hormone receptors. In: Franks LM (ed) Cancer Surveys. Cold Spring Harbor, Cold Spring Harbor Laboratory Press, Vol. 14. 1992, pp. 240
4. Vancutsem PM, Lazarus P, Williams GM: Frequent and speci c mutations of the rat *P53* gene in hepatocarcinomas induced by tamoxifen. Cancer Res 54: 3864–3867, 1994
5. Fisher B, Constantino JP, Redmond CK et al.: Endometrial cancer in tamoxifen treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 86: 527–537, 1994
6. Rutqvist LE, Johansson H, Signumklao T et al.: Adjuvant tamoxifen therapy and second primary malignancies. J Natl Cancer Inst 87: 645–651, 1995
7. Lahti E, Blanco G, Kavppila A et al.: Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. Obstet Gynecol 81: 660–664, 1993
8. Buzdar AU, Hortobagyi GN: Tamoxifen and toremifene in breast cancer: Comparison of safety and ef cacy. J Clin Oncol 16: 348–353, 1998
9. Wärri AM, Houvinet RL, Laine AM et al.: Apoptosis in toremifene – induced growth inhibition of human breast cancer cells *in vivo* and *in vitro*. J Natl Cancer Inst 85: 1412–1418, 1993
10. Wiseman LA, Goa KL: Toremifene: A review of its pharmacological properties and clinical ef cacy in the management of advanced breast cancer. Drugs 54: 141–160, 1997
11. Miller AM, Hoogstraten B, Staquet M, Winkler A: Reporting results of cancer treatments. Cancer 47: 207–214, 1981
12. Ojen MM, Creech RH, Tormey DC et al.: Toxicity and response criteria of Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649–655, 1982
13. WHO Adverse Reactions Dictionary: WHO Collaborating Center for International Drug Monitoring. Uppsala, Sweden, 1988
14. Meinert CL: Clinical Trials: Design, Conduct and Analysis. Oxford University Press, New York, 1986
15. Agresti A: Categorical Data Analysis. Wiley, New York, 1990
16. Fleiss JPL: Statistical Methods for Rates and Proportions. Wiley, New York, 1990
17. Dixon WJ, Merdian K: ANOVA and Regression with BMDP 5 V. Dixon Statistical Associates, 1992
18. Lee ET: Statistical Methods for Survival Data Analysis. Wiley, New York, 1993
19. Shapiro SS, Wilks MB: An analysis of variance test for normality. Biometrika 52: 591–611, 1965
20. BMDP Statistical Manuals, 1991, vol. 1: 579. University of California Press
21. Snedecor GW, Cochrn WG: Statistical Methods. Ames, The Iowa State University Press, 1967
22. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481, 1958
23. Peto R, Pike MC, Armitage P et al.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient .I. Introduction and Design. Brit J Cancer 34: 585–612, 1976
24. Jordan VC, Morrow M: Should clinicians be concerned about the carcinogenic potential of tamoxifen? Eur J Cancer 30: 1714–1721, 1994
25. Robinson DC, Bloss JD, Schiano MA: A retrospective study of tamoxifen and endometrial cancer in breast cancer patients. Gynecol Oncol 59: 186–190, 1995

26. Curtis ER, Boice JD, Shiner DA et al.: Second cancers after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 88: 832–834, 1996
27. Wilking N, Isaksson E, Schooltz E: Tamoxifen and secondary tumours: An update. Drug Safety 16: 104–117, 1997
28. Williams GM, Ross PM, Jeffrey AM, Karlsson S: Genotoxicity studies with the antiestrogen toremifene. Drug Chem Toxicol 21: 449–476, 1998
29. Hayes DF, Van Zyl JA, Hacking A et al.: Randomized comparison of Tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. J Clin Oncol 13: 2556–2566, 1995
30. Gershanovich M, Garin A, Baltina D et al.: A phase III comparison of two toremifene doses to tamoxifen in postmenopausal women with advanced breast cancer. Breast Cancer Res Treat 45: 251–262, 1997
31. Pyrhönen S, Valavaara R, Modig H et al.: Comparison of Toremifene and Tamoxifen in postmenopausal patients with advanced breast cancer: A randomized double-blind, the nordic phase III study. Brit J Cancer 76: 270–277, 1997

Address for offprints and correspondence: A. Milla-Santos, Centro de Especialidades Médicas, 41 Madrazo st. 08006, Barcelona, Spain